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Acknowledgements:
Acknowledgements of general support, grants, technical assistance, etc., should be indicated. Authors are responsible for obtaining the consent of those being acknowledged.

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Rampal L, Liew BS, Choolani M, Ganasegeran K, Pramanick A, Vallibhakara SA, et al. Battling COVID-19 pandemic waves in six South-East Asian countries: A real-time consensus review. Med J Malaysia 2020; 75(6): 613-25.
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Books and Other Monographs:
Personal Author(s)
Goodman NW, Edwards MB. 2014. Medical Writing: A Prescription for Clarity. 4 th Edition. Cambridge University Press.

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

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Original Articles

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Refractive error and amblyopia among primary school children in remote islands of East Coast of Peninsular Malaysia

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ABSTRACT

Introduction: Little is known about the prevalence of refractive errors and amblyopia among school children on the islands of East Coast Malaysia. This study aimed to investigate the prevalence of these conditions and their associated factors in this unique and remote geographical location.

Materials and Methods: This multicentre cross-sectional school-based study included 480 children aged 7 to 12 year from primary schools on the islands of the East Coast of Malaysia. All children underwent visual acuity assessment, orthoptic evaluation, anterior and posterior segment examinations and manifest refraction. Demographic data, history of parental refractive error, parental education level, duration of digital screen time and time spent outdoors were documented in a questionnaire distributed to the parents.

Results: The mean age was 9.53 ± 1.69 years, with an equal distribution of genders. The ethnic composition of the subjects was 99.4% Malay and 0.6% Orang Asli. The overall prevalence of refractive errors was 11.9% (95% CI: 9.1 to 15.1%), with myopia at 7.1% (95% CI: 5.0 to 9.8%), hyperopia at 2.5% (95% CI: 1.3 to 4.3%), astigmatism at 2.3% (95% CI: 1.1 to 4.1%) and amblyopia at 2.5% (95% CI: 1.3 to 4.3%). Older age, an absence of parental history of refractive error and reduced daily outdoor time were significantly associated with refractive errors ($p < 0.05$).

Conclusion: The prevalence of refractive error is 11.9% and amblyopia is 2.5% among primary school children on the islands of the East Coast of Peninsular Malaysia. Older age, an absence of parental history of refractive error and reduced daily outdoor time are associated with refractive error.

KEYWORDS:
Refractive error, amblyopia, primary school children, islands, East Coast Malaysia, associated factors

INTRODUCTION

Given its high prevalence, understanding the epidemiology of refractive error is crucial for developing national health policies. With a global prevalence of 43%, refractive error is a significant public health concern.[1] Uncorrected refractive error in childhood is a major risk factor for amblyopia, leading to impaired visual acuity (VA) and a negative impact on a child's abilities, academic performance and quality of life. The prevalence of amblyopia in children worldwide ranges from 1.44 to 4.3%.[2]

While numerous studies have attempted to ascertain the prevalence of refractive error in Malaysia, the majority have concentrated on the population residing in the mainland regions of East and West Malaysia.[3-11] As a result, the prevalence of refractive error in the island population remains unknown.

The islands of Redang, Perhentian and Tioman are located at a distance range of 19 to 60 km from the mainland, can be accessed in 1 to 2 hours by water transportation and are well equipped with their primary healthcare centres. However, the nearest ophthalmology and optometry facilities are only available on the mainland, which may pose challenges in accessing specialised eye care services for the island-dwelling population. On top of that, there is a lack of dedicated and regular eye-screening programs for children residing in these islands, with most eye-screening being conducted through volunteer initiatives by governmental and non-governmental organisations. Therefore, our study aimed to determine the prevalence of refractive error and amblyopia in children and the associated factors with refractive error in these remote areas.

MATERIALS AND METHODS

This multicentre cross-sectional study was conducted in the islands of the East Coast Malaysia, specifically in the states of Terengganu and Pahang, Malaysia, from December 2022 to

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November 2023, adhering to the principles of the Declaration of Helsinki. The study protocol received approval from the Research and Ethical Committee, School of Medical Sciences, Universiti Sains Malaysia (No. USM/JEPeM/22060444).Written informed consent was obtained from all parents/legal guardians, and verbal assent was obtained from the recruited children.

The inclusion criteria encompassed all primary school children aged 7 to 12 years old residing in the Redang, Perhentian, and Tioman Islands. Exclusion criteria comprised children already under ophthalmology follow-up for known ocular diseases or those absent from school. Participants were categorised into two age groups: 7 to 9 years old and 10 to 12 years old, following the age stratification guidelines of the Malaysian Ministry of Education.

Questionnaires were distributed to parents to collect demographic data, family history of refractive error, parental education (based on the parent with the highest level of education), digital screen time and time spent outdoors. Visual screening for these children included various assessments such as VA testing using the Snellen chart for distance, cover test, external ocular assessment, ophthalmoscopy and non-cycloplegic refraction. Spectacles were prescribed when indicated, and children diagnosed with ocular anomalies were referred to the nearest ophthalmology service.

Myopia is defined as spherical equivalent (SE) of at least -0.50 D, hyperopia of +0.50 D or more, and astigmatism of 0.50 D or more in either eye. Amblyopia was defined as the best corrected VA worse than or equal to 20/30 using Snellen VA or 0.2 logarithm of the minimum angle of resolution unit in the absence of ocular pathology.

Data were analysed using Statistical Package for Social Sciences (SPSS version 27.0; IBM Corp, Armonk, NY, USA) software. Descriptive statistics were used to analyse demographic data and the prevalence of refractive error, myopia, astigmatism, hyperopia and amblyopia. Data were expressed as mean, standard deviation, median, frequency and percentage. Logistic regression analyses were conducted to identify factors associated with refractive error. All p-values were considered statistically significant when less than 0.05. Pearson's Chi-Square and Fisher's exact test were conducted to investigate the association between variables and amblyopia. All analyses conducted were two-tailed, with an alpha level set at a significance level of 0.05.

RESULTS

A total of 480 children participated in the study, with the majority belonging to the Malay ethnicity (99.4%) and an equal distribution of males and females. Refractive error was identified in 57 children (11.9%) with a 95% confidence interval of 0.091 to 0.151. Other ocular pathologies observed included strabismus (3.3%) and oculodermal melanosis (1.7%).

The average age of children with refractive error was 9.53±1.69 years. Refractive error was most prevalent among older individuals (61.4%), females (56.1%), those without a family history of myopia (77.2%), children who spent less than 2 hours outdoors daily (94.7%) and those with more than 2 hours of daily digital screen time (70.2%). Myopia was the most common type of refractive error, affecting 34 children and accounting for 7.1% of the total refractive errors. Hyperopia was found in 12 (2.5%) children, and astigmatism in 11 children (2.3%). A majority of children with refractive error spent less than 2 hours outdoors (94.7%) and more than 2 hours on electronic devices (70.2%) daily. These are presented in Table I.

Table II shows that unilateral amblyopia was diagnosed in 10 children (83.3%), with refractive amblyopia being the primary cause (83.3%), followed by sensory deprivation amblyopia (16.7%). Amblyopia was identified in 12 children (2.5%), with a mean age of 9.75 ± 2.38 years, predominantly among males (58.3%) from households with a monthly income of RM 1000 or less (33.3%).

Multiple logistic regression analysis revealed that children aged 10 to 12 years old had 2.94 times higher odds of developing refractive error compared to those aged 7 to 9 years old after controlling for outdoor time and digital screen hours (OR: 2.94, 95% CI: 1.02 to 8.48, p = 0.047). Furthermore, children with a history of parental refractive error had 52% lower odds of developing refractive error compared to those without after controlling for age and outdoor time (OR: 0.48, 95% CI: 0.23 to 1.00, p = 0.049). Children who spent 2 hours or more outdoors had 98% lower odds of refractive error compared to those who spent less than 2 hours outdoors after adjusting for age and digital screen time (OR: 0.02, 95% CI: 0.01 to 0.05, p < 0.001) as illustrated by the Table III.

Table IV describes the association of identified variables and amblyopia using Chi-square test in view of small number of children with amblyopia. A higher proportion of the amblyopia group spent less than 2 hours outdoors compared to the non-amblyopia group, 91.7% and 29.5%, respectively (p < 0.001). Other factors tested for amblyopia showed no significant association with amblyopia (p > 0.05).

DISCUSSION

In this study, we examined the prevalence of refractive error, amblyopia and their associated factors on the islands of the East Coast of Peninsular Malaysia. The observed prevalence of refractive error was 11.9%, aligning with findings from similar studies conducted in the United States of America, Indonesia and Saudi Arabia, where rates ranged from 13.1 to 16.8%.[12-14] However, the prevalence of refractive error in our study is notably lower than that reported in New Zealand, Kazakhstan, and China (26.3 59.6%).[15-17] Table V describes refractive error prevalences reported in previous studies conducted in Malaysia, ranging from 70 to 75.6%, including our own study.[7-14]

Several factors contribute to this wide variation in prevalence rates. Notably, individuals of Chinese ethnicity are more

Table I: Sociodemographic characteristics of study subjects (n = 480)

Variables	n (%)	Refractive error, n (%)		Myopia, n (%)		Hyperopia, n (%)		Astigmatism, n (%)	
		Yes (n=57)	No (n=423)	Yes (n=34)	No (n=446)	Yes (n=12)	No (n=468)	Yes (n=11)	No (n=469)
Age group (year)									
7 - 9	228 (47.5)	22 (38.6)	206 (48.7)	11 (32.4)	217 (48.7)	7 (58.3)	221 (47.2)	4 (36.4)	224 (47.8)
10 - 12	252 (52.5)	35 (61.4)	217 (51.3)	23 (67.6)	229 (51.3)	5 (41.7)	247 (52.8)	7 (63.6)	245 (52.2)
Gender									
Female	240 (50)	32 (56.1)	208 (49.2)	18 (52.9)	222 (49.8)	7 (58.3)	233 (49.8)	7 (63.6)	233 (49.7)
Male	240 (50)	25 (43.9)	215 (50.8)	16 (47.1)	224 (50.2)	5 (41.7)	235 (50.2)	4 (36.4)	236 (50.3)
Race									
Malay	477 (99.4)	57 (100)	420 (99.3)	34 (100)	443 (99.3)	12 (100)	465 (99.4)	11 (100)	466 (99.4)
Orang Asli	3 (0.6)	0 (0)	3 (0.7)	0 (0)	3 (0.7)	0 (0)	3 (0.6)	0 (0)	3 (0.6)
Monthly household income (RM)									
RM 1000 and less	137 (28.5)	13 (22.8)	124 (29.3)	6 (17.6)	131 (29.4)	5 (41.7)	132 (28.2)	2 (18.2)	135 (28.8)
RM 1001 - 2999	276 (57.5)	40 (70.2)	236 (55.8)	26 (76.5)	250 (56.1)	7 (58.3)	269 (57.5)	7 (63.6)	269 (57.4)
RM 3000 and more	67 (14)	4 (7)	63 (14.9)	2 (5.9)	65 (14.6)	0 (0)	67 (14.3)	2 (18.2)	65 (13.9)
Parental refractiveerror									
Yes	169 (35.2)	13 (22.8)	156 (36.9)	9 (26.5)	160 (35.9)	2 (16.7)	167 (35.7)	2 (18.2)	167 (35.6)
No	311 (64.8)	44 (77.2)	267 (63.1)	25 (73.5)	286 (64.1)	10 (83.3)	301 (64.3)	9 (81.8)	302 (64.4)
Parental education level									
Primary school	19 (4)	1 (1.8)	18 (4.3)	1 (2.9)	18 (4)	0 (0)	19 (4.1)	0 (0)	19 (4.1)
Secondary school	388 (80.8)	49 (86)	339 (80.1)	29 (85.3)	359 (80.5)	10 (83.3)	378 (80.8)	10 (90.9)	378 (80.6)
University	73 (15.2)	7 (12.3)	66 (15.6)	4 (11.8)	69 (15.5)	2 (16.7)	71 (15.2)	1 (9.1)	72 (15.4)
Daily hours of outdoor activities									
Less than 2 hours	149 (31)	54 (94.7)	95 (22.5)	31 (91.2)	118 (26.5)	12 (100)	137 (29.3)	11 (100)	138 (29.4)
2 hours and more	331 (69)	3 (5.3)	328 (77.5)	3 (8.8)	328 (73.5)	0 (0)	331 (70.7)	0 (0)	331 (70.6)
Daily hours of digital screen time									
Less than 2 hours	110 (22.9)	17 (29.8)	93 (22)	7 (20.6)	103 (23.1)	6 (50)	104 (22.2)	4 (36.4)	106 (22.6)
2 hours and more	370 (77.1)	40 (70.2)	330 (78)	27 (79.4)	343 (76.9)	6 (50)	364 (77.8)	7 (63.6)	363 (77.4)

RM = Ringgit Malaysia

Table II: Distribution of amblyopia according to laterality and aetiology (n = 12)

Amblyopia	n (%)
Laterality	
Right	6 (50)
Left	4 (33.3)
Bilateral	2 (16.7)
Aetiology	
Refractive	
Myopia	4 (33.3)
Hyperopia	2 (16.7)
Anisometropia	4 (33.3)
Sensory deprivation	2 (16.7)

Table III: Association of refractive error and sociodemographic factors

Variables	Simple logistic regression		Multiple logistic regression	
	Crude OR (95%CI)	p-value	Adjusted OR (95%CI)	p-value
Age (years)				
7 - 9	1		1	
10 - 12				
Gender	1.51 (0.86, 2.66)	0.154	2.94 (1.02, 8.48)	0.047*
Female	1			
Male	0.76 (0.43, 1.32)	0.324		
Monthly household income				
RM 1000 and less	1			
RM 1001 - 2999	1.65 (0.52, 5.27)	0.397		
RM 3000 and more	2.67 (0.92, 7.74)	0.071		
Parental refractive error				
No	1		1	
Yes	0.51 (0.26, 0.97)	0.040*	0.48 (0.23, 1.00)	0.049*
Parental education level				
Primary School	1.00			
Secondary School	0.52 (0.06, 4.54)	0.557		
University	1.36 (0.59, 3.14)	0.467		
Daily hours of outdoor activities				
Less than 2 hours	1		1	
2 hours and more	0.16 (0.05, 0.53)	0.000*	0.02 (0.01, 0.05)	0.000*
Daily hours of digital screen time				
Less than 2 hours	1		1	
2 hours and more	0.66 (0.36, 1.22)	0.189	0.23 (0.08, 0.65)	0.085

OR = odds ratio
CI = confidence interval
p < 0.05 is significant for simple logistic regression
* Statistically significant value
No multicollinearity and no interaction.
Hosmer Lemeshow test, p-value = 0.578

Table IV: Association of amblyopia and sociodemographic factors

Variable	Amblyopia, n (%)		c^2 (df)	p-value
	Yes (n = 12)	No (n = 468)		
Age (years)				
7 - 9	6 (50)	222 (47.4)		
10 - 12				
Gender	6 (50)	246 (52.6)	0.031 (1)	>0.950[a]
Female	5 (41.7)	235 (50.2)		
Male	7 (58.3)	233 (49.8)	0.342 (1)	0.772[a]
Monthly household income				
RM 1000 and less	6 (50)	131 (28)		
RM 1001 - 2999	4 (33.3)	272 (58.1)		
RM 3000 and more	2 (16.7)	65 (13.9)		0.157[b]
Parental refractive error				
No	6 (50)	305 (65.2)		
Yes	6 (50)	163 (34.8)		0.359[b]
Parental education level				
Primary School	0 (0)	19 (4.1)		
Secondary School	11 (91.7)	377 (80.6)		
University	1 (8.3)	72 (15.4)		0.817[b]
Daily hours of outdoor activities				
Less than 2 hours	11 (91.7)	138 (29.5)		
2 hours and more	1 (8.3)	330 (70.5)		0.000*[b]
Daily hours of digital screen time				
Less than 2 hours	3 (25)	107 (97.3)		
2 hours and more	9 (75)	361 (77.1)		0.742[b]

[a]Pearson's chi-square
[b]Fischer's-exact test
*p-value < 0.05.

Table V: Summary of refractive error and amblyopia prevalence in children in Malaysia.

Variables	Saw et al., 2006 [9]	Goh et al., 2005 [3]	Hashim et al., 2008 [6]	Jayaraman et al., 2016 [10]	Min et al., 2017 [7]	Omar et al. 2019 [4]	Ismail et al., 2022 [11]	Omar et al., 2022 [5]	Current study 2024
Place, Country	Singapore and Gombak, Malaysia	Gombak, Selangor, Malaysia	Kota Bahru, Kelantan, Malaysia	Urban Malaysia	Segamat, Johor, Malaysia	Negeri Sembilan, Malaysia	Wang Maju, Kuala Lumpur, Malaysia	Bentong, Pahang, Malaysia	East Coast Islands, Malaysia
Locality	Urban	Urban	Rural	Urban	Rural	Rural	Urban	Rural	Island
Sample size	3714	5528	840	168	1287	110	245	82	480
Age (years)	7 - 9	7 - 15	6 - 13	10 -12	4 - 6	7 - 12	8 - 12	7 - 12	7 - 12
Prevalence (%)									
Refractive error	-	17.1	7.0	66.7	12.5	38	47.8	75.6	11.9
Myopia	9.2 – 40.9	9.8 - 34.3	5.4	58.4	9	5.5	30.2	64.6	7.1
Hyperopia	1.2 – 3.9	1 – 3.8	1.0	0	6.9	28.2	1.2	15.9	2.5
Astigmatism	18.7 – 44.3	15.7	0.6	8.3	84	NA	16.3	NA	2.3
Amblyopia	-	2.9	-	-	7.53	2.7	-	NA	2.5
Criteria	M≤ -0.50D H≥ +2.0D A≥ 0.75D	M≤ -0.50D H≥ +2.0D A≥ 0.75D	M≤ -0.50D H≥ +2.0D A≥ 0.75D	-	M≤ -0.50D H≥ +2.0D A≥ 0.75D	M≤ -0.50D H≥ +1.50D A≥ 0.75D	M≤ -0.50D H≥ +2.0D A≥ 0.75D	M≤ -0.25D H≥ +0.25D	M≤ -0.50D H≥ +0.50D A≥ 0.50D
Method of assessment	CAR, CRS	CAR, CRS	NCAR, NCRS	Not stated	CRS, NCRS	CRS	NCAR, CRS	CRS	NCRS

NCRS: Non-cycloplegic retinoscopy; CRS: Cycloplegic retinoscopy; NCAR: Non-cycloplegic autorefraction; CAR: Cycloplegic autorefraction; M: Myopia; H: Hyperopia; A: Astigmatism, D: Dioptre

susceptible to refractive errors, particularly myopia,[3,5,9,10,18,19] whereas most of our study participants were Malay. Moreover, our study was conducted in rural Malaysia, likely contributing to the lower prevalence of refractive errors. This is supported by various refractive error prevalence studies done in Malaysia, Indonesia, China, India, Bhutan and Iran.[3,4,6,8,18,20-24] The high prevalence of refractive error in urban areas was thought to be related to factors like increased near work, academic pressures, and reduced outdoor time.[17,23,24]

In our study, refractive error was associated with older age, no parental history of refractive error and reduced daily outdoor time. The prevalence of refractive error increases with age aligns with findings from other studies.[3,5,6,9,10,25,26] During pre-pubertal childhood, rapid growth can cause myopia to escalate due to changes in the refractive power, corneal curvature and axial length.[27,28]

Our data revealed a significant association between a positive history of parental refractive error and a reduced refractive error rate. This contradicts data reported by studies done in Malaysia, China and Sweden in which a positive history of parental refractive error is associated with development of refractive error.[6,10,11,22,29,30] This difference could be attributed to heightened awareness among myopic parents regarding refractive error prevention, including the adoption of healthy visual habits and early identification of refractive issues at home.

Our study also reported that increased outdoor time is significantly associated with a reduced rate of refractive error. This aligns with findings from other studies conducted in Malaysia, Kazakhstan, China and New Zealand.[4,6,7,10,11,15-17] Recent evidence supports the notion that spending more time outdoors in natural light offers protection against myopia by producing higher levels of retinal dopamine, which can delay the onset and progression of myopia.[25,27,31-33] While reducing screen time may help prevent refractive error, our study did not find a statistically significant association between digital screen time and refractive error, contrary to the findings of a meta-analysis by Foreman et al.[34]

In our study, the prevalence of myopia is 7.1%, making it the most common type of refractive error, consistent with the findings of numerous previous studies.[2–7,9–11,21,35] The global prevalence of myopia ranges from 4.4 to 55%.[5,6,9,18,20,22,23,36,37] This variability may stem from differences in study design and methodology. Myopia is closely linked to emmetropisation, particularly its feedback theory. This theory suggests that several factors, such as increased near work, atropine, lenses, defocus and reduced outdoor time may contribute to myopia development. Near vision is optically similar to using a minus lens, a known myopigenic factor. Therefore, spending more time outdoors may decrease myopia development.[38] Additionally, increased exposure to bright light outdoors may slow ocular axial length growth, further supporting this theory. Our study reveals a statistically significant association, indicating that increased outdoor time is linked to a 65% lower odd of developing myopia ($p < 0.001$).

The prevalence of hyperopia in our study was 2.3%. Previous studies in Malaysia have shown hyperopia prevalence rates varying from 1 to 28.2%.[3–11] The global pooled prevalence of hyperopia is 4.6%.22 A meta-analysis conducted by Mavi and colleagues indicates that uncorrected hyperopia has been associated with lower academic achievement and literacy abilities in children.[39] Left undetected, this condition could significantly impact one's economic and academic prospects throughout life.

The prevalence of astigmatism in our study population is 2.3%, which is significantly lower than the astigmatism prevalence reported in China (41.6%) and Norway (8.4 to 57%).[18,40] Tang et al. postulated that ethnicity significantly influenced astigmatism development due to anatomical differences in Asian eyes, such as narrow palpebral apertures and tight eyelids.[18] However, Hashemi et al. discovered that astigmatism prevalence among Caucasians, ranging from 22 to 45.6%, mirrors the high rates among Asians, challenging the theory of anatomical variation as the sole influence.[22] Further research is needed to uncover additional factors contributing to astigmatism.

In our study, the prevalence of amblyopia was 2.5%, a figure similar to that reported by Goh et al. (2.9%) and Omar et al. (2.7%).[3,4] A larger proportion of the amblyopia group spent less than 2 hours outdoors compared to the non-amblyopic group, 91.7% vs 29.5% respectively ($p < 0.001$). This finding supports the theory that children who spend less time outdoors are more prone to amblyopia. Early diagnosis and treatment before the age of 10 can fully resolve amblyopia. However, if not properly diagnosed and treated, the condition can result in lifelong visual impairment. Studies on amblyopia indicate that refractive errors pose a prevalent risk across all age demographics.[21]

An inherent limitation of our study was the reliance on recall-based estimations to assess outdoor and digital screen time, lacking the precision of objective measures. To mitigate this limitation, future research endeavours should incorporate more robust methodologies, such as objective monitoring devices or electronic tracking systems, to provide accurate and real-time data on these variables.

CONCLUSION

The present study reported a low prevalence of refractive error and amblyopia among school children in the East Coast Islands of Peninsular Malaysia. Increased time spent outdoors was consistently linked to refractive error and amblyopia. Early detection and treatment of refractive error are crucial in preventing amblyopia.

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CONFLICT OF INTEREST

The authors have no conflict of interest to declare.

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Adverse event following immunisation of adsorbed-inactivated Coronavac (Sinovac) and ChAdOx1 nCOV-19 (Astra Zeneca) of COVID-19 vaccines

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ABSTRACT

Introduction: Countries around the world organised mass vaccinations using various types of vaccines against COVID-19, like inactivated viruses and mRNA. The study aimed to look at adverse events following immunisation (AEFI) of Coronavac® (SIN) and ChAdOx1 nCOV-19 ® (AZ) COVID-19 vaccines in Indonesia.

Materials and Methods: Subjects who received SIN or AZ vaccines were sent questionnaires twice: after they received the first and the second doses of vaccine, respectively. AEFI data on the first- and second-day post-vaccination were collected and analyzed descriptively.

Results: A total of 1547 people vaccinated with SIN vaccine, 529 (33.3%) responded to the first-dose and 239 (47%) to the second-dose questionnaires, whereas 936 people vaccinated with AZ vaccine, 483 (51.6%) answered the first-dose and 123 (25%) to the second-dose questionnaires. Some important AEFIs on the first- and second-day post receiving SIN vs. AZ vaccination were as follows: fever 4% vs 59%; pain at the injection site 27% vs 87%; redness and swelling at the injection site 4% vs 18%; nausea 5% vs 30%; diarrhea 1.8% vs 5.7%, respectively.

Conclusion: SIN seemed to have fewer AEFIs than AZ. Apart from different vaccine materials and excipients, the gap in AEFIs between SIN and AZ could be caused by the distinct population where AZ recipients were more exposed to COVID-19.

KEYWORDS:
AEFI, COVID-19, real-world evidence

INTRODUCTION

Numerous instances of pneumonia with an unknown eatiology were reported to the World Health Organisation (WHO) on December 31, 2019, in Wuhan City, Hubei Province, China. The SARS-CoV-2 new coronavirus was identified as the culprit. The distinctive illness-causing virus has been given the name COVID-19, which was declared pandemic in March 2020. Since then, the disease has expanded, having a significant negative influence on the health and welfare of people and populations around the world. The pandemic has caused major disruptions to the society and the economy across the globe. SARS-CoV-2 vaccines have been produced by numerous nations, organizations, and pharmaceutical firms.[1] The Food and Drug Administration (FDA), Centers for Disease Control and Prevention (CDC), and WHO were compelled to grant Emergency Use Authorization (EUA) of the vaccinations because to the urgent necessity for vaccination.[2] It is beneficial to get immunised against the COVID-19 pandemic to stop the disease's spread and transmission. The present emphasis across all nations, including Indonesia, is on planning large immunization campaigns for their populations. Indonesia originally selected Sinovac, a vaccination based on inactivated viruses rather than the mRNA vaccine, from among the several vaccines that were already in use and those that were being developed. The Sinovac vaccine is developed with inactivated virus.

Its phase III clinical trials have been conducted in Indonesia, Brazil and China, with good efficacy results.[3,4] Aside from the vaccine's effectiveness, adverse event following immunisation (AEFI) is also crucial as it often happens within 24 to 72 hours of receiving the shot. Sometimes, reactions persisted for as long as 14 days.[5]

The Sinovac vaccine contains 3 ug/0.5 mL (equivalent to 600 SU per dose) of inactive viruses with aluminium hydroxide adjuvant (Al2OH3), which can also give a crossroads effect.[6,7] Astra Zeneca vaccine, like Sputnik and Johnson & Johnson is based on genetically engineered viral vector (adenovirus).[8] An extremely concerning side effect that can occur during vaccine development is thrombo-embolism, which can occur with or without bleeding and have a variety of symptoms, including cerebral venous sinus thrombosis and pulmonary embolism.[9] Some European countries like Germany, Finland and Denmark have suspended the use of this vaccine. After listening to the WHO Strategic Advisory Group of Experts on

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Table I: Demographics and list of adverse events following immunization

Vaccinated subjects	Coronavac (SIN) NSIN = 1547		ChAdOx1 nCOV-19 (AZ) NAZ = 936		Total	
	First dose n = 530 f (%)	Second dose n = 239 f (%)	First dose n = 483 f (%)	Second dose n = 123 f (%)	First dose n = 1013 f (%)	Second dose n = 372 f (%)
Female*	322 (61)	131 (55)	224 (46)	64 (52)	546 (53.9)	195 (52.4)
Male*	208 (39)	108 (45)	259 (54)	59 (48)	467 (46.1)	167 (44.9)
Fever 1st day	22 (4.2)	6 (2.4)	285 (59.0)	20 (16.3)	307 (30.3)	26 (7.0)
Fever 2nd day	5 (0.9)	3 (1.2)	155 (32.1)	8 (6.5)	160 (15.8)	11 (3.0)
Took pain killer	6 (1.1)	0 (0)	293 (60.7)	20 (16.3)	299 (29.5)	20 (5.4)
Pain at injection site	147 (27.7)	79 (33)	420 (87.0)	70 (56.9)	567 (56.0)	149 (40.1)
Bump at injection site	22 (4.2)	8 (3.3)	86 (17.8)	14 (11.4)	108 (10.7)	22 (5.9)
Drowsiness	112 (21,1)	28 (11,7)	30 (6.2)	12 (9.8)	142 (14.0)	40 (10.8)
Headache	3 (0.6)	6 (2.5)	311 (64.4)	35 (28.5)	314 (31.0)	41 (11.0)
Nausea	30 (5.7)	18 (7.5)	143 (29.6)	8 (6.5)	173 (17.1)	26 (7.0)
Vomit	6 (1.1)	2 (0.8)	19 (3.9)	1 (0.8)	25 (2.5)	3 (0.8)
Bloating	35 (6.6)	16 (6.4)	100 (20.7)	10 (8.1)	135 (13.3)	26 (7.0)
Diarrhea	10 (1.9)	5 (2.0)	27 (5.6)	9 (7.3)	37 (3.7)	14 (3.8)

Immunisation (SAGE) opinion, WHO finally approved the use of Astra Zeneca vaccine.[10]

In accordance with the national vaccination program; Sinovac, Astra Zeneca and Moderna vaccines have been used and given to the people through many public and private-sectors. The aim of the study was to assess and compare AEFIs between Sinovac and Astra Zeneca vaccines, as real-world evidence.[11,12]

MATERIALS AND METHODS

Universitas Kristen Indonesia organised a mass vaccination program. The vaccine was supplied by the Community Health Center of Kramat Jati, Jakarta. Vaccination was carried out in March to April 2021.

Two sets of questionnaires were developed to assess the AEFIs, each of which was developed for the first and second dose of vaccination.

AEFI data included symptoms on the first- and second-day post vaccination (fever, pain and swelling at the injection site, headache, vomiting, bloating, and/or diarrhea); as well as actions taken by the respondents if they experienced adverse events (i.e., pain-killers, consultation to health care workers, etc.).

Indonesian FDA approved the vaccination with SIN and AZ, which was carried out in accordance with the protocols outlined in the product description. Two separate 0.5 ml doses of Sinovac were administered; the second dose were given four weeks after the first dose.[13] The AZ vaccination consists of two separate doses of 0.5 mL each; where the second dose were administered between 4 and 12 weeks (28 to 84 days) after the first dose.[14]

The survey was ethically approved by the Ethical Committee: No. 15/Etik Penelitian/FKUKI/2021. An online questionnaire using Microsoft Form was distributed to all vaccine recipients recorded by the committee via WhatsApp (WA). The questionnaire consists of 14 questions for Sinovac respondents and 17 questions for Astra Zeneca respondents consisting of (1) demographics information (gender, age), (2) adverse effects, which were divided into nervous system and brain, skin, digestive system, and other adverse effects and (3) Actions taken by respondents if they experienced adverse effects. In the questionnaire for AZ respondents, we added questions on whether they were diagnosed or have had thrombose and had or were receiving blood thinning therapy.

The first questionnaire was sent to all first dose vaccine recipients and those who responded were sent the second questionnaire following the second dose. To increase response rate, each questionnaire was sent three times with one-week interval. Data were extracted from the MS forms. Distributions of the demographics, AEFIs and actions taken by the respondents were analysed descriptively. Analysis was done using SPSS version 25 (IBM, Armonk, NY, USA).

RESULTS

There was a total of 1574 subjects who were vaccinated with SIN and 936 subjects with AZ vaccines. In the SIN group 529 subjects responded (response rate 33%), whereas in the AZ group there were 483 respondents (response rate 51.6%). The response rate for the second questionnaire was lower in the AZ group. The low response rate could have occurred due to the delivery of the questionnaire through the WhatsApp application, in which people could receive hundreds of notifications per day. This could have made respondents did not pay attention to notifications of the questionnaire sent to them, despite our effort to send each questionnaire three times with one-week interval. This study was not a clinical trial with strict protocols that should be followed by subjects to increase adherence to the treatment. In this study, subjects were voluntarily asked to fill-out the questionnaire sent to them. Although web-based survey has many advantages such as: wider spread of distribution, lower cost, and efficient, comparison studies between web-based versus paper-based survey showed that response rate of wed-based or internet-based survey were lower up to 10-20% than paper-based.[15]

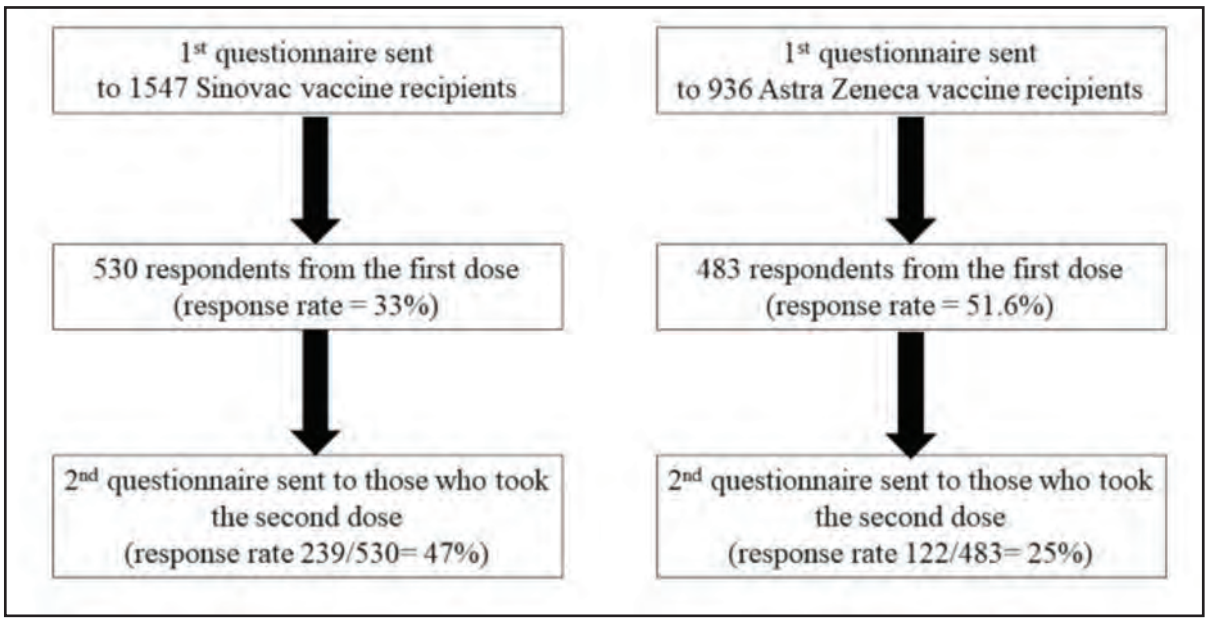

Fig. 1: Respondents' recruitment and number of subjects who responded to questionnaire.

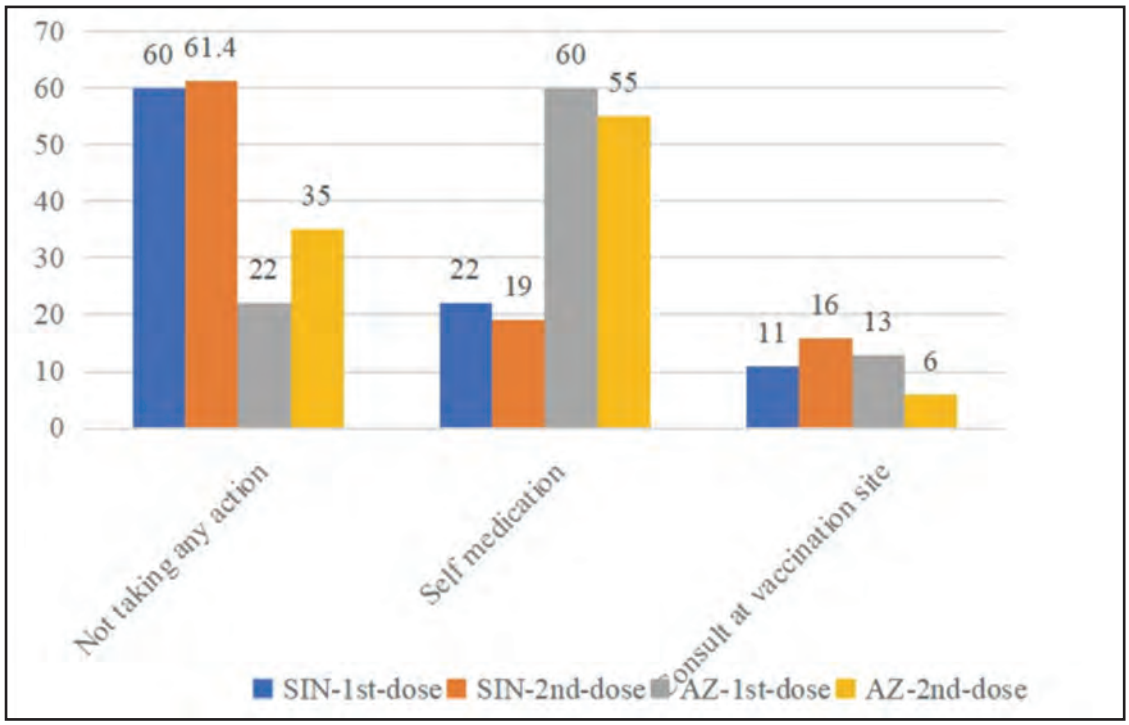

Fig. 1: Percentages of actions taken to the adverse effects experienced by the COVID-19 vaccine recipients (numbers represent percentages of respondents within each group of vaccine). SIN: Sinovac; AZ: Astra Zeneca.

The AEFI is shown in Table I, the most prominent adverse event in both vaccine groups was pain at the injection site, whereas the percentage was higher in the AZ than the SIN group (58.6% vs 20.5%, respectively). Fever both on the first day and the next day is also more prominent in the Astra Zeneca group. Overall, the percentages of AEFIs appeared to decrease after the second-dose compared to the first-dose of the vaccine. In contrast, drowsiness was more prominent in the SIN group than AZ. While the headaches were more in the AZ group. According to the Centers for Disease Control and Prevention (CDC), pain at the injection site was the most commonly reported local reaction among Pfizer-BioNTech COVID-19 vaccine users aged 18 to 55 years, and the percentage decreased after the second injection.[16,17]

Out of 483 AZ first dose vaccine recipients, 28 acknowledged that prior to vaccination they were diagnosed with symptoms of thrombo-embolism and 12 of them taking blood thinning

drugs such as Aspilet® or Ascardia®, which contains acetylsalicylic acid (n = 3); clopidogrel (n = 4), Plavix® (a brand name of clopidogrel, n = 1), or other blood-thinning medications (n = 4). No vaccine-induced immune thrombotic thrombocytopenia (VITT), or anaphylaxis reaction reported by recipients in both vaccine groups. Although it is possible that thromboembolism may occur. However, with the national integrated AEFI reporting system, if a vaccine recipient subject reports a severe AEFI, the local vaccine injection centre will be informed.

Figure 2 demonstrated actions taken by the vaccine recipients in the presence of adverse effect. Only a few respondents (≤3%, not shown in the figure) who consulted their concern to the nearest public health center, doctor, or hospital. None reported a severe adverse effect that required further treatment in the hospital. In the implementation of this mass immunization, the government established a tiered reporting system. If there are complaints that are directly felt by the subject after vaccination, can be directly handled by the doctors who serve at the vaccination sites. Interestingly, 60% respondents in AZ group (first dose) and 55% (second dose), whereas, in SIN group only 22% (first dose) and 19% (second dose) who took self-medication. It is certainly shown that more respondents in the SIN group did not take action for the side effects. This suggests that most of the adverse events in the SIN group were milder than AZ group (Table I). This also in accordance with a meta-analysis study by Chen at al., the AEFI report due to inactivated vaccines was lower than other types of vaccines.[18]

DISCUSSION

In general, the results of our analysis of the data from the AZ group were generally consistent with those of Jeon et al, who observed that the two AEFIs that were most frequently reported were tenderness at the injection site (94.5%) and fatigue (92.9%). Both the severity and number of AEFI were lower in the older age group. Sultana no significant incidents necessitated further medical treatment, and the majority of AEFIs subsided within a few days.[19] Recent report on safety of AZ (EudraVigilance) has added information that 28 people consisting of 19 women and nine men were diagnosed with AEFI associated with thrombosis problem, such as deep vein thrombosis (DVT), pelvic vein thrombosis, pulmonary embolism, etc. Three people died and six did not recover.[20] In our study, none reported VITT nor anaphylaxis reaction. As is stated elsewhere, the aetiology of AEFI due to inactivated virus could be from its vaccine material or its excipients. While the problem of thrombosis that appeared in the group of subjects who were vaccinated with Astra Zeneca triggered the expression of antiplatelet antibodies.[21] In contrast to our study, Hyun et al discovered that patients who got the ChAdOx1 nCOV-19 (AstraZeneca) vaccination experienced substantial adverse effects after just one dosage, including polyarthralgia and myalgia syndrome that lasted up to 47 days.22 Other non comparison study by Jain et al (2022) showed AEFI with ChAdOx1 nCOV-19 vaccine was generally mild and moderate, although one case of severe allergic reaction was obtained (mild – 31 [83.7%]; moderate – 5 [13.5%] and severe – 1 [2.7%]), respectively.[23] Although our study showed higher AEFI in AZ group than SIN, which may be due to differences in vaccine ingredients and excipients, no severe AEFI was found as other studies reported. In our center, AZ vaccine was administered to anyone, not limited to healthcare workers (HCWs). Profession with higher exposure to COVID-19 such as HCWs might pose higher risk of AEFIs.[24] However, unfortunately data on occupation (health care workers vs non health care worker) was not available.

CONCLUSION

This study focuses on the adverse events following immunisation (AEFI) of the Sinovac and Astra Zeneca COVID-19 vaccines and presents real-world evidence. Sinovac appeared to have fewer AEFI than ChAdOx1 nCOV-19 (Astra Zeneca), according to this investigation. No major adverse event, such vaccine-induced immune thrombotic thrombocytopenia or anaphylactic reaction, occurredA total of 60% respondents from the SIN group did not take any action concerning the adverse effect they experienced. On the contrary, 60% AZ vaccine recipients at least took pain-killer to reduce the pain at the injection site and their fever. To overcome AEFI, especially fever, respondents preferred self-medication. The limitation of this study is that the response given by respondents was not confirmed by medical examination. The response rate is small, especially the response obtained from the second dose of vaccination.

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ORIGINAL ARTICLE

Understanding Halal pharmaceuticals: Views from outpatients in a Malaysian state hospital

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ABSTRACT

Introduction: Halal pharmaceuticals are paramount in healthcare settings catering to Muslim patients. The COVID-19 pandemic ignited discussions on the Halal status of pharmaceuticals, especially vaccines. This study aims to explore the understanding and views of hospital outpatients regarding Halal pharmaceuticals.

Materials and Methods: A qualitative study by in-depth interviews was undertaken among adult Muslim outpatients. Utilising a semi-structured interview guide in Malay, content reliability of the guide was ensured through expert reviews. Potential participants were approached in the outpatient pharmacy waiting area. All interviews were audio recorded and transcribed verbatim. These Malay transcripts were translated into English and subjected to thematic content analysis.

Results: Data saturation was achieved through interviewing ten outpatients. The findings indicated that patients were vigilant in checking labels to confirm the correctness of their medications. Yet, the terms 'Halal pharmaceuticals' and 'Shariah-compliant hospital' were unfamiliar to all and did not evoke curiosity. The respondents expressed trust in the government's commitment to dispense safe and Halal-certified drugs. The majority of the participants did not consider Halal status as a primary factor when selecting medications. Nevertheless given a choice, many voiced a preference for Halal-certified drugs, irrespective of their cost or efficacy. For life-threatening situations, participants were willing to accept non-Halal treatments.

Conclusion: Despite non-familiarity, the general sentiment towards Halal pharmaceuticals remain positive. This study underscores the need for enhanced education and awareness regarding Halal pharmaceuticals for better align healthcare practices with the cultural and religious values of Muslim patients.

KEYWORDS:
Islam, exploratory behaviour, trust, pharmaceutical preparations, Halal

INTRODUCTION

Halal goes beyond conventional industry-sector, geographical, cultural and even religious boundaries. 'Halal' means allowed or legal as per Islamic laws.[1] As per definition, Halal foods are defined as those that are free from any prohibited element. Recently, 'Halal' and 'Haram' terms have been extensively used to help consumers make educated choices.[2] Halal pharmaceuticals have expanded globally. According to research conducted by the World Halal Secretariat, it was estimated that the global Halal market in 2010 was USD 2.3 trillion, of which 22% represents the pharmaceutical industry.[3,4] This is especially true for Malaysia as a Muslim-majority country and a leading global Halal Hub.

Halal pharmaceuticals are defined in the standard MS2424:2019 as "pharmaceutical products that contain ingredients permitted under the Shariah law and fulfill the condition."[5] Halal comprises both safety and trustworthy elements, especially in Shariah-compliant hospitals.

Patients have rights, especially the right to be informed as not everyone has the same knowledge and awareness of Halal pharmaceuticals. Nevertheless, some patients refuse to follow treatments due to hesitations or unclear information on their medications' origin, leading to possible treatment failure.[6] Despite being fundamental issue, not everyone has the same knowledge and awareness of Halal pharmaceuticals. The Halal status of pharmaceuticals also raised many doubts, especially recently with the introduction of COVID-19 vaccines. For example, a general practitioner spread false news that the CoronaVac COVID-19 vaccine (Sinovac Biotech Ltd., Beijing, China) contains pig's blood in the state of Perlis, Malaysia.[7]

To the best of our knowledge, no published qualitative study in Malaysia regarding Halal pharmaceuticals exists. In Malaysia, there was only one quantitative research study conducted in Penang regarding knowledge, attitude and perception on Halal pharmaceuticals among the general public: better knowledge of Halal pharmaceuticals is associated with positive perceptions and behaviour.[8] This gap in the literature highlights the need to understand patient perspectives to improve healthcare delivery and align it with cultural and religious values. Our study aims to explore the understanding of Halal pharmaceuticals among outpatients of Hospital Tuanku Fauziah (HTF), the state hospital of Perlis, Malaysia.

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MATERIALS AND METHODS

A qualitative study was conducted through face-to-face, in-depth interviews from August 2021 to April 2022 among adult Muslim patients who collected their medications in the outpatient pharmacy. Patients on routine management of chronic diseases were targeted for inclusion as they were constant medicine users. Semi-structured interviews were chosen to encourage patients to give their understanding and enable them to voice out opinions more comprehensively. Those unable to communicate in Malay or English were excluded.

A semi-structured interview guide was prepared and underwent content trustworthiness with the State Mufti, a Malaysian pharmacy professor, two pharmacists with a special interest in Halal pharmaceuticals and Islamic Affairs Officers from the Ministry of Health Malaysia (MOHM) and the hospital. Subsequent iterations were made based on their feedback, improving clarity and relevance. A pilot interview was conducted to test the guide, leading to minor adjustments for better comprehensibility.

Potential candidates were recruited by purposive sampling, focusing on information-rich cases concerning the phenomenon of interest. Patients of various sociodemographics, medical conditions and the number and types of medicines were considered. Potential subjects were screened based on the prescriptions collected and were approached in the waiting area to collect their medications. Those interested were invited to a pharmacy counselling room and were briefed on the study.

The interview began after obtaining the participants' informed consent. The interviews were conducted by a trained co-investigator with a background in pharmacy and training in Halal pharmaceuticals. To ensure impartiality, the co-investigator received specific training on conducting qualitative interviews and maintaining objectivity. The sessions were audio-recorded using digital recorders and transcribed verbatim. Field notes were taken during the sessions to capture contextual information. The transcripts were prepared by the same interviewer. Counterchecking of the transcripts was done by an independent co-investigator to ensure accuracy and consistency. The transcripts further underwent member-checking by emailing participants to check for accuracy and resonance with their experiences.

All transcripts were back-translated into English. The transcripts were analysed by thematic content analysis independently by all four investigators. The analysis was conducted iteratively after each interview to identify emerging themes and determine data saturation. Six phases method was used, including Phase 1: Researchers familiarised with all the data collected, Phase 2: Generating initial codes, Phase 3: Searching for themes, Phase 4: Reviewing themes, Phase 5: Defining and naming themes and Phase 6: Producing the report.9 All the discrepancies were resolved by consensus.

Data saturation guided the determination of the sample size.[9,10] Data saturation is a point in qualitative research where additional interviews no longer provide new insights or themes. This concept ensures that the sample size is sufficient to capture the necessary depth and breadth of information for the study. Ethical approval was obtained from the Medical Research & Ethics Committee, MOHM (NMRR-21-1548-6089) before the conduct of the study. The study was conducted and reported according to the consolidated criteria for reporting qualitative studies (COREQ) guideline.[10]

RESULTS

Data saturation was achieved at the 10th interview. The interview lasted 30 to 60 minutes for each session. Most were elderly, male, having secondary education, retiree or self-employed and under medical clinic follow-up for about 10 years (Table I). Four themes emerged inductively: (1) Experience with medicines, (2) Concept of Halal pharmaceuticals and Shariah-compliant hospitals, (3) Confidence in Halal medicines and (4) Acceptance of Halal medicines and vaccines. Despite the high importance of Halal pharmaceuticals in Shariah-compliant hospitals, there is a notable gap in awareness among patients. The study participants were generally not familiar with the concepts of Halal pharmaceuticals or Shariah-compliant hospitals, which did not pique their curiosity.

Experience with Medicines

All participants mainly focused on receiving the correct medication. They read the name of the medication except for some who observed the packaging and confirmed with the internet or pharmacists.

"First, I look at the name of the medicines and expiry date. I looked in the envelope, for anything in there. Sometimes, the brand name is different. So, I rechecked on the internet." (P1)

"I do ask the pharmacist about it, like why the medications were changed." (P9)

"Like metformin, recently they changed the brand. I do ask about it, the pharmacist explained that they are the same medication." (P10)

Some were particular about the expiry date due to bad experiences.

"When buying from the pharmacy, there are some incidents that they mistakenly sell expired medicines." (P5)

Respondents had the confidence to self-purchase after doctors' recommendations besides prescribed medicines.

"The two medications that I bought from a pharmacy were suggested by the doctor." (P6)

Concept of Halal Pharmaceuticals and Shariah-Compliant Hospitals

Most had not heard of 'Halal pharmaceutical' and 'Shariah-compliant hospitals'. P4 and P6 were not sure what was meant by 'Halal pharmaceuticals'. P7 and P9 had heard the term 'Shariah-compliant hospital' but never dug deeper.

Table I: Sociodemographics and conditions of patients

Patient	Age	Gender	Education level	Occupation level	Clinic: No. of medicine prescribed	Year of treatment
P1	72	M	Tertiary	Teaching assistant	Medical:11	20
P2	38	M	Secondary	Administrative assistant	Medical: 7	4
P3	51	M	Secondary	Self-employed	Medical:7	6
P4	66	F	Primary	Housewife	Medical:9; Ortho.:7; Skin:6	11
P5	55	M	Secondary	Police officer	Medical:7	3
P6	60	F	Tertiary	Ex-teacher	Medical:8; Psy:1	19
P7	76	M	Primary	Self-employed	Medical:7	5
P8	65	M	Secondary	Retired clerk	Medical:8; Surgical:1; Ortho:4; ENT:3; Skin:6	6
P9	52	F	Tertiary	Teacher	ENT:3	3
P10	52	F	Tertiary	Nurse	Medical:9; Skin:6; ENT:1	25

Ortho: Orthopedics, Psy: Psychiatry, ENT: Ear, Nose, and Throat.

"I think it has the same concept as Halal food, but applied to medicines. For example, making medicines from Halal sources, including the process of making it and the responsible party to approve it as Halal." (P9)

"I have heard of 'Shariah-compliant hospitals', but never investigated it." (P9)

"I never know about these terms." (P10)

Those who have heard it based their understanding on the word Halal itself.

"From the process of making to finish, it needs to follow Islamic procedures, Halal." (P1)

"I think it has the same concept as Halal food, but applied to the medicines." (P9)

"Similar to Halal food. Since both of them go inside our body." (P10)

Confidence in Halal Medicines

Most respondents were confident about the Halal status of their medicines as long as the government provided them.

"For that, we assume it's under government because they are the ones that supply it…." (P1)

"If MOHM wants to bring the drugs into use, they must have referred to any religious department. For example, like the COVID-19 vaccines that were bought from overseas." (P3)

Some never think about it and assume all medicines were Halal as long as the government provided them.

"If the medicines from public hospitals, I thought of them as Halal. I was prescribed insulin, I heard from my friends that it is not Halal. There is no way the government would give non-Halal medicine." (P6)

"Never thought about it. I believe in the public hospital. Because before procuring the medications, the pharmacists and doctors will go through the details." (P8)

Acceptance of Halal Medicines and Vaccines

Only one respondent (P3) did not accept any non-Halal treatment, while others agreed with life-saving conditions.

"If it were not for life-saving and other options are available, I would reconsider." (P2)

"I agree (to take non-Halal medicines) if it falls under an emergency state." (P5)

Patients chose Halal medicines over affordability and effectiveness, provided it is non-emergency.

"Would choose haram but more effective, if an emergency." (P2)

"I agree since it falls under an emergency state." (P5)

"It will depend on our condition. If we are in critical condition, I will choose the more effective one. If we can still tolerate the disease, I will choose the Halal one." (P10)

All patients had taken the second and third doses of the COVID-19 vaccine regardless of Halal status. A patient will not take it if the vaccine is not Halal. Only a fraction would like to receive the fourth dose of the COVID-19 vaccine.

"I never thought about the Halal status of the vaccine. If it is mandatory in my workplace, then I have no choice." (P2)

"I went for vaccination immediately when allowed to the public. Halal status of the vaccine did not influence our family's decision to get COVID-19 vaccine."(P8)

DISCUSSION

In our study, the patients were more alert on the medication labelling of the expiry date. Hence, this is the first thing they would look at when receiving medicines. As supported by a study, patients expressed concerns about taking medications if they had bad experiences in the past.[11]

There is a notable gap in awareness of Halal pharmaceuticals and Shariah-compliant hospitals among patients. The study participants were generally not familiar

with the concept of Halal pharmaceuticals or Shariah-compliant hospitals, which did not pique their curiosity. Our findings are similar to a qualitative study in Nigeria in which only half of patients and doctors were conversant with the Halal pharmaceuticals concept.[12] In contrast, a quantitative study in Penang, Malaysia found that about 91.2% of general public were aware of the term 'Halal medicine'.[8]

All patients trust the authority or government to choose the safest and Halal medicine. Patients said it was the doctors' responsibility to provide information to them.[13] Government initiatives are essential to increase access to Halal products, including pharmaceuticals, leading to public trust.[14] There is a strong trust among the outpatients in the Malaysian government's ability to regulate and provide safe and Halal-certified pharmaceuticals. This trust seems to override the need for personal vigilance concerning the Halal status of their medications.[15]

Vaccines produced from porcine origin are not permissible in Malaysia unless there is an urgent need to use these kinds of vaccines.[12] Halal medicine knowledge has a positive and significant effect on Halal medicine purchase repetition.[16] Patients preferred being informed regarding the Halal status of the treatment.[14] Hence, healthcare professionals must acknowledge that patients make independent assessments regarding medication adherence.[17]

In life-threatening situations, the acceptance of non-Halal treatments highlights the pragmatic approach taken by patients. This finding is in line with Islamic teachings, which allow for the consumption of non-Halal substances if one's life is in danger.[18]

The findings of this study highlight the complex interplay between religious beliefs, trust in government and healthcare decisions. The general unfamiliarity with 'Halal pharmaceuticals' and 'Shariah-compliant hospitals' among participants suggests a significant knowledge gap. Despite this, there was a high level of trust in the government-provided medications, with patients generally assuming their Halal status. This trust underscores the importance of government and healthcare providers in shaping patients' perceptions and acceptance of pharmaceutical products.

The lack of knowledge may negatively impact medication adherence if patients harbour doubts or misconceptions about their medications' Halal status. As the results showed, most patients currently have confidence in medications provided by government hospitals. However, misleading information or rumours could easily shake this trust. Proactive education is essential to preemptively combat misinformation.

The market potential for Halal pharmaceuticals remains untapped locally. Participants expressed willingness to prefer Halal pharmaceuticals if given a choice. However, they currently lack the background knowledge to make informed decisions. Both public and private sectors can leverage this interest by improving consumer education on Halal pharmaceutical concepts, choices and benefits.

This study has some limitations. Firstly, the focus on a single-state hospital limits the generalisability of the findings to the broader Malaysian Muslim population. Furthermore, as the study relied on self-reported data from interviews, there might be biases in the responses, such as social desirability bias. Also, the study did not include non-Muslim patients, who may have different perspectives on Halal pharmaceuticals.

Further research with larger and more diverse samples is recommended. Mixed-methods approach could be employed to collect quantitative and qualitative data to provide a more comprehensive understanding of the issue. Additionally, exploring healthcare professionals' perspectives and subsequently their roles in educating patients about Halal pharmaceuticals is crucial as well. Finally, examining the impact of education and awareness programs on the understanding and acceptance of Halal pharmaceuticals would be beneficial.

CONCLUSION

There was a gap in the understanding of Halal pharmaceuticals among hospital outpatients, although Halal status was not a priority. Most of them relied entirely on doctors or pharmacists to decide on the medicines. If options were available, most of them would choose Halal medication regardless of its price and effectiveness. Most accept any treatment regardless of Halal status under life-saving conditions. As the global Halal pharmaceutical industry expands rapidly, Muslim-majority Malaysia is well-positioned to take a leading role. However, realising this potential will require proactive efforts to educate consumers and leverage market interest.

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Real-world efficacy and safety of intravenous ferric carboxymaltose for the management of iron deficiency anaemia in Malaysia: A single centre cohort study

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ABSTRACT

Introduction: Up to 24.2% Malaysians are estimated to be affected by anaemia. Iron deficiency is the most common nutritional deficiency leading to anaemia. Oral iron therapy may not be well tolerated or efficient. Ferric carboxymaltose (FCM), a non-dextran intravenous iron formulation, may be an appealing alternative for iron replacement therapy. This retrospective study aimed to investigate the efficacy and safety of intravenous FCM infusion for the management of iron deficiency anaemia in a single centre in Malaysia.

Materials and Methods: All patients who received at least one dose of 500 mg intravenous FCM infusion from January to December 2023 in Bukit Tinggi Medical Centre (BTMC) were identified from the electronic medical record database. Inclusion criteria were patients: (1) ≥ 14 years old and (2) with iron deficiency anaemia. The primary outcome was the mean change in haemoglobin level before treatment and 30 day after treatment. Secondary outcomes included reasons for intravenous FCM infusion, median dose, adverse drug reactions, mean change in haemoglobin levels for different subgroups and percentage of patients with normalised haemoglobin after treatment. The efficacy outcome was analysed using per-protocol analysis while the safety outcome used intention-to-treat analysis. Paired t-test was used to compare the mean difference between the haemoglobin measurements before and 30-day after treatment.

Results: A total of 144 administrations were given to 141 patients requiring intravenous iron replacement therapy during the 1-year study period in BTMC. Intravenous FCM infusion was administered for the management of iron deficiency related to: (1) increased blood loss, including menorrhagia, haemorrhoids and GI-related surgery, (2) low iron intake, including poor nutrition and gastrointestinal-related malabsorption and (3) haematological disorders, including autoimmune haemolytic anaemia, myelodysplastic syndrome, diffuse large B-cell lymphoma and idiopathic thrombocytopaenia purpura. The median dose of intravenous FCM infusion was 1000 mg. At 30 day post-infusion, the mean haemoglobin level increased significantly from 8.9 g/L to 11.6 g/L ($p < 0.05$), an increase of 2.68 g/L (95% CI: 2.45 – 2.90 g/L). No adverse drug reactions were reported. Subgroup analysis showed that patients with haematological disorders had significantly higher improvement in haemoglobin levels after intravenous iron infusion compared to those without. At 7-day, 14-day, 21-day post-infusion, 33% (33/99), 34% (34/99) and 36% (36/99) patients had a normalised haemoglobin level, respectively. The proportion of patients with a normalised haemoglobin level increased to 36% (36/99) and 42% (42/99) at 30-day and 90-day post-infusion.

Conclusion: Within the limit of this single-centre retrospective study, intravenous FCM infusion was well tolerated and effective in increasing the haemoglobin level among patients with iron deficiency anaemia.

KEYWORDS:
Iron deficiency, anaemia, efficacy, safety, ferric carboxymaltose

INTRODUCTION

In 2021, the global prevalence of anaemia across all ages was 24.3%.[1] The Malaysian population suffers a similar trend with a prevalence of 24.2%, approximating 5 million people.[2] Iron deficiency (ID) is the most common nutritional deficiency leading to anaemia, contributing to nearly 50% of all cases of anaemia.[3] ID often occurs when iron requirements are especially high (i.e. during infancy and pregnancy), when dietary iron intake is too low to meet the body's requirements (e.g. due to poor diet or malnutrition), when there is impaired iron absorption (e.g. due to a high intake of phytates or phenolic compounds, gastrointestinal disturbances such as inflammatory bowel syndrome, or chronic inflammatory conditions such as chronic kidney disease, heart failure and cancers), or when iron losses exceed iron intake over a prolonged period (e.g. from blood loss from childbirth or menstruation).[4]

Iron is a key nutrient for haemoglobin and red blood cells production. In normal situations, the body will mobilise the iron stores in the liver, spleen and bone marrow to increase haemoglobin level and thus red blood cell production. However, in the late stages of iron deficiency, when the body's iron store has been depleted, the haemoglobin level decreases below normal level, and iron deficiency anaemia (IDA) develops.[5] While iron is an essential trace mineral that plays a role in many other cellular processes including optimal mitochondrial function for respiration and energy production, iron deficiency can occur without anaemia and is

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associated with a multitude of non-specific symptoms such as fatigue and reduced exercise tolerance.[3]

IDA, which is frequent in pregnancy, can adversely affect both the mother (increased risk of preterm delivery, Caesarean delivery and transfusion) and the neonate (increased risk of intensive care admission, delayed growth and development and an increase in behavioural problems that persist up to 10 years after iron repletion).[3] IDA is also prevalent among patients with gastrointestinal pathologies such as inflammatory bowel disease, gastric bypass, coeliac disease, Helicobacter pylori infection and atrophic gastritis,[3] leading to an array of clinical symptoms such as fatigue, sleeping disorders, attention deficit and agitation, that affected patients' health-related quality of life.[6] While perioperative IDA are associated with increased risk of blood transfusion, in-hospital complications, in-hospital mortality, delayed hospital discharge and poor recovery,[7] ID with and without anaemia in patients with chronic heart failure was independently associated with higher risk of all-cause and cardiovascular mortality.[8] Recent studies also suggested the association of IDA with the development of gastrointestinal (GI) cancers[9] and right-sided colorectal cancer.[10]

Due to the adverse clinical outcomes associated with IDA, the prevention and treatment of IDA become a major public health goal, especially in women, children and individuals in low-income countries.[3] Oral iron remains the first-line therapy for ID and IDA. However, the use of oral iron therapy is limited by: (1) its high incidence of gastrointestinal adverse events such as nausea, vomiting and constipation which can reduce patients' tolerance and compliance to treatment, (2) low iron absorption and bioavailability due to drug interactions and increased hepcidin release associated with chronic inflammatory conditions and (3) slow onset of action. Intravenous iron formulations may potentially solve these issues in the settings of intolerance, or refractoriness to oral iron, inflammatory conditions, need for a rapid recovery of haemoglobin such as active bleeding and severe iron-deficiency anaemia.[3]

Ferric carboxymaltose (FCM), which was approved in Malaysia in late 2021, is a single-dose non-dextran intravenous iron preparation that enables replenishment of iron at a dose of 1000 mg (20 mg iron/kg of body weight) within 15 minutes of infusion.[11,12] This allows total iron replacement in one or two infusions and encourages routine use in a busy outpatient clinic with minimal or no additional resource requirements due to its convenience to both healthcare providers and patients.[3] Moreover, since FCM is a dextran-free iron-carbohydrate complex and it does not react with dextran antibodies, iron replacement with intravenous FCM has been demonstrated to be safe and well tolerated in various disease populations, including gastrointestinal disorders, chronic kidney disease, chronic heart failure, gynaecological and obstetrics disorders.[12,13] Intravenous FCM was also shown to be effective in correcting IDA as well as improving symptom control and quality of life of different populations.[6,12-14]

Given that socioeconomic, cultural and medical conditions in low-resource settings might influence the effectiveness and safety of iron substitution modality compared with high-income countries,[13] this study aimed to evaluate the real-world efficacy and tolerability of intravenous FCM in the management of IDA among patients attending an outpatient hospital clinic setting in Malaysia, an upper middle-income multi-ethnics and multi-cultural country.

MATERIALS AND METHODS

Study Population

All patients who received at least one dose of complete 500 mg intravenous FCM infusion from January to December 2023 at Bukit Tinggi Medical Centre (BTMC) were identified from the electronic medical record database. Following the approved indication for intravenous FCM in Malaysia,[15] inclusion criteria were: patients age ≥14 years old, and diagnosed with IDA. IDA is defined by baseline haemoglobin level pre-infusion < 13 g/dL (men) and < 12 g/dL (women) and serum ferritin < 50 ng/mL (patients without chronic inflammatory conditions) or serum ferritin < 600 ng/mL with transferrin saturation < 20% (patients with chronic inflammatory conditions).[16] Exclusion criteria were: patients who did not complete the intravenous FCM infusion, those without any follow-up haemoglobin level measured post-treatment and those received blood transfusion between infusion and measurement of haemoglobin level.

Study Outcome

The primary outcome was the mean change in haemoglobin level before treatment and 30-days after treatment. Secondary outcomes included adverse drug reactions related to intravenous FCM infusion, reasons for intravenous FCM infusion, median dose of intravenous FCM infusion, mean change in haemoglobin levels for different subgroups and percentage of patients with normalised haemoglobin at 7, 14, 21, 30 days and 90 days after treatment (i.e. haemoglobin level ≥ 12g/dL for women and haemoglobin level ≥ 13 g/dL for men). Demographics and outcomes were collected through a retrospective medical record review. This study was conducted according to the principles outlined in Malaysian Good Clinical Practice, International Council for Harmonisation Good Clinical Practice, Declaration of Helsinki, and any other pertinent local and institutional guidelines. The study was approved by the ethics committee of the Ramsay Sime Darby and National Medical Research Register (RSCH ID-23-03299-8LU, NMRR ID-23-02908-MY5). Ethical permission for collection of anonymous data was granted prior to transcription from patient medical records to a case report form.

Sample Size

The minimum sample size required was 34 patients, calculated using R studio 2024.04.0 + 735 (2024.04.0 + 735) with type 1 error probability set at 0.05, power at 0.80% and effect size at 0.5 g/dL.

Statistical Analysis

While the safety analysis included all patients who all have received at least one dose of intravenous FCM (i.e. intention-to-treat analysis), efficacy analysis included patients who fulfilled the eligibility criteria pre-specified in the protocol (i.e. per-protocol analysis), which were patients aged 14 years and

Table I: Baseline demographics of study participants

Demographics	Safety analysis (n = 141)	Efficacy analysis (n = 99)
Mean age (SD)	40.6 (16.6)	42.2 (16.2)
Gender, n (%)		
Male	14 (9.9)	11 (11.1)
Female	127 (90.1)	88 (88.9)
Ethnicity, n (%)		
Malay	18 (19.9)	19 (19.2)
Chinese	49 (34.8)	36 (36.4)
Indian	64 (45.4)	44 (44.4)
Aetiology		
Increased blood loss		
Menorrhagia	115 (81.6)	85 (85.9)
Haemorrhoids	4 (2.8)	1 (1.0)
GI-related surgery	3 (2.1)	2 (2.0)
Reduced iron intake		
Malnutrition	12 (8.5)	8 (8.1)
Malabsorption	2 (1.4)	1 (1.0)
Haematological disorder		
Autoimmune haemolytic anaemia	12 (8.5)	10 (10.1)
Myelodysplastic syndrome	4 (2.8)	2 (2.0)
DLBCL	1 (0.8)	1 (1.0)
Idiopathic thrombocytopenic purpura	1 (0.8)	1 (1.0)
Comorbidities, n (%)		
Hypertension	10 (7.1)	9 (9.1)
Type 2 Diabetes	3 (2.1)	3 (3.0)
Ischaemic heart disease	3 (2.1)	3 (3.0)
Hypothyroid- related disorder	2 (1.4)	0 (0)
Hyperthyroid-related disorder	1 (0.7)	0 (0)
Liver diseases	2 (1.4)	2 (2.0)
GI-related diseases	5 (3.5)	2 (2.0)
Chronic kidney disease	1 (0.7)	1 (1.0)
Sepsis	4 (2.8)	2 (2.0)
Chronic inflammatory states	16 (11.4)	9 (9.1)
Baseline laboratory level before IV FCM infusion†		
Mean Hb level (g/dL)	8.9 (1.9)	8.9 (1.7)
Mean MCV (fL)	74.9 (11.2)	74.6 (11.2)
Mean MCH (pg)	22.5 (5.0)	22.4 (5.0)
Mean reticulocyte count (cells x 10^9/L)	61.6 (25.8)	59.9 (20.5)
Median serum iron level (µmol/L)	3.7 (2.7, 7.4)	3.6 (2.7, 6.6)
Median serum ferritin level (µg/L)	15.0 (6.0, 74.0)	13.0 (5.0, 65.0)
Median TSAT (%)	6.0 (3.0, 16.0)	5.0 (3.0, 10.5)
Mean serum phosphate level (mmol/L)	1.2 (0.3)	1.2 (0.3)
Median Vitamin D level (nmol/L)	38.0 (28.8, 46.0)	36.5 (26.0, 46.0)
Median Vitamin B12 level (pmol/L)	363.0 (274.0, 476.0)	361.5 (272.5, 467.2)
Median serum folic acid level (nmol/L)	15.9 (10.5, 22.4)	16.4 (10.1, 22.3)
Erythropoietin use	131 (92.9)	92 (92.9)
Blood transfusion	19 (13.5)	0 (0)
1 pack	2 (1.4)	
2 packs	15 (10.6)	

Data presented in number (%) unless otherwise stated. †Normally distributed data were presented in mean (SD) while skewed data were presented in median (IQR). Liver diseases included hepatitis B and cirrhosis. GI-related diseases included cholescystitis, Crohn's disease, inflammatory bowel disease, ulcerative colitis. Chronic inflammatory conditions included chronic kidney disease, chronic liver diseases, chronic GI disorder, MDS, DLBCL, sepsis.

SD: Standard deviations; IQR: Interquartile range (i.e. first quartile and third quartile). DLBCL: Diffuse large B-cell lymphoma; GI: Gastro-intestinal. TSAT: Transferrin saturation.

above, with IDA and at least one follow-up haemoglobin level after intravenous FCM infusion without blood transfusion between intravenous FCM infusion and the measurement of haemoglobin level.

Descriptive statistics were used to summarise the baseline characteristics of study population. Normally distributed data were summarised in mean ± standard deviation while skewed data were summarised in median (first quartile, third quartile). Linear mixed model was used to evaluate the changes in haemoglobin level over time, adjusted for age, gender, ethnics, haematological disorders and use of erythropoietin and accounted for repeated measurements and within-patient correlations. Given the retrospective observational nature, all patients have different follow-up time. The 30-day post-treatment haemoglobin levels were

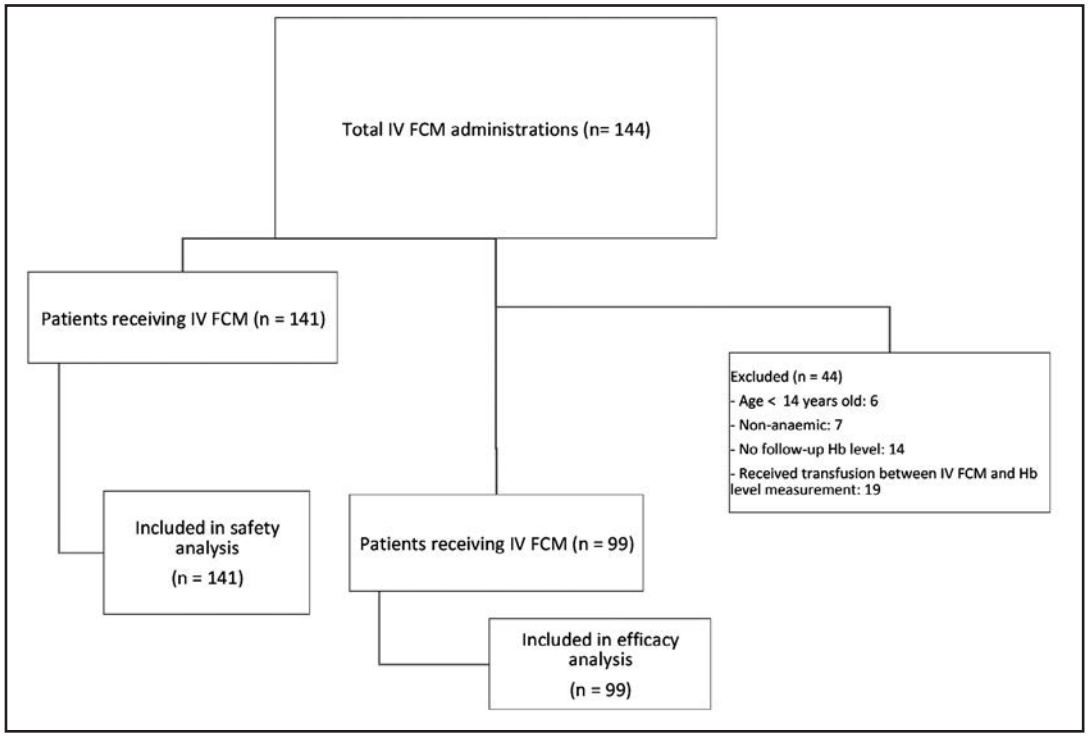

Fig. 1: Study participants flowchat.

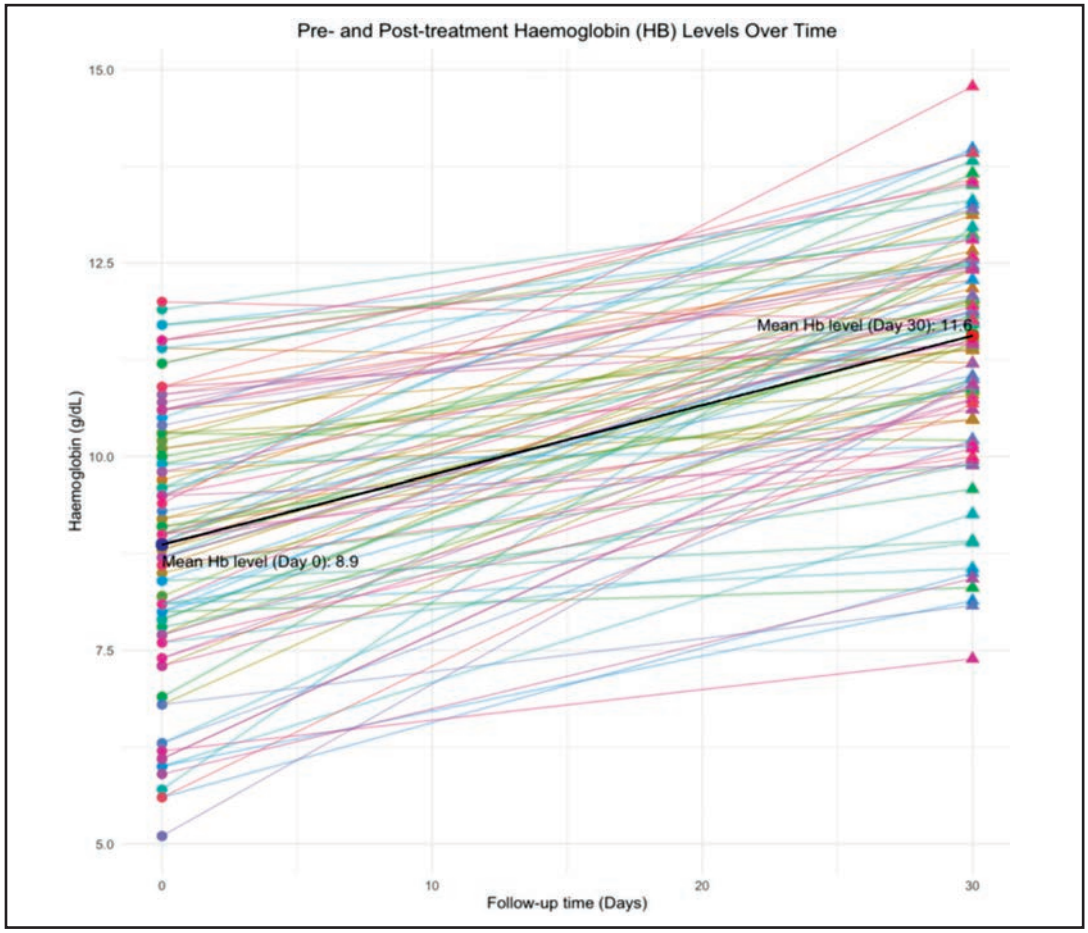

Fig. 2: Model prediction for individual patients at 30-day follow-up.

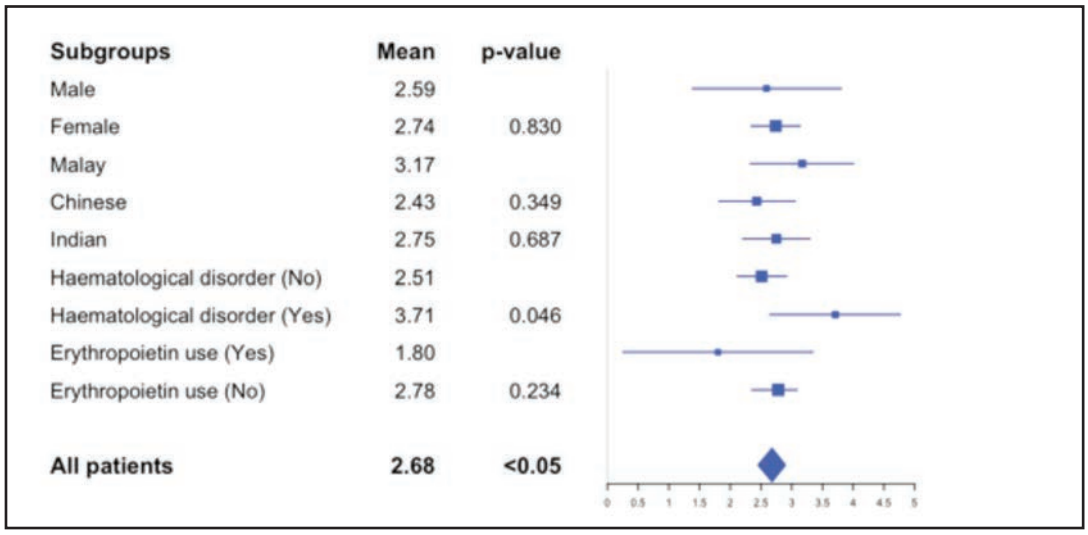

Fig. 3: Subgroup analysis for the mean change in haemoglobin.

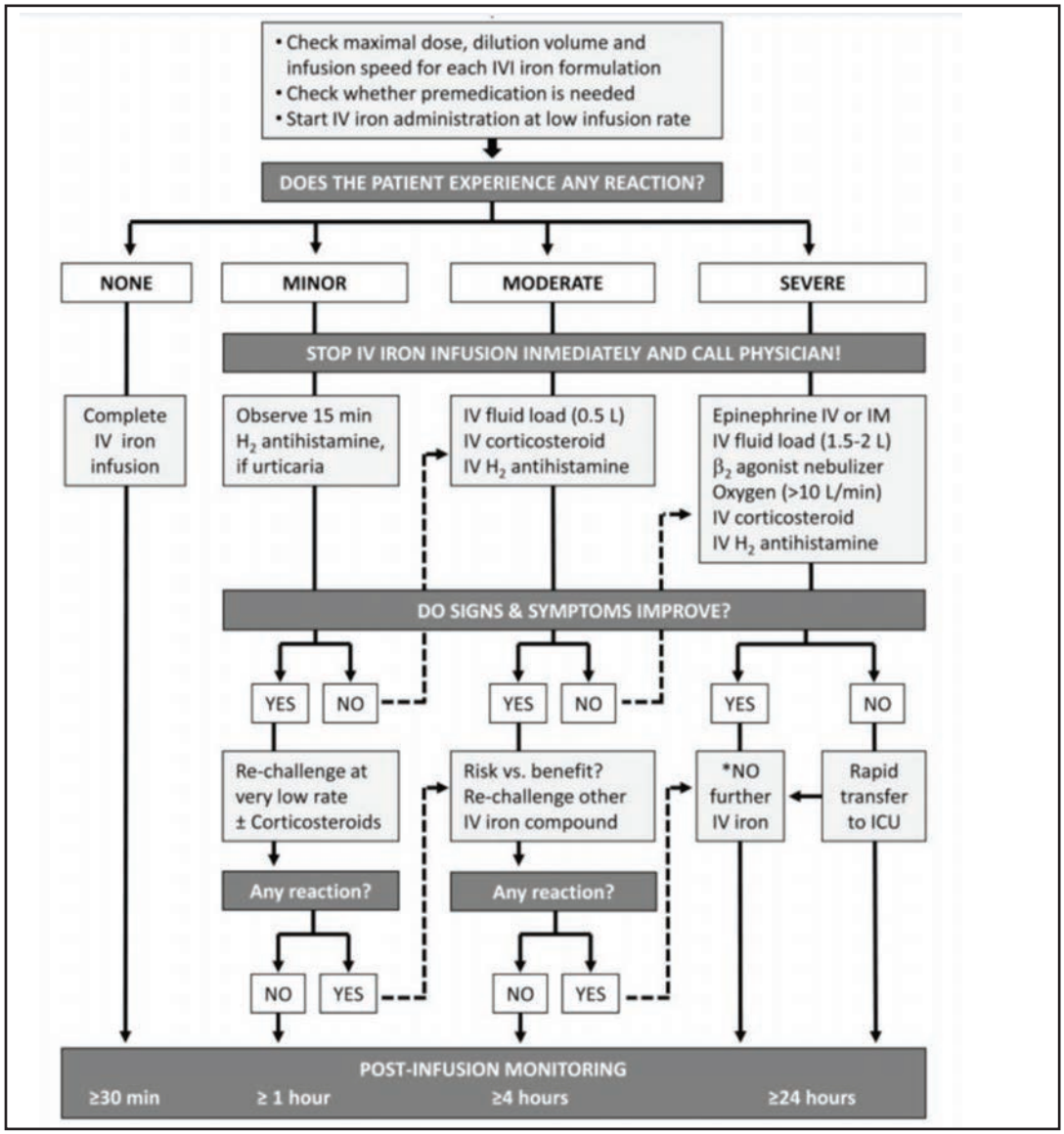

Fig. 4: An algorithm for prevention and management of reactions to intravenous iron administration (Adapted from Gómez-Ramírez et al)[21].

predicted for all per-protocol study population and the mean haemoglobin levels before and after intravenous FCM infusion was compared using paired t-test. Subgroups were compared using paired t-test with Kenward-Roger adjustment. All analyses were performed using R version 4.2.2.

RESULTS

A total of 144 administrations were given to 141 patients requiring intravenous iron replacement therapy (mean age of 40.6 ± 16.6 years old, predominantly Indian and female) during the 1-year study period in BTMC. Intravenous FCM infusion was administered for the management of ID related to: (1) increased blood loss, including menorrhagia, haemorrhoids and GI-related surgery, (2) low iron intake, including poor nutrition and gastrointestinal-related malabsorption and 3) haematological disorders, including autoimmune haemolytic anaemia, myelodysplastic syndrome, diffuse large B-cell lymphoma and idiopathic thrombocytopaenia purpura (Table I). The median dose of intravenous FCM infusion was 1000 mg. No adverse drug reactions were observed among all the 141 patients who received at least one complete intravenous FCM infusion (age ranged from 14 to 88 years old).

The efficacy analysis included 99 patients receiving intravenous FCM infusion with a median follow-up of 47 days (Figure 1). The mean haemoglobin level at pre-infusion was 8.9 ± 1.7 g/dL. At 30-day post-infusion, the model predicted that the mean haemoglobin level increased significantly from 8.9 g/dL to 11.6 g/dL ($p < 0.05$), an increase of 2.68 g/dL (95% CI: 2.45 – 2.90 g/dL) (Figure 2). Post-hoc analysis (Table III) showed no subgroup difference in the change of haemoglobin level except patients with haematological disorders had significantly higher improvement in haemoglobin levels after intravenous iron infusion compared to those without.

At 7-day, 14-day, 21-day post-infusion, 33% (33/99), 34% (34/99) and 36% (36/99) patients had a normalised haemoglobin level, respectively. The proportion of patients with a normalised haemoglobin level increased to 36% (36/99) and 42% (42/99) at 30-day and 90-day post-infusion. There was one patient (1%) who required a repeat intravenous FCM infusion after of 174 days (5.8 months) of first infusion. The drop in haemoglobin level is related to severe menorrhagia. Mean haemoglobin level before the second infusion was 9.9 g/dL, which increased 11.1g/dL and 13.1g/dL after 14 days and 51 days after infusion.

DISCUSSION

This is the first retrospective study that examined the real-world efficacy and safety of intravenous FCM infusion for the treatment of IDA in Malaysia, a multi-ethnicity and multi-cultural upper-middle-income setting. This study provided solid evidence, supporting the safe use of the currently available parenteral iron formulation (i.e. intravenous FCM infusion) in an outpatient setting of a tertiary hospital in Malaysia while overcoming the long-standing clinicians' fear against intravenous iron administration related to the reports of severe adverse events including anaphylaxis, hypotension and shock. This study also shed light on the real-world efficacy of intravenous FCM infusion in improving haemoglobin level for patients with IDA.

Safety

Consistent with many systematic reviews[17-19] and real-world studies,[20,21] our study confirmed that intravenous FCM infusion therapy was well tolerated among patients requiring intravenous iron replacement therapy, without signs of infusion-related reactions (also known as fish-bane reaction) and hypersensitivity. This could be explained by the fact that FCM is a robust and stable molecule with low labile iron, minimising the release of free iron during its administration and allowing greater iron delivery to tissues and a faster repletion of iron stores.[12] Nevertheless, it should be emphasised that adverse events related to intravenous iron infusion can occur. Although our study did not observe any infusion-related reactions such as flushing, headache, dizziness and nausea, these reactions which are due to vascular reaction to labile iron and not hypersensitivity are mild and often self-limiting. They usually abate spontaneously within 5 to 10 min of infusion pause without any intervention and rarely recur upon re-challenge at a lower infusion rate, especially if the patient has been pre-medicated with steroid prior to re-challenging. Skin discoloration from extravasation is also a possible complication and patients should be well informed of this particular risk.[22]

Although hypophosphatemia is frequently reported in intravenous FCM clinical trials,[23] this study did not observe any symptomatic hypophosphatemia. Monitoring serum phosphate levels is recommended in symptomatic patients, particularly in those who require repeated infusions, or in those at higher risk for low phosphate levels (e.g. patients treated with renal replacement therapy, those with chronic diarrhoea and those who have undergone a parathyroidectomy secondary to end-stage renal disease), or in those on medications associated with low absorption or increased excretion of phosphate (antacids, phosphate binders, niacin, acetazolamide, imatinib and sorafenib).[22]

Acute hypersensitivity reactions, which are believed to be caused by complement activation-related pseudo-allergy (CARPA),[22] are uncommon (≥1/1,000 to < 1/100).[11] It is believed that fast infusion of IV iron results in the production rate of anaphylotoxin exceeding its clearance rate from the blood. These anaphylotoxins activate mast cells and basophils, which produce secretory products (i.e. histamine, thromboxanes, leukotrienes and PFA) to trigger hypersensitivity reactions such as bronchospasm, laryngeal oedema, tachycardia, hypo- or hypertension and hypoxia. Given that rapid infusion rate is one risk factor for hypersensitivity, hypersensitivity can be prevented by reducing the rate of infusions. In severe cases, though exceedingly rare (< 1:250,000 administrations), CARPA can lead to anaphylaxis which are life-threatening if not promptly treated and can result in loss of consciousness, shock and cardio-respiratory arrest.[22]

As a preventive measure, it is important to highlight that intravenous iron should be administered only at facilities where staff is trained to identify patients with increased risk of hypersensitivity (e.g., previous mild-to-moderate reactions to IV iron, other drug allergies, severe asthma, eczema, mastocytosis, respiratory or cardiac disease, treatment with hypotensive drugs) or contraindications for intravenous iron (e.g. previous severe reaction to other IV iron, severe hepatic disease, iron overload, first trimester of pregnancy, active infection). Moreover, the staff should be adequately competent to evaluate and manage different types of adverse reactions (Figure 4). Appropriate pharmacological interventions and equipment should be immediately available at the administration sites to manage serious hypersensitivity reaction. Apart from that, before starting intravenous FCM infusion, patients should be well informed about potential adverse events.[22]

During administration, staff should be familiar with and be adherent to the appropriate maximum dose, dilution volume and infusion speed for each intravenous iron formulation, as recommended by the manufacturer, though it is advisable to start all infusions at low rates (< 50% of recommended rate), increasing this after a few minutes if no infusion reaction occurs (Figure 4). An even lower initial infusion rate (10% of the recommended rate during the first 10 to 15 min) is suggested in patients at risk of hypersensitivity reactions. A test dose is no longer recommended, as it does not accurately predict reactions to the subsequent intravenous iron infusion and has never been shown to alter the therapeutic plan. Close monitoring during and at least 30-minutes post-infusion remains a crucial step to ensure patient safety and exclude possibilities of late manifestation of hypersensitivity reactions and anaphylaxis.[22]

Efficacy

Our study underscores the efficacy of intravenous FCM infusion in significantly improving haemoglobin level by 2.7g/dL at 30 days after infusion for patients with IDA at a mean baseline level of 8.9g/dL, consistent with a systematic review of ten observational studies by Srimathi et al17 which found that haemoglobin level rises by 1.3 to 2.5g/dL at 4 weeks post intravenous FCM infusion. This improvement, which was independent of blood transfusion, might be important gain for pregnant mothers, particularly in the third trimester. Pregnant mothers in the third trimester require rapid increase in haemoglobin level before delivery, to prevent both maternal and neonatal complications, including premature birth, maternal death and low birth weight.[3] After 4 weeks of intravenous FCM infusion, while Srimathi et al.[17] estimated that haemoglobin rises up to 3.6g/dL, the effect of intravenous FCM infusion is expected to continue increasing the haemoglobin level beyond 30 days in this study and therefore provide benefits to mothers postnatal such as reducing the risks of depression, fatigue and impaired cognition associated with postpartum anaemia.[24]

Notably, intravenous FCM infusion rapidly corrected anaemia after 7 days of infusion in one-third of patients in this study, suggesting rapid replenishment of iron stores by intravenous FCM for the production of red blood cells. While Van Wyck et al.[25] also reported an increase of haemoglobin by 2 g/dL within 7 days, administering intravenous FCM therapies in patients who require rapid correction of anaemia, including patients with active bleeding and those who will be undergoing surgeries, could potentially reduce the need for blood transfusion and the associated transfusion-related reactions, as well as complications related to peri-operative IDA.[26]

Besides that, intravenous FCM seems to be an appealing therapeutic option compared to the conventional oral iron therapies for patients with menorrhagia as the correction of anaemia was found to be durable, with 42% patients had a sustained correction of anaemia for up to 90 days post-infusion and only one patient required a subsequent repeat infusion for body iron store replenishment, which observed continuous haemoglobin improvement at second infusion without refractories to prior infusion. Those patients who did not sustain the anaemia correction might need more than 1000 mg for iron repletion, require treatment continuation with oral iron or require treatment for the underlying disease that caused IDA.

In this study, 9% patients had chronic inflammatory conditions. In the event when oral iron cannot be absorbed due to hepcidin-mediated blockade associated with chronic inflammation, intravenous FCM is a viable option to increase the haemoglobin level and treat chronic anaemia due to iron deficiency. While patients with underlying haematologic disorders, including autoimmune haemolytic anaemia, myelodysplastic syndrome, diffuse large B-cell lymphoma and idiopathic thrombocytopenic purpura, often requires blood transfusion to correct anaemia, our subgroup analysis suggested that iron therapies significantly improve their haemoglobin levels by up to 3.7g/dL at 30 days after infusion and could potentially reduce the need for blood transfusion.

Given that FCM is a parenteral iron formulations that is strongly bound to carbohydrates (carboxymaltose) with minimal amount of labile iron, it allows rapid administration of total dose of iron in an outpatient setting, requiring fewer hospital visits and reducing treatment costs to the patients or the payers.[22] The routine use of total-dose iron infusion such as intravenous FCM is particularly important in a low-resource setting with high patients load.

Study Limitations

First, this study only included patients receiving intravenous FCM in a single centre, primarily females and Indians, limiting the generalisability of safety and efficacy of intravenous FCM to the entire Malaysian population. Secondly, all patients in this study received pre-medications of hydrocortisone and antihistamine, we cannot exclude the possibility of infusion-related and other adverse reactions in patients not given these medications. Additional monitoring of side effects and precautions are encouraged if pre-medications are not administered. Lastly, most patients received subcutaneous erythropoietin in this study. Although we have adjusted for erythropoietin use in the generalised linear mixed model, we cannot exclude that the improvement in haemoglobin level is in some part due to the erythropoietin use as well as the treatment of the underlying disease not related to the iron replacement therapy only.

CONCLUSION

Within the limits of this single-centre retrospective study, intravenous ferric carboxymaltose (FCM) infusion was well tolerated and effective in increasing the haemoglobin level among patients with iron deficiency anaemia (IDA). Intravenous FCM infusion is an appealing therapeutic option for iron replacement therapy in patients requiring significant increase in haemoglobin levels and rapid correction of anaemia related to iron deficiency, reducing the need for blood transfusion.

DECLARATIONS

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Contact sensitisation pattern of patients with eczema at the face and neck region: A retrospective study in Kuala Lumpur

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ABSTRACT

Introduction: Allergic contact dermatitis (ACD) involving the face and neck region (FNR) is not uncommon. We aimed to determine the sensitisation pattern among patients with dermatitis involving FNR who underwent skin patch tests between 2016 and 2022.

Materials and Methods: This is a 7-year retrospective review on contact sensitisation patterns in patients with dermatitis over the FNR who underwent skin patch tests between 2016 and 2022 in the Department of Dermatology Hospital Kuala Lumpur.

Results: There were 291 patients (female-to-male ratio of 7.8:1; mean age of 34.1 ± 14.0 years) with dermatitis at the FNR who underwent patch tests. The majority (n = 116,39.9%) were aged between 20 and 29 years. About 8% were below 19 years of age. Nearly 50% had dermatitis over the perioral region, 8.6% at the periorbital area and 50.6% at the other parts of the face and neck region. The clinical diagnoses included contact dermatitis (n = 145, 49.8%), cheilitis (n = 81, 27.8%), endogenous eczema (n = 28, 9.6%) and others. All were tested with European baseline series, with 91.4% and 77.0% tested with extended series, and own products, respectively. About 70.1% were sensitised to at least one allergen. The most common sensitizing allergen was nickel sulfate (34.0%), followed by cobalt chloride (11.7%), fragrance mix (10.7%), methylchloroisothiazolinone/ methylisothiazolinone (8.9%), and formaldehyde (8.9%). Clinical relevance was documented in 58.8% of them.

Conclusion: Contact sensitisation was detected in about 70% of patients with dermatitis at the FNR who were patch-tested. Nickel, cobalt chloride and fragrance mix were the most common sensitising allergens in these patients.

KEYWORDS:
Allergic contact dermatitis, dermatitis, face and neck region, skin patch test, European baseline series

INTRODUCTION

Allergic contact dermatitis (ACD) is an inflammatory dermatosis caused by a type IV hypersensitivity reaction to an allergen, which leads to a subsequent T-cell-mediated response.[1] The face and neck region (FNR), being more susceptible to environmental stressors, is a common site for ACD. The triggering factors include aeroallergens, ultraviolet radiation, and cosmetic products.[2] Patch testing is the gold standard to diagnose ACD. It is performed when ACD is suspected in patients with FNR dermatitis.[3] The findings of patch testing will identify the culprit allergen. Avoidance of future exposure eventually will result in the resolution of clinical symptoms. There is limited local data on the sensitisation pattern of FNR dermatitis in our region. This study aimed to determine the sensitisation pattern among patients with suspected allergic contact dermatitis over the FNR who had undergone patch testing in Dermatology Clinic, Hospital Kuala Lumpur from the year 2016 to 2022.

MATERIALS AND METHODS

This was a retrospective, single-centre study conducted at Hospital Kuala Lumpur, Malaysia. We retrieved data from the clinical record of all patch tests done between January 2016 and December 2022. Those patients with dermatitis involving their face and neck including the perioral and periorbital region were included. Subsequently, medical records were retrieved from the Medical Record Unit, hospital Kuala Lumpur with permission. Demographic data, clinical characteristics of the FNR and the initial diagnosis were recorded. The patch tests included were European baseline series, extended series such as cosmetic series, dental series, and hairdressing series. The patch test was done over 5 days with patching of the allergen on day 1, followed by reading on day 3 and day 5. Information on the patch test series done and their finding were obtained. Descriptive analysis and inferential analysis were performed using SPSS Version 26.0

RESULTS

There was a total of 1224 patch testing done between 2016 and 2022. Of these, 291 (23.8%) of the patients had dermatitis at the FNR. Their clinical characteristics were summarised in Table I. The mean age of the patients was 34.1±14.0 years when they were patch-tested. The youngest patient patch-tested was 11 years old. The female-to-male ratio was 7.8:1. White collar workers (110, 37.8%) and healthcare workers (61, 21.0%) were the two most common occupations in the cohort.

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Table I: Characteristics of 291 patients who underwent patch test for FNR dermatitis (2016-2022)

Characteristic	Total n = 291	Female n = 258	Male n = 33	P-value
Age (range)	34.1 (11- 77)	33.6 9 (11- 77)	37.8 (15- 72)	0.104
Age group in years, n(%)				
10- 19	22 (7.6)	20 (7.9)	2 (6.1)	1.000
20- 29	116 (39.9)	104 (40.3)	12 (36.4)	0.710
30- 39	85 (29.2)	77 (30.6)	8 (24.2)	0.547
40- 49	19 (6.5)	18 (7.1)	1 (3.0)	0.708
50 -59	25 (8.6)	19 (7.5)	6 (18.2)	0.053
60 -69	17 (5.8)	14 (5.6)	3 (9.1)	0.428
70 -79	7 (2.4)	6 (2.4)	1 (3.0)	0.582
Ethnicity, n(%)				
Malay	172 (59.1)	155 (60.1)	17 (51.5)	0.346
Chinese	81 (27.8)	68 (26.4)	13 (39.4)	0.116
Indian	32 (11.0)	30 (11.6)	2 (6.1)	0.336
Others	6 (2.1)	5 (1.9)	1 (3.0)	0.678
Occupations, n(%)				
White collar workers	110 (37.8)	98 (38.0)	12 (36.4)	0.857
Healthcare workers	61 (21.0)	59 (22.9)	2 (6.1)	0.026
Blue collar	25 (8.6)	16 (6.2)	9 (27.3)	<0.001
Pink collar	15 (5.2)	14 (5.4)	1 ((3.0)	0.558
Unemployed	80 (27.5)	71 (27.5)	9 (27.3)	0.976
Provisional diagnosis, n (%)				
Cheilitis	81 (27.8)	77 (29.8)	4 (12.1)	0.032
Contact dermatitis	145 (49.8)	124 (48.1)	21 (63.6)	0.092
Endogenous eczema	28 (9.6)	24 (9.3)	4 (12.1)	0.605
Face dermatitis	22 (7.6)	19 (7.4)	3 (9.1)	0.724
Photodermatitis	8 (2.7)	7 (2.7)	1 (3.0)	0.916
Others	7 (2.4)	7 (2.7)	0 (0.0)	0.338
Sites involved, n (%)				
Face (except perioral, periorbital area)	148 (50.9)	125 (48.4)	23 (69.7)	0.022
Perioral	136 (47.4)	131 (50.8)	7 (21.2)	0.001
Periorbital	25 (8.6)	22 (8.5)	3 (9.1)	0.913
Non facial area (trunk, upper and lower limbs)	70 (24.1)	60 (23.3)	10 (30.3)	0.372

FNR = Face and neck region

The clinical diagnoses before the patch test include contact dermatitis (145, 49.8%), cheilitis (81, 27.8%), endogenous eczema (28, 9.6%), non-specific facial dermatitis (22, 7.6%) and others. The majority of patients had involvement of the face other than perioral and periorbital area (n = 148, 50.9%), followed by perioral (n = 136, 47.6%), and periorbital (n =25, 8.6%) region. About a quarter of them reported dermatitis involving other parts of the body as well.

All were tested with the European Baseline Series (Table II). About 91% (n = 266) were also tested with at least one extended series. Among these, 76.6% (n = 223) were tested with cosmetic series. Other extended series used include dental series (25, 8.6%), hairdressing series (20, 6.9%), rubber series (15, 5.2%), metal series (14, 4.8%), medicaments (13, 4.5%), photoallergen series (10, 3.4%), shoe chemical series (4, 1.4%), textile and leather dye (2, 0.7%) and plastic and glue series (1, 0.3%). Own products were also tested in 224 (77%) of the patients.

About 70.1% (n = 204) developed at least one positive reaction (range 1 to 12 allergens). Of these, more than 80% (n = 169) had at least one positive reaction in the European baseline series. About 54.4% (n =111) and 19.6% (n = 40) of them had positive reactions to the extended series and their products. There was about 12.7% (n = 26) of them had a negative reaction in the European baseline series but a positive reaction in the extended series. There were nine patients (4.4%) who only tested positive for their own product but had negative reactions in the European Baseline Series and extended series. Clinical relevance was found in 58.8% (n = 120) of the patients with positive reactions. The positivity of the patch tests was not significantly associated with ethnicity, occupations, pretest diagnoses and site of involvement.

The most frequently tested positive allergen was nickel sulfate (99, 34.0%), followed by cobalt chloride (34, 11.7%), fragrance mix (31, 10.7%), kathon CG (Methylchloroisothiazolinone/methylisothiazolinone) (26, 8.9%) and formaldehyde (n = 26, 8.9%) (Table III). A similar pattern of sensitisation was found in the sub-analysis among the female patients. In male patients (n = 33), nickel sulfate remained the most common sensitising allergen detected (n = 7, 21.2%). This was followed by para-phenylenediamine (PPD) (4, 12.1%), and textile dye mix (3, 9.1%).

Female patients (Mean age = 33.6 years) were younger than their male counterparts (mean age 37.8 years) although it was not statistically significant (Table I). In terms of occupations, a higher proportion of females worked as healthcare workers (22.9% vs 6.1%, p = 0.026) whereas a higher proportion of male patients were blue-collar workers (27.3% vs 6.2%, p < 0.001) compared to their counterparts. For the pretest diagnosis, there were significant differences in the cheilitis group (29.8% in females vs 12.1% in males). No

Table II: Patch test findings among patients with FNR dermatitis (2016 to 2022)

Patch testing	Total n = 291	Female n = 258	Male n = 33	p-value
Patch test series used				
European baseline	291 (100)	258 (100)	33 (100)	
Own products	224 (77.0)	207 (80.2)	17 (51.5)	
Cosmetic	223 (76.6)	208 (80.6)	15 (45.5)	
Dental	25 (8.6)	24 (9.3)	1 (3.0)	
Hairdressing	20 (6.9)	18 (7.0)	2 (6.1)	
Rubber	15 (5.2)	13 (5.0)	2 (6.1)	
Metal	14 (4.8)	8 (3.1)	6 (18.2)	
Medicaments	13 (4.5)	10 (3.9)	(9.1)	
Photoallergen	10 (3.4)	10 (3.9)	0 (0.0)	
Shoe chemicals	4 (1.4)	4 (1.6)	0 (0.0)	
Textile and leather dye	2 (0.7)	2 (0.8)	0 (0.0)	
Plastic and glue	1 (0.3)	1 (0.4)	0 (0.0)	
Number with ≥1 positive reaction (%)	204 (70.1)	187 (72.5)	17 (51.5)	0.013
1 allergen	54 (18.6)	51 (19.8)	3 (9.1)	0.160
2 allergens	63 (21.6)	58 (22.5)	5 (15.1)	0.500
3 allergens	37 (12.7)	31 (12.0)	6 (18.2)	0.401
>3 allergens	50 (17.2)	47 (18.2)	3 (9.1)	0.229
Number with positive reaction in European baseline series (%), n = 204	169 (82.8)	153 (81.8)	16 (94.1)	0.316
Number with positive reaction in extended series (%), n = 204	111 (54.4)	98 (52.4)	13 (76.5)	0.009
Number with positive reaction with testing own products (%), n = 204	40 (19.6)	38 (20.3)	2 (11.8)	1.000
Number with negative reaction in European baseline but positive in extended series (%), n = 204	26 (12.7)	25 (13.4)	1 (5.9)	0.697
Number with negative reaction in European baseline & extended series but positive reaction with testing own products (%), n = 204	9 (4.4)	9 (4.8)	0 (0.0)	1.000
Clinical relevance	120/204 (58.8)	108/187 (57.8)	12/17 (70.6)	0.040

FNR = Face and neck region

Table III: The sensitisation pattern among patients with FNR dermatitis 2016 to 2022 (Top 10 allergens)

No	All (n = 291)		Female (n = 258)		Male (n = 33)	
	Types of allergen	n(%)	Types of allergen	n(%)	Types of allergen	n (%)
1	Nickel sulfate	99 (34.0)	Nickel sulfate	92 (35.7)	Nickel sulfate	7 (21.2)
2	Cobalt chloride	34 (11.7)	Cobalt chloride	33 (12.8)	4-Phenylenediamine	4 (12.1)
3	Fragrance mix	31 (10.7)	Fragrance mix	29 (11.2)	Textile dye mix	3 (9.1)
4	Kathon CG	26 (8.9)	Kathon CG	25 (9.7)	Fragrance mix	2 (6.1)
5	Formaldehyde	26 (8.9)	Formaldehyde	25 (9.7)	Colophony	2 (6.1)
6	Thimerosal	25 (8.6)	Thimerosal	25 (9.7)	Tea tree oil	2 (6.1)
7	Methylisothiazolinone	20 (6.9)	Methylisothiazolinone	19 (7.4)	2,5-Diaminotoluene sulfate	2 (6.1)
8	Colophony	19 (6.5)	Colophony	17 (6.6)	Hexahydro-1,3,5-tris-(2-hydroxyethyl)triazine	2 (6.1)
9	Balsam Peru	17 (5.8)	Balsam Peru	16 (6.2)		
10	gallate mix	16 (5.5)	gallate mix	16 (6.2)		

FNR = Face and neck region

significant differences were found in the other diagnosis groups. For the site of involvement, there was a significantly higher proportion of male patients with FNR (non-periorbital and perioral) involvement (69.7% in males vs 48.4% in females, p = 0.022). On the other hand, significantly more female patients had perioral involvement compared to male patients (50.8% vs 21.2%, p = 0.001). No differences were found for the periorbital or other body site groups.

There was a significantly higher rate of positive patch test reaction among the females (72.5% vs 51.5%, p = 0.013) compared to males. More male patients reported a positive reaction in the extended series (n = 13, 76.5% vs n = 98, 52.4%, p = <0.009) compared to female patients (Table II).

DISCUSSION

This study population had a mean age of 34.1 years which is similar to other studies done earlier in China, Thailand, India and Turkey.[4-7] The female-to-male ratio was as high as 7.8:1. A similar observation was reported by Kasemsarn et al., with a female-to-male ratio of 9.1:1.[6] Others had a female-to-male ratio of 2.5 to 6.3:1.[4-8] This was likely due to females applying more cosmetics than their male counterparts.[9] Use of

Table IV: Comparison of different studies on patch testing among patients with facial dermatitis or cosmetic allergy

Country	Malaysia	Turkey[4]	India[5]	Thailand[6]	China[7]	United State[8]
Authors	Teo et al.	Adisen et al.	Garg et al.	Kasemsarn et al.	Li et al	Katz et al.
Study year	2016 - 2022	2001 -2007	2013 -2015	2006 -2011	2003 -2005	1995- 1997
n	291	404	58	244	92	85
Mean age	34.7	33	36.3	37.3	35.3	47.0
F: M	7.8:1	-	6.25:1	9.1:1	2.5:1	4.6:1
Test series	European baseline and extended series	European baseline series only	ISS, ICFS	SiSS, cosmetic series (44.9%)	Modified European standard series	NACDG standard series
Top 3 allergens	Nickel sulfate 34% Cobalt chloride 11.7% Fragrance mix 10.7	NA	Cetrimide 20.7%	Thimerosal 15.5% Nickel 13.8%	Nickel sulfate 28.5% Benzalkonium chloride 20.3% Gold sodium Thiosulfate 18.5% Nickel sulfate-26.1% Thimerosal 15.2% Potassium dichromate 8.7%	NA

ISS: Indian standard series (ISS), ICFS: Indian cosmetic and fragrance series, SiSS: Siriraj Standard Series, NACDG: Northen America contact dermatitis group

Table V: The sensitisation pattern of the top 10 allergens according to age groups

		All patients	Nickel sulfate	Cobalt chloride	Fragrance mix	Kathon CG	Formal dehyde	Thimerosal	MI	Colophony Peru	Balsam	Gallate mix
Age group	10-19	22	7	2	1	0	0	1	0	1	2	1
	20-29	116	43	11	7	11	14	11	8	7	3	10
	30-39	85	30	16	13	3	6	11	4	5	7	4
	40-49	19	6	0	4	8	1	1	5	4	2	0
	50-59	25	6	1	4	1	2	1	1	1	1	0
	60-69	17	4	3	0	2	3	0	1	1	0	0
	70-79	7	3	1	2	1	0	0	1	0	2	1
Total		291	99	34	31	26	26	25	25	19	17	16
p -Value			0.829	0.149	0.048	<0.001	0.365	0.444	0.025	0.271	0.06	0.330

MI = Methylisothiazolinone

cosmetics was found to be a trigger factor for sensitive skin.[10] Females with sensitive skin also have higher use of moisturisers and facial products to improve the sensation of skin sensitivity, thus rendering them more vulnerable to allergic contact dermatitis.[10] On the other hand, females are more likely to report any allergic dermatitis and seek treatment due to concern about their appearance.[11]

Nickel sulfate (34.0%), cobalt chloride (11.7%) and fragrance mix (10.7%) were the three most common allergens with positive reactions in the current study (Table IV). Most of the other studies reported similar findings as well.[6,7] Kasemsarn et al. reported benzalkonium chloride and gold sodium thiosulfate as the common allergens after nickel among 244 patients with facial allergic contact dermatitis in Thailand.[6] Li et al. found that thimerosal and potassium dichromate were common allergens after nickel in their study among 92 patients in China with facial contact dermatitis.[7] On the other hand, Garg et al. reported cetrimide, thimerosal and nickel as the commonest allergens in their study.[5] The differences among these studies were partly due to the different target populations and test series used in different centres.

Nickel allergies are mostly caused by non-occupational exposures (jewellery, clothing, metal tools and medical devices), although occupational exposures are common as well for those who work as mechanics, platers, hairdressers and metal and construction workers.[12] It was also found in cosmetics, eyeshadow, and beauty tools, predisposing to facial and neck region ACD.[13,14] However, due to the abundance of nickel in the environment, it was difficult to determine the relevance of nickel in patients with FNR dermatitis. On the other hand, most cases of cobalt sensitisation are associated with nickel co-sensitisation and many products that contain nickel will also contain cobalt.[15] Studies showed that both nickel and cobalt can be present in inorganic pigments rich in iron and manganese used in cosmetics such as eyeshadow. Cobalt was detected in yellow, purple and black pigments.[15] Silverberg et al. reported an 11.9% positive patch test to cobalt in children, with facial involvement in 10.6% of their patients.[16] Previous studies had revealed that fragrance mix are present in 15 to 100% of cosmetic products, and these included deodorants and fine fragrances.[16] It is difficult to avoid fragrance exposure as even products labelled as 'fragrance-free' may contain fragrance ingredients as preservatives or the use of botanicals.[17]

The most common allergens that tested positive beyond European baseline series were thimerosal (8.6%) and gallate mix (5.5%). Thimerosal is an organic mercurial that has been used as a preservative and it has been incorporated into vaccines, test solutions and topical creams.[18] Many studies reported a high rate of sensitisation to thimerosal, but they were of little clinical relevance.[19] It has been removed from most of the childhood vaccines in the United States since 2001. Currently, thimerosal use in cosmetics has been diminished and may be found in ophthalmic solutions.[20] Gallate mix is a preservative commonly found in food products and cosmetics such as lipstick, and facial products and may contribute to allergic cheilitis.[21] However, it is difficult to determine the presence of gallate mix in processed food as labelling in the food industry is not strictly regulated.

Sub-analysis showed that PPD and textile dye mix were the important sensitising allergens in male patients after nickel sulphate. In three out of the four patients with positive reactions to PPD, hair dye was identified as the likely source of reagents. None of these cases were occupational-related. In patients with PPD sensitisation or hair dye allergies, apart from the face, dermatitis can also be found on the side of the neck and hands.[22] Scalp is sometimes spared due to the thickness of the skin in these areas, protective sebum production and moderation by hair follicle regulation which promotes tolerance.[23] Interestingly, the three patients with positive reactions to textile dye mix were co-sensitised to PPD. PPD had been reported to have cross-reactivity with other dyes such as textile dye, local anaesthetics and rubber chemicals.[24]

In current study, 70.1% of patients had at least one positive reaction in the patch test. This finding is comparable to earlier studies which reported at least one positive reaction in 41.8 to 69.0% of the patients.[4,5,25] Kasemsarn et al. reported a higher positive patch test reaction at 81.6% in their study as it was conducted in a contact dermatitis clinic among patients with likely diagnosis of allergic contact dermatitis. We reported a high clinical relevance among patients with positive reactions (120 out of 204 patients, 58.8%). In addition, patch testing with extended series and own products was important as it increased the sensitivity of the patch tests. Otherwise, patch tests with the European standard series alone may lead to misdiagnosis in nearly 20% of cases.

The present study showed significantly more patients in the age group of 20 to 39 to have positive patch tests on fragrance mix (p = 0.048), Kathon CG (p = <0.001), and methylisothiazolinone (p = 0.025) (Table V). These allergens are commonly found in cosmetic products that are used more often by young patients than older ones.[26] There were significantly more females who experienced cheilitis compared to their male counterparts (29.8% vs 12.1%, p = 0.032). For the area of involvement, females also had significantly higher involvement of perioral (50.8% vs 21.2%, p = 0.001) compared to males. On the other hand, FNR dermatitis in males tends to involve facial areas other than periorbital and perioral such as cheek and forehead, compared to females (69.7% vs 48.4%, p = 0.001). Cheilitis is commonly caused by allergic hypersensitivity especially to cosmetic and hygiene products.[27] Other culprits include personal care products and toiletries like toothpaste, musical instruments, and others. Female patients tend to use more cosmetic products on the lips such as lipstick, lip balm, lip gloss, lip serum and lip paint compared to males, which could explain their higher prevalence of allergic cheilitis. Getachew et al. reported that 80.1% of females had a habit of using cosmetic products and 86.8% of them used lipstick, lotion, toothpaste or eye makeup.[26]

The study is limited by the single-centred data from a tertiary hospital in an urban area. A prospective multicentre study will be more informative to compare the differences in sensitisation patterns in different regions of Malaysia. The male patients in the current study remain low (n = 33, 11.3%). As a result, several trends of differences were observed but did not reach statistical significance. Given the retrospective nature of the study, there is a likelihood of incomplete data, particularly in terms of demographic information, clinical findings, and the objective assessment of clinical response.

CONCLUSION

Contact sensitisation was detected in about 70% of patients with dermatitis at the face and neck region (FNR) who were patch-tested. Nickel sulfate, cobalt chloride and fragrance mix were the most common allergens in the current study. Females had a significantly higher rate of positive patch tests compared to males. The addition of an extended series and patients' own products helps to improve the sensitivities of the patch test.

ETHICAL APPROVAL AND CONSENT TO PARTICIPATE

This study was registered to the National Medical Research Register, Ministry of Health Malaysia (RSCH ID-23-03846-TXV)

CONFLICT OF INTEREST

The authors declare no competing interests

FUNDING

The authors declare no financial disclosure

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Knowledge, attitude and practices of indigenous people towards non-communicable disease in Bera, Malaysia: A community-based study

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ABSTRACT

Introduction: With the current trend of increasing non-communicable diseases (NCD), like hypertension, diabetes and dyslipidaemia worldwide and in Malaysia, a comprehensive study is essential to find the local population's knowledge, attitude and practice towards NCD. Little is known about the indigenous people of Orang Asli's health conditions and health-seeking behaviours towards these chronic diseases. The study aimed to assess knowledge, attitudes and practices (KAP) status towards non-communicable disease and its association with demographic background among Orang Asli adults of the Semelai subgroup in central Pahang, Malaysia.

Materials and Methods: A cross-sectional study was conducted among 251 adult Semelai people in Bera district, Pahang. Data was collected through face-to-face interviews to obtain socio-demographic data, KAP towards NCD. Bivariate analysis was performed to test the association between the socio-demographic factor and the KAP score.

Results: Among respondents, 57.4% were female, 82.5% were married, and 46.2% completed primary school. The majority were animism believers (83.3%), self-employed (75.3%) and earning less than RM1000 (87.6%). The respondents' ages ranged from 18 to 77, with a mean age of 41.1 (S.D ± 13.9). The prevalence of known type-2 diabetes mellitus (T2DM), hypertension, and dyslipidaemia was 9.6%, 20.7%, and 8.8%, respectively. About 23.1% of respondents have a family history of chronic disease. Regarding KAP parameters, only 12.7% have good knowledge, and 35.5% have good practice in prevention and treatment. However, more than half (59.8%) have a positive attitude towards chronic diseases. This study also showed that higher household income and education levels were positively associated with higher scores of KAP (p < 0.001).

Conclusion: This study presented a low-to-moderate percentage of Orang Asli who have good KAP towards NCD. KAP levels were significantly associated with education levels and household income. Hence, improving education and poverty in the Orang Asli community may successively increase the knowledge level, impart a positive attitude towards NCDs, and improve the practice level toward treatment and prevention.

KEYWORDS:
Indigenous, knowledge, attitude and practices, non-communicable disease

INTRODUCTION

Non-communicable diseases (NCDs) such as diabetes, hypertension and dyslipidaemia are the main leading causes of death globally. The World Health Organisation (WHO) reported that NCDs caused about 74% of all deaths annually around the globe, mainly resulting from a combination of genetic, social, environmental and behavioural factors.[1] NCDs disproportionately affect people in different countries, where 86% of people die from NCDs before the age of 70, particularly in low- and middle-income countries.[1] Non-modifiable risk factors, such as gender and age, and modifiable elements, such as smoking, a diet rich in lipids and carbohydrates, fewer vegetables and fruit intake, and a sedentary lifestyle increase the risk of metabolic diseases. Modifiable risk factors for metabolic disorders can be preventable by modifying lifestyles with a balanced diet, regular physical activity, and inhibiting excessive alcohol consumption and tobacco use. According to the 2019 National Health and Morbidity Survey (NHMS), cardiovascular diseases such as stroke and coronary heart disease are the leading cause of death in Malaysia.[2] NCDs are estimated to account for 74% of all deaths in Malaysia[3], where about half (54.1 %) of Malaysian adults have at least one of three non-communicable diseases, either diabetes (18.3%), hypertension (30.0%) or hypercholesterolemia (38.1%).[2] This issue becomes more alarming as an estimated 17.2% of the population have undiagnosed hypertension, 8.9% undiagnosed diabetes mellitus and 38.6% undiagnosed hypercholesterolemia.[4] Late diagnosis and inadequate management of chronic NCDs will cause a surge in patients with complications, such as ischemic heart disease and stroke.

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The Orang Asli, also known as the aborigines, are the indigenous minority people living in Peninsular Malaysia. Currently, little is known about the Orang Asli community concerning their health condition, health-seeking behaviour and socioeconomic status. Furthermore, the changing environment and health factors have impacted Orang Asli's quality of life and exposed the community to diseases that were more prevalent among urban populations as they were marginalised from financial and life quality development. This study aims to investigate the knowledge, attitude, practice (KAP) and sociodemographic status of Orang Asli, the Semelai community situated in central Pahang, Malaysia, towards NCDs (diabetes, hypertension and hypercholesterolemia). Additionally, the associations between the KAP levels and socio-demographic factors (gender, educational level and household income) were explored in this study. The results would contribute to the development of strategies and policies to assist the community of indigenous people in improving their health and enhancing NCDs intervention and prevention.

MATERIALS AND METHODS

Study Area Design, Sample Size and Sampling Method

A cross-sectional study was conducted by collecting data from the indigenous population of the Semelai community in Bera, Pahang, Malaysia. The data were collected from January 2020 to June 2021 to assess the level of KAP of NCDs and their socio-demographic data.

This study was part of a larger main study; hence, the sample size was calculated based on the main study's objective using a single proportion formula with an expected prevalence of NCDs of 14.8%,5 using OpenEpi version-3. The calculated sample size was 238 at the 95% confidence level. After considering a possible non-response rate of 5%, the required sample size was 251. A smaller non-response rate was used because of the planned face-to-face data collection where not many non-responses were expected.

A face-to-face interview with convenience sampling was conducted in the Malay language. A mobile Orang Asli team by Pejabat Kesihatan Daerah (PKD) in Bera visits the Orang Asli's villages daily for medical surveillance and health services. Three investigators in this research group followed the mobile team to conduct the interview. This study was conducted on a targeted sample size of 251 indigenous adults out of 9228 adults (based on information provided by Jabatan Kemajuan Orang Asli (JAKOA) from a total of 33 Orang Asli's villages in Bera, Pahang, Malaysia, selected by purposive sampling method.

Sampling Method

Inclusion criteria:

- Adults 18 years old and above
- Orang Asli people living in Bera
- Orang Asli from other states but staying permanently in the listed villages, were considered participants.

Exclusion criteria:

- Not willing to participate
- Unable to communicate in Malay.

Study Instrument:

The questionnaire was designed by adopting three different scales from three articles.[6-8] The questionnaire was developed and validated in Malay language for use in its original form. It was rectified for the content validation qualitatively by three experts' opinions, namely a public health specialist and two family medicine specialists. A pilot study was conducted at Kampung Orang Asli Sungai Tuang with a sample size of 40. The pilot study focused on the flow of the study and tested the data collection form. The consistency of the questions was checked, and internal consistency was found to be acceptable, with the Cronbach Alpha value of > 0.6 for all domains.

The questionnaire comprised two sections: social-demographic data and KAP regarding NCDs. Section I referred to the respondent's socio-demographic details, and Section II was divided into a, b and c on the KAP regarding NCDs, respectively.

Section IIa – Knowledge - focused on respondents' knowledge and understanding towards NCDs in terms of how the diseases are acquired, risk factors, prevention and treatment. Marks were calculated based on the cumulative points collected from five main questions, which carry a total of 15 marks. The knowledge scores were then categorised proportionately into poor (0 – 5 marks), fair (6 – 10 marks) and good (11 – 15 marks), almost similar to the categorisation by Anita et al.[9]

Section IIb – Attitude - assessed the general feelings and beliefs towards NCD treatment and prevention, which could either be positive, neutral or negative. A 5-point Likert scale was adopted for this section. The total score was categorised as either a positive attitude or a negative attitude based on the mean/median of the total score.[6]

Section IIc - Practice - assessed the practices of different prevention and treatment options for NCD. A 4-point Likert scale was adopted for this section, and the total score was categorized either as good practice or poor practice based on the mean/median of the total score.[6]

The study obtained ethical approval from the University Research Ethics Committee, International Islamic University Malaysia (IREC—2020-024), and written permission was granted from the Jabatan Kemajuan Orang Asli Malaysia (JKOAM), Jabatan Perdana Menteri, Kuala Lumpur. (Rujukan: JAKOA/PP.30.032Jld 47). All the data were kept confidential. Informed consent was obtained from all participants prior to data collection. This research did not receive any specific grants from public, commercial or not-for-profit funding agencies.

Statistical Analysis

All collected data were analysed using SPSS version 22.0 for descriptive statistics where the categorical variables were expressed as frequency and percentage. The KAP scores were categorised to explain their levels but used as their original forms (numerical) to assess their associated factors. To assess the factors associated with the KAP levels, simple and multiple linear regression were used for the univariate and multivariable analysis to control for the possible

Table I: Socio-demographic characteristics of respondents (n = 251)

Socio-demographic variables	Frequency (%)
Age (years)	
18 – 39	123 (49.0)
40 – 59	97 (38.6)
60 and above	31 (12.4)
Gender	
Male	107 (42.6)
Female	114 (57.4)
Marital status	
Single	44 (42.6)
Married	114 (57.4)
Religion	
Animism	209 (83.3)
Islam	32 (12.7)
Buddhism	9 (3.6)
Christian	1 (0.4)
Education level	
None	62 (24.7)
Primary school	116 (46.2)
Secondary school	64 (25.5)
Tertiary education	9 (3.6)
Occupation	
Self-employed	189 (75.3)
Employed	28 (11.2)
Unemployed	32 (12.7)
Retired	2 (0.8)
Household income (RM per month)	
1000 and lessb	220 (87.6)
1001 - 4000	28 (11.2)
More than 4000	3 (1.2)
Transport to health clinics	
Motorcycle	190 (75.7)
Car	59 (23.5)
Walking	2 (0.8)
Family history of NCDsa	
Yes	58 (23.1)
No	193 (76.9)

[a]Non-communicable diseases
[b]Pendapatan Garis Kemiskinan (PGK) Mangikut Negeri dan Strata, 2019 (Data Asas Kementerian Pembangunan Luar Bandar (KPLB)

confounders, respectively, using Stata Intercooled software version 15. The level of significance was set at 0.05.

RESULTS

Section-A: Socio-demographic Characteristics of Participants

The survey was conducted among 251 respondents and their socio-demographic characteristics are summarized in Table I.

The majority were married (82.5%), practiced animistic (83.3%), had a household income of less than RM 1000 per month (87.6%) and were self-employed (75.3%), with 46.2% only attending primary school. The most common transportation used to the healthcare centre was by motorcycle (75.7%). Only 58 (23.1%) respondents had a positive family history of NCDs. The respondents' ages ranged from 18 to 77, with a mean age of 41.1 (S.D ± 13.9). The prevalence of known type-2 diabetes mellitus (T2DM), hypertension and dyslipidaemia was 9.6%, 20.7% and 8.8%, respectively. About 23.1% of respondents have a family history of chronic disease.

Section-B: Knowledge, Attitude and Knowledge of Orang Asli Regarding NCDs

Figure 1 reflects that only 12.7% of participants have good knowledge of NCDs, the majority (59.8%) have fair knowledge, and 35.5% have good practices on treatment and prevention. However, the majority (59.8%) demonstrated a positive attitude towards NCDs.

Section-C: Factors Associated with Knowledge, Attitude and Practice Regarding NCDs

The factors associated with KAP regarding NCDs are shown in Tables II and III for univariate and multivariable analysis using simple and multiple linear regression, respectively. As seen from those two tables, the KAP regarding NCDs are significantly positively associated with the education levels and significantly negatively associated with those who had no family history of NCDs on both the univariate and multivariable levels.

On the other hand, even though religion and income also show significant association with each of the KAP regarding NCDs at the univariate level, after controlling for the confounders on the multivariable level, only practice is found

Table II: Factors associated with knowledge, attitude and practices score regarding non-communicable diseases (NCDs) using simple linear regression (n = 251)

Socio-demographic variables	Knowledge		Attitude		Practices	
	β-coeffient (95% CI[a])	p-value	β-coeffient (95% CI[a])	p-value	β-coeffient (95% CI[a])	p-value
Age (years)						
18 – 39[b]	0.000	1.000	0.000	1.000	0.000	1.000
40 – 59	-0.093 (-0.914, 0.728)	0.824	-0.290 (-1.485, 0.905)	0.633	-0.358 (-1.558, 0.842)	0.558
60 and above	-1.090 (-2.305, 0.125)	0.079	-0.484 (-2.253, 1.285)	0.590	-0.967 (-2.743, 0.809)	0.284
Gender						
Maleb	0.000	1.000	0.000	1.000	0.000	1.000
Female	0.282 (-0.493, 1.056)	0.474	0.865 (-0.252, 1.981)	0.129	1.295 (0.178, 2.411)	0.023
Marital status						
Single[b]	0.000	1.000	0.000	1.000	0.000	1.000
Married	-1.590 (-2.579, -0.602)	0.002	-0.665 (-2.122, 0.792)	0.369	-0.942 (-2.405, 0.520)	0.206
Religion						
Anemism[b]	0.000	1.000	0.000	1.000	0.000	1.000
Islam	1.967 (0.856, 3.078)	0.001	2.653 (1.050, 4.256)	0.001	1.314 (-0.345, 2.973)	0.120
Buddha	7.373 (1.508, 13.239)	0.014	5.684 (-2.781, 14.149)	0.187	1.627 (-7.134, 10.389)	0.715
Christian	2.151 (0.159, 4.143)	0.034	5.129 (2.254, 8.003)	0.001	3.627 (0.651, 6.602)	0.017
Education level						
None[b]	0.000	1.000	0.000	1.000	0.000	1.000
Primary school	1.133 (0.320, 1.946)	0.006	0.991 (-0.227, 2.210)	0.110	1.640 (0.351, 2.930)	0.013
Secondary school	3.584 (2.663, 4.505)	<0.001	4.203 (2.823, 5.583)	<0.001	3.932 (2.472, 5.393)	<0.001
Tertiary education	6.694 (4.850, 8.537)	<0.001	9.222 (6.460, 11.985)	<0.001	7.116 (4.192, 10.041)	<0.001
Occupation						
Self-employed[b]	0.000	1.000	0.000	1.000	0.000	1.000
Employed	1.306 (0.091, 2.520)	0.035	0.619 (-1.154, 2.392)	0.492	1.417 (-0.365, 3.198)	0.119
Unemployed	0.582 (-0.564, 1.729)	0.318	0.615 (-1.059, 2.288)	0.470	1.354 (-0.327, 3.036)	0.114
Retired	4.270 (0.008, 8.532)	0.050	5.833 (-0.389, 12.156)	0.066	1.667 (-4.586, 7.919)	0.600
Household income (RM per month)						
1000 and less[b,c]	0.000	1.000	0.000	1.000	0.000	1.000
1001 - 4000	2.981 (1.836, 4.125)	<0.001	4.482 (2.835, 6.129)	<0.001	4.645 (2.975, 6.316)	<0.001
More than 4000	5.076 (1.760, 8.392)	0.003	7.732 (2.961, 12.503)	0.002	4.562 (-0.278, 9.402)	0.065
Transport to health clinics						
Motorcycle[b]	0.000	1.000	0.000	1.000	0.000	1.000
Car	1.793 (0.914, 2.672)	<0.001	0.604 (-0.702. 1.910)	0.363	0.595 (-0.714, 1.904)	0.371
Walking	-0.063 (-4.254, 4.128)	0.976	4.316 (-1.913, 10.545)	0.174	6.011 (-0.233, 12.254)	0.059
Family history of NCDs						
Yes[b]	0.000	1.000	0.000	1.000	0.000	1.000
No	-1.904 (-2.782, -1.026)	<0.001	-3.612 (-4.849, -2.375)	<0.001	-2.640 (-3.922, -1.358)	<0.001

[a] Confidence Interval
[b] Reference group –
[c] Pendapatan Garis Kemiskinan (PGK) Mangikut Negeri dan Strata, 2019 (Data Asas Kementerian Pembangunan Luar Bandar (KPLB)

Table III: Factors associated with knowledge, attitude and practices score regarding non-communicable diseases (NCDs) using multiple linear regression[a] (n = 251)

Socio-demographic variables	Knowledge		Attitude		Practices	
	β-coeffient (95% CI[b])	p-value	β-coeffient (95% CI[b])	p-value	β-coeffient (95% CI[b])	p-value
Gender						
Male[c]	-	-	-	-	0.000	1.000
Female	-	-	-	-	1.195 (0.175, 2.216)	0.022
Marital status						
Single[c]	-	-	0.000	1.000	-	-
Married	-	-	1.507 (0.151, 2.864)	0.030	-	-
Education level						
None[c]	0.000	1.000	0.000	1.000	0.000	1.000
Primary school	1.071 (0.270, 1.872)	0.009	1.035 (-0.151, 2.222)	0.087	1.401 (0.148, 2.655)	0.029
Secondary school	3.374 (2.438, 4.310)	<0.001	4.091 (2.679, 5.503)	<0.001	2.802 (1.284, 4.320)	<0.001
Tertiary education	5.598 (3.653, 7.544)	<0.001	9.154 (6.212, 12.096)	<0.001	3.952 (0.737, 7.166)	0.016
Household income (RM)						
1000 and less[c, d]	-	-	-	-	0.000	1.000
1001 - 4000	-	-	-	-	2.746 (0.913, 4.578)	0.003
More than 4000	-	-	-	-	2.792 (-2.004, 7.588)	0.253
Transport to health clinics						
Motorcycle[c]	0.000	1.000	-	-	-	-
Car	0.919 (0.122, 1.716)	0.024	-	-	-	-
Walking	-1.911 (-5.581, 1.759)	0.306	-	-	-	-
Family history of NCDs						
Yes[c]	0.000	1.000	0.000	1.000	0.000	1.000
No	-0.821 (-1.618, -0.023)	0.044	-2.217 (-3391, -1.043)	<0.001	-2.640 (-3.922, -1.358)	<0.001

[a] Only the significant variables in the final models for each knowledge, attitude and practice are presented in the table
[b] Confidence Interval
[c] Reference Group
[d] Pendapatan Garis Kemiskinan (PGK) Mangikut Negeri dan Strata, 2019 (Data Asas Kementerian Pembangunan Luar Bandar (KPLB)

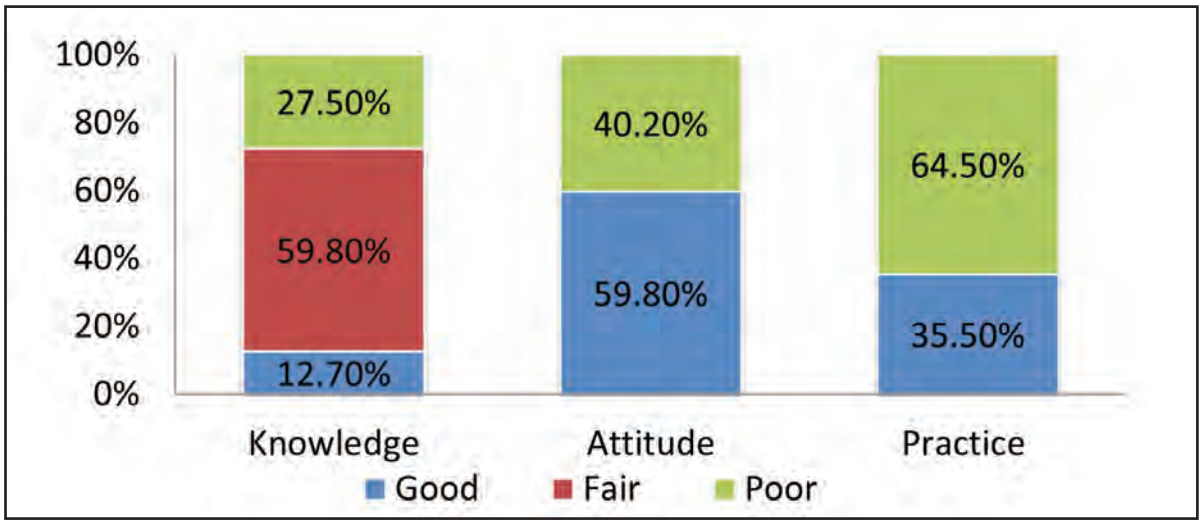

Fig. 1: Knowledge, attitude and practice scores of Orang Asli regarding non-communicable diseases (n = 251).

to have a positive significant association with income still. It is interesting to note that those who use a car to go to the clinic have better knowledge regarding NCDs compared to those who use motorcycles, and females have better practices than males at both the univariate and multivariable levels.

Comparison of the results in Tables II and III also shows that marital and employment status are only significantly associated with knowledge at the univariate level, while those who were married are found to significantly have better attitudes regarding NCDs compared to those who were single at the multivariable level.

DISCUSSION

Socio-Demographic Characteristics

In this study, participants were equally balanced by gender, unlike other studies, where more respondents were women.[7] This might be due to data collection visits in the evening when male respondents were back home after work. Most respondents attained only primary education and nearly a quarter had never received any formal education. Poverty and lack of social and family support might contribute to these circumstances, especially in older generations. Those with higher education were expected to have a better level of knowledge and attitude regarding NCDs. Several studies reported that the risk of developing NCDs was firmly related to the educational background.[7,10] The present study found that about three-quarters were self-employed with an income of less than RM 1000 per month and their occupations were mostly rubber tappers or palm fruit collectors. This finding is comparable to other studies in which most Orang Asli in Peninsular Malaysia live in poverty.[9,11] Although the national poverty rate of Malaysia has declined over the years, the Orang Asli community are still in the poverty group, hence contributing to inadequate self-support for healthy food and living. Poverty is a risk factor for chronic diseases and is prevalent among indigenous peoples worldwide.12 This insufficient income would make it difficult for Orang Asli to pay for their healthcare expenses.

The most common transportation utilised to the adjacent healthcare service centre was motorcycles (75.7%). This is due to low household income and unsuitable roads through their villages, which are mostly earthen roads (village roads). However, their transportation burden may be reduced following periodic services of mobile health clinics provided by the government.

Knowledge, Attitude and Practice Towards Non-Communicable Diseases

The results from this study reflect that the respondents generally have a fair knowledge of NCDs. Poor knowledge towards NCDs may result in a negative attitude, poor practices and ignorance of a healthy lifestyle. Another study exploring understanding diabetes disease among Orang Asli reported similar poor knowledge scores.[13] Nevertheless, more than half (59.8%) exhibited a positive attitude towards NCDs. For example, when asked in the questionnaire whether they 'will give extra attention to control chronic diseases effectively', 'will take preventive measures to reduce the risk of getting chronic diseases', or 'will receive treatment from a doctor for a chronic illness even if it is inconvenient', more than half of the respondents agreed with the statements.

In addition, this study revealed one-third (35.5%) had good practice. When asked in the questionnaire about 'steps that can be taken to reduce the risk of chronic disease', less than half of the participants chose reducing sugar intake, reducing salt intake or stopping smoking as their 'preferred and most preferred' practices. Most of them preferred to listen to family or friends for advice or take traditional medication. Nevertheless, the majority claimed they would get a health screening for NCDs as a preferred practice. This result is consistent with the finding from a previous study reporting a high percentage of good attitudes and a moderate practice level toward lifestyle-related NCDs among Orang Asli.[5]

Association Between Knowledge, Attitude and Practices Regarding Non-Communicable Diseases with Socio-Demographic Characteristics

This study found a positive significant association between the KAP regarding NCDs and the respondents' education level at both the univariate and multivariable levels, similar to a few other studies done among Orang Asli in rural Malaysia.[5,8,9] This result also correlates with the findings by Jaafar et al., which indicate that higher education leads to better health literacy.[14] The revised definition of health literacy by WHO is 'the achievement of a level of knowledge, personal skills and confidence to take action to improve personal and community health by changing personal lifestyles and living conditions.'[15] This indicates that health literacy not only limits the ability of someone to read health materials, but it is also critical to the empowerment of a person to take care of their health. Hence, better education can indirectly lead to better population health status.

On the other hand, this study also found that those with no family history of NCDs had lower KAP scores as compared to those with a positive family history of NCDs at both the univariate and multivariable levels. This is understandable because having someone with the disease in the family can familiarize the person with the condition.

Similar to the study by Ithnin et al., found that females have better practice regarding NCDs compared to males with the KAP regarding NCDs. They explained that females are less prone to smoking and consuming alcohol, hence the better practice scores.[5]

In this study, at the univariate level, the respondents with higher household incomes had significantly better KAP scores than those with lower household incomes. The lower incomes among the Orang Asli posed a severe financial limitation for acquiring knowledge practice on health-related diseases, including NCDs. The financial burden also makes them avoid modern medicine and opt for cheaper traditional medicine. Several international and local studies revealed that poverty will cause chronic disease burdens in the future as it leads to a lack of prevention and health-seeking behaviour.[3,13,16]

Limitations

Logistic issues and fear among the respondents about interacting with researchers during the COVID-19 pandemic were among the challenges faced in this study. Data was collected among the Orang Asli Semelai community using convenience sampling. Thus, the present results may not represent the entire Orang Asli population in Pahang. The study only disclosed the levels and association between the KAP toward NCDs with the socio-demographic data and did not report the cause-and-effect relationship between them.

CONCLUSION

This study provides a community-based picture of the Orang Asli community's knowledge, attitude and practices (KAP) regarding non-communicable diseases (NCDs). Although the Orang Asli community's knowledge of NCDs was found to be low, they have a decent attitude and moderate practice levels. KAP levels were significantly associated with education levels, household income, and the presence of a family history of NCDs. Hence, improving education and poverty in the Orang Asli community may successively increase the knowledge level, impart a positive attitude towards NCDs, and improve the practice level toward treatment and prevention.

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DISCLOSURE STATEMENT

No potential conflict of interest was reported by the authors.

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ORIGINAL ARTICLE

Evaluation of the relationship between the frequency of attention deficit, hyperactivity disorder symptoms and nutritional habits in children

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ABSTRACT

Introduction: Attention deficit and hyperactivity disorder (ADHD) is a common chronic neurodevelopment disorder characterised by inattention, hyperactivity and impulsivity at levels that are not compatible with age. ADHD is one of the high social and individual costs for the population of the country. In the present study, it was aimed to investigate the relationship between some sociodemographic characteristics, nutrition and sleep patterns, certain habits and various factors with ADHD in primary school children aged between 6 to 10 years.

Materials and Methods: In the study, a total of 600 children's parents were asked to fill in the Conners Parent Rating Scale – Short Form (CPRS-48), which consists of 48 questions. The questions in the scale are answered by the parents on a four-point Likert scale. The responses were scored as 0, 1, 2 and 3 for 'never', 'rarely', 'often' and 'always', respectively. It was accepted that the children who scored at least 18 for the behaviour problem subscale, at least five for the learning problem subscale, at least six for the aggression, hyperactivity subscale, and at least seven for the defying subscale were considered to be in the problematic category. In order to determine the eating habits of the children included in the study, their parents filled out the food consumption frequency form. Foods in the form of food consumption frequency are divided into two groups as healthy and unhealthy foods. Individuals were given scores between 0 and 6 according to the frequency of food consumption. The healthy food group and unhealthy food group scores were collected separately.

Results: Of the children included in the study, 312 (52%) were male, with a mean age of 8.24±1.30 (range: 6 10) years. The mean CPRS-48 score was 23.88±19.71. The Cronbach's Alpha value of the CPRS-48 scale, which consists of 48 questions in total, was obtained as 0.957.

The mean CPRS-48 score was significantly higher in boys (p = 0.014), in those whose mothers smoked during pregnancy (p = 0.008), those who did not receive breast feeding at birth or those who received less than 2 months (p = 0.035), those who frequently skipped meals (p < 0.001), those who do not have breakfast regularly (p = 0.002), those who spend more than four hours a day using a tablet/computer (p = 0.007), those who watch television more than 2 hours a day (p = 0.003), those who do not have regular sleep (p = 0.012), those who sleep less than 8t hours a night (p = 0.031), those who do not spend quality time with their families at least 2 days a week (p = 0.002) and those who do not have a hobby or sport that they were constantly interested in (p = 0.007).

Conclusion: The finding of the present study show that CPRS score in children is associated with some factors such as mother's habits in pregnancy, behaviours in having meals, daily habits and regular sleep. Although eating habits are a risk factor for ADHD, when the right eating habits are acquired, they can reduce the risk or symptoms of ADHD. However, more extensive and valid studies should be conducted to better explain this issue.

KEYWORDS:
Attention deficit and hyperactivity disorder, nutritional habits, child

INTRODUCTION

Attention deficit hyperactivity disorder (ADHD) is the most common neurobehavioural disorder of childhood. The main components of this disorder are; developmentally inappropriate attention levels, hyperactivity and impulsivity that result in functional impairment in one or more academic, social and emotional domains.[1] ADHD usually appears in early childhood and continues to manifest throughout life. Although the aetiology of ADHD is multifactorial, it is defined as a multifactorial disorder associated with various genetic, biological, environmental and psychosocial factors. Studies show that in addition to genetic factors, environmental factors also play an active role on ADHD.[2]

It has been shown in some studies that providing nutritional supplements (such as minerals, vitamins and omega-3 fatty acids) to children with ADHD reduces the symptoms of the disease. Zinc, iron and copper deficiency, which are used as cofactors in the production of noradrenaline and dopamine, are thought to be associated with the aetiology or symptoms of ADHD.[3] It is thought that the intake of food with a high glycaemic index may be associated with careless and hyperactive behaviours, and behavioural disorders may be

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caused by additives such as preservatives and food coloring.[4] ADHD has a high impact on the way individuals participate in activities of daily living. Studies show that it has a negative effect on behaviour. Affected areas include social skills, interpersonal relationships and educational success.[5] ADHD is a life-long disorder with behavioural problems, which, when ignored, causes increased risks of committing illegal acts or substance use and side costs. Therefore, it is a disease that is also important for the society.[6]

In the present study, it was aimed to investigate the relationship between some sociodemographic characteristics, nutrition and sleep patterns, certain habits and various factors with ADHD in primary school children aged between 6 to 10 years.

MATERIALS AND METHODS

The present study was carried out on 1st, 2nd, 3rd and 4th grade primary school students aged between 6 to 10 years those who admitted to Family Medicine clinics of our tertiary care hospital between April 2022 and June 2022. Sociodemographic and clinical data form, Conners Parent Rating Scale (CPRS-48), and food consumption frequency form were answered by the parents of the students included in the study. The present study was carried out in cross-sectional type. Ethics committee approval of the study was obtained with the protocol number 2022.39.03.07 dated 29 March 2022 of Tekirdag Namik Kemal University Faculty of Medicine Scientific Research Ethics Committee. Permission was obtained from the Tekirdag Governorship Provincial Directorate of National Education to carry out the study in primary schools affiliated to the Süleymanpasa District Directorate of National Education. Permission to use the scale was obtained from Cigdem Dereboy, who made the Turkish adaptation of CPRS-48. Informed consent form and parent consent form were read to the parents of the students included in the study and their consents were obtained. The questions in the study were prepared by the researchers as a result of the literature research.

In order to determine the eating habits of the children included in the study, their parents filled out the food consumption frequency form. Foods in the form of food consumption frequency are divided into two groups as healthy and unhealthy foods. In the healthy foods group, milk and dairy products, red and white meat, legumes, fresh vegetables and fruits, homemade desserts, cakes, pastries, pastries, fruit yoghurt, ice cream and freshly squeezed fruit juice; in the unhealthy foods group, ready-made breakfast cereals and spread chocolate, sausage and bacon, beef, turkey, chicken salami and sausage, confectionery, sweets bought from the patisserie, cake, cake, pastry, ready-made dessert, cake, cake, ice cream, flavoured milk, fruit juice; pudding, fruit yogurt, chocolate, biscuits, wafers, fast food-style foods, fries, chips and crackers, milkshakes and hot chocolate, carbonated drinks. Individuals were given scores between 0 and 6 according to the frequency of food consumption. The healthy food group and unhealthy food group scores were collected separately. The questionnaire included a total of 29 questions about healthy and unhealthy foods. Each question in this group was like 'How often does your child consume this food?' The responses were 'never', 'once a month or less frequently', '2 to 3 times a month', 'once a week', '3 to 4 times a week', 'once a day' and 'several times a day', and those responses were scored between 0 and 6 according to the frequency of food consumption. Then, all scores were summed and a total score of healthy food consumption frequency and a total score of unhealthy food consumption frequency were created.

Conners Rating Scales (CRS) are among the tools frequently used to evaluate behavioural disorders. Various forms of Child Behaviour Checklist (CBL) have been developed and presented under different headings by different researchers throughout the process until today. Among these scales, CPRS-48, published in 1978, was developed by Goyette et al. Developed by In CPRS-48, there are questions related to hyperactivity, learning and behaviour problems, as well as psychosomatic problems and anxiety. It was adapted into Turkish by Dereboy et al.[7] in 2007. CPRS-48 is a Likert-type scale consisting of 48 questions. The questions in the scale are answered by the parents on a four-point Likert scale. The responses were scored as 0, 1, 2 and 3 for 'never', 'rarely', 'often' and 'always', respectively. It was accepted that the children who scored at least 18 for the behaviour problem subscale, at least 5 for the learning problem subscale, at least 6 for the aggression, hyperactivity subscale, and at least 7 for the defying subscale were considered to be in the problematic category.

Collection of socio-demographic data was done using a questionnaire.

Inclusion Criteria

Children aged between 6 to 10 years, with no known diagnosis of psychiatric, genetic or neurological diseases, those with parents volunteering to participate in the study and children living with parents were included in the study.

Exclusion Criteria

Children under the age of 6 years or over the age of 10 years, whose parent's refuse to participate in the study, those with cognitive disability in them or in their parents were not included in the study.

Statistical Analysis

Data were transferred to IBM SPSS.23 (IBM Inc., Chicago, IL, USA) program and analysed with statistical analysis. Before proceeding with the analysis, it was checked whether there was an error in the way the data was entered and whether the variables were within the expected range. Mean and standard deviation values for continuous variables, number of people (n) and percentage (%) for categorical variables are given. Shapiro Wilk's test of normality and Levene's test for homogeneity of variance were applied to continuous variables. Pearson's correlation test was used for the relationship between continuous variables. The Mann Whitney-U test was used in the analysis of two-group variables with continuous variables, and the Kruskal-Wallis H test in the analysis of three or more grouped variables. A value of $p < 0.05$ was accepted as the level of significance in all analyses.

Table I: Distribution of some variables

Variables	n	%
Total	600	100
Gender		
Male	312	52
Female	288	48
Education level of the mother		
Primary school	97	16
Secondary school	82	13.6
High school	212	35
Bachelor's or higher	210	34.7
Number of children in the family		
1	157	26
2	330	54.5
3	84	13.9
4	23	3.8
Smoking in pregnancy		
Yes	91	15
No	505	83.5
Alcohol abusement in pregnancy		
Yes	5	0.8
No	593	98
Drug use in pregnancy		
Yes	103	17
No	494	81.7
Delivery type		
Normal vaginal delivery	191	31.6
Caesarean delivery	410	67.8
Week of delivery		
Before 37th gestational week (premature)	27	4.5
In 37th week (early term)	98	16.2
Between 38th-42nd week (term)	446	73.7
After 42nd week (postterm)	25	4.1
Duration of breast feeding		
Never	10	1.7
0-2 months	67	11.1
2-6 months	143	23.6
More than 6 months	380	62.8
Skipping meal		
No	157	26.25
Sometimes	360	60.2
Yes (frequently)	81	13.55
Number of meals a day		
1	8	1.34
2	114	19.06
3	442	73.91
≥4	34	5.69
Regular breakfast		
Yes	80	13.2
No	525	86.8
Taking nutritional supplements		
Yes	77	24.14
No	242	75.86

RESULTS

Of the children included in the study, 312 (52%) were male, with a mean age of 8.24±1.30 (range: 6 to 10) years. A total of 35% of the mothers graduated from high school, and 34.7% had bachelor's degree or higher. A total of 15% of the mothers had a history of smoking in pregnancy, and 67.8% underwent caesarean delivery. A total of 4.5% of the children were born before complete term (Table I).

The mean CPRS-48 score was 23.88±19.71. The Cronbach's Alpha value of the CPRS-48 scale, which consists of 48 questions in total, was obtained as 0.957. The mean scores of subscales of CPRS-48 have been shown on Table II. According to this, 4.7% of the children had lower score than the cut-off value in Behaviour Problem Subscale, 26% had lower scores in Aggression hyperactivity subscale, 29.8% had lower scores in Learning Problem subscale, and 34.5% of the children had lower scores than the cut-off value in Defying subscale (Table II).

The mean CPRS-48 score was significantly higher in boys ($p = 0.014$), in mothers who smoked during pregnancy ($p = 0.008$), in those who did not receive breast milk at birth or those who received less than two months ($p = 0.035$), in those

Table II: Data regarding CPRS-48 subscales

CPRS-48 subscales	Mean	SD	Cut-off value	Number of children under the cut-off value	
				n	%
Total score	23.88	19.71			
Behaviour Problem subscale	4.4	6.0	18	28	4.7
Aggression, Hyperactivity subscale	4.2	2.9	5	156	26.0
Learning Problem subscale	3.0	3.0	6	179	29.8
Defying subscale	5.6	4.0	7	207	34.5

Table III: Comparison of mean CPRS-48 scores according to some variables

Variables	n	%	CPRS-48 (mean±SD)	p
General	600	100	23.88±19.71	-
Gender				0.014*
Male	312	52	26.35±21.51	
Female	288	48	21.13±17.13	
Education level of the mother				0.269
Primary school or undergraduates	97	16	26.11±21.81	
Secondary school	82	13.6	21.74±21.01	
High school	212	35	24.67±18.94	
Bachelor's / Master / Doctorate	210	34.7	23.01±19.05	
Number of children in the family				0.07
1	157	26	25.46±21.05	
2	330	54.5	22.21±17.56	
3	84	13.9	28.88±23.99	
4	23	3.8	21.22±22.47	
Smoking in pregnancy				0.008*
Yes	91	15	29.13±20.41	
No	505	83.5	22.83±19.31	
Alcohol abusement in pregnancy				0.069
Yes	5	0.8	51.4±36.18	
No	593	98	23.64±19.33	
Drug use in pregnancy				0.19
Yes	103	17	26.70±21.20	
No	494	81.7	23.23±19.22	
Delivery type				0.684
Normal vaginal delivery	191	31.6	24.89±20.6	
Caesarean delivery	410	67.8	23.33±19.14	
Week of delivery				0.397
Before 37th gestational week (premature)	27	4.5	31.67±25.60	
In 37th week (early term)	98	16.2	22.32±17.00	
Between 38th-42nd week (term)	446	73.7	23.47±19.56	
After 42nd week (postterm)	25	4.1	25.72±20.74	
Duration of breast feeding				0.035*
Never	10	1.7	33.5±18.00	
0-2 months	67	11.1	27.97±19.72	
2-6 months	143	23.6	23.80±19.27	
More than 6 months	380	62.8	22.84±19.71	
Skipping meal				<0.001*
No	157	26.25	19.48±18.43	
Sometimes	360	60.2	23.47±18.86	
Yes (frequently)	81	13.55	33.79±22.03	
Number of meals a day				0.259
1	8	1.34	29.13±21.03	
2	114	19.06	25.51±17.91	
3	442	73.91	22.87±19.10	
≥4	34	5.69	27.94±25.86	
Regular breakfast				0.002*
Yes	80	13.2	22.88±18.97	
No	525	86.8	30.41±23.09	
Taking nutritional supplements				0.176
Yes	77	24.14	24.74±14.89	
No	242	75.86	25.96±23.49	

*p < 0.05. CPRS-48: Conners Parent Rating Scale – Short Form. SD: Standard deviation.

Table IV: Comparison of mean CPRS-48 scores according to certain habits and family history variables

	n	%	CPRS-48 (mean±SD)	p
Mean daily duration of tablet/computer usage				0.007*
<1 hours	109	18.51	23.80±21.46	
1-2 hours	239	40.58	21.96±19.66	
2-3 hours	165	28.01	23.97±18.50	
>4 hours	76	12.9	29.68±19.09	
Mean daily duration of watching TV				0.003*
<1 hours	242	40.54	23.29±19.32	
1-2 hours	262	43.89	21.38±16.83	
2-3 hours	75	12.56	30.91±24.73	
>4 hours	18	3.02	38.22±28.05	
Regular sleep				0.012*
Yes	485	80.8	22.85±19.34	
No	115	19.2	28.17±20.69	
Daily mean sleep time				0.031*
<6 hours	5	0.8	31.6±22.77	
6-8 hors	132	22	28.42±22.26	
8-10 hours	425	71	22.59±18.93	
>10 hors	37	6.2	21.0±16.30	
Spending quality time with the child at least 2 days a week				0.002*
Yes	493	82.72	22.45±18.55	
No	103	17.28	30.31±23.54	
The sport or hobby that the child is constantly interested in				0.007*
Present	100	16.5	23.31±20.02	
Absent	487	80.5	27.04±18.41	
Any diagnosed disease in mother				0.158
Present	86	23.3	27.97±21.06	
Absent	285	76.8	24.99±21.38	
Any diagnosed disease in father				0.139
Present	46	9.1	28.41±22.21	
Absent	446	90.9	25.02±21.24	
Mother's psychiatric disease other than ADHD				0.06
Present	9	2.4	31.11±13.82	
Absent	366	97.6	23.77±19.77	
ADHD in mother				0.959
Present	3	0.8	21.00±12.00	
Absent	372	99.2	23.89±19.76	
Father's psychiatric disease other than ADHD				0.06
Present	8	1.4	51.00±36.33	
Absent	563	98.6	23.77±19.48	
ADHD in the family other than the parents				0.104
Present	37	10.6	21.92±17.79	
Absent	312	93.7	25.55±21.10	

*p < 0.05. CPRS-48: Conners Parent Rating Scale – Short Form. SD: Standard deviation. ADHD: Attention deficit and hyperactivity disorder.

Table V: Mean scores of healthy and unhealthy food consumption questionnaire according to some variables

	Healthy food (mean±SD)	Unhealthy food (mean±SD)
General	32.58±11.24	26.03±10.31
Education level of the mother		
Primary school	36.30±12.66	24.92±9.84
Secondary school	32.28±11.92	26.66±11.03
High school	32.15±11.24	25.66±9.91
Bachelor's or higher	31.25±9.85	26.80±10.67
p	0.001*	0.193
Number of children in the family		
1	31.82±10.76	27.52±10.45
2	32.24±11.29	25.70±10.24
3	34.37±11.26	24.83±10.27
4	30.52±11.87	26.87±10.87
p	0.291	0.151
Regular breakfast		
Yes	30.95±13.20	24.67±8.96
No	32.83±10.91	26.24±10.49
p	0.202	0.204

*p < 0.05. SD: Standard deviation.

who frequently skipped meals ($p < 0.001$) and in those who did not have breakfast regularly ($p = 0.002$) compared to the other groups (Table III).

Of the children, 12.9% spent more than 4 hours a day in front of a tablet/computer and 3% in front of the television, 485 (80.8%) had regular sleep, 493 (82.72%) spent quality time with their families at least 2 days a week (Table IV).

The mean CPRS-48 score was found in those who spend more than 4 hours a day in front of a tablet/computer ($p = 0.007$), those watch television more than two hours a day ($p = 0.003$), those do not have regular sleep ($p = 0.012$), those with mean daily sleep time less than 8 hours ($p = 0,031$). It was found to be significantly higher in those who do not spend quality time with their families at least two days a week ($p = 0.002$) and those who do not have a hobby or sport that they are constantly interested in ($p = 0.007$) compared to the other groups (Table V).
The mean of food consumption frequency (FCF) score in children was 58.52±14.95; the mean healthy FCF score was 32.58±11.24; the mean unhealthy FCF score was found to be 26.03±10.31. The mean healthy FCF score of children whose mothers' education level was primary school or undergraduates was significantly higher than those whose mothers had a higher education level ($p = 0.001$) (Table V).

A significant inverse correlation was found between the healthy FCF score and the CPRS-48 score ($p = 0.024$; $r = -0.092$). There was no significant correlation between unhealthy FCF score and CPRS-48 score ($p=0.224$; $r=0.05$).

DISCUSSION

ADHD is a common chronic neurodevelopmental disorder characterised by inattention, hyperactivity, and impulsivity at levels that are not compatible with age. ADHD is typically believed to begin in early childhood, but the diagnosis is often made at school age. Current studies in Turkey report that the prevalence of ADHD in school-age children is approximately 13%.[1,2,8]

The prevalence of ADHD was found to be more common in boys than in girls.[8] In the present study, the mean CPRS-48 score of boys was found to be significantly higher than that of girls. Our study is compatible with the literature in terms of this finding. This data showed us that we need to be more careful in terms of ADHD in boys.

A total of 91 (15%) of the mothers stated that they used cigarettes or hookahs during pregnancy. Prenatal smoking exposure has been associated with ADHD in a number of epidemiological studies. In two meta-analysis studies, it was shown that the mother's smoking during pregnancy increased the risk of ADHD in the child.[9,10] In the present study, in accordance with the literature, the mean CPRS-48 score of the children of mothers who used cigarettes or hookahs during pregnancy was found to be statistically significantly higher than the mean CPRS-48 score of the children of mothers who did not. These data we obtained indicating that smoking during pregnancy increases the risk of ADHD is very important in terms of reducing the incidence of ADHD.

Only five (0.8%) of the mothers stated that they used alcohol during pregnancy. It has been shown that there is a positive relationship between maternal alcohol use during pregnancy and ADHD symptoms in children. In a prospective Danish birth cohort study of 1628 mothers and children, no association was found between ADHD symptoms in children and alcohol use during pregnancy when mothers who abstained from alcohol were compared with mothers who consumed low to moderate levels of alcohol. In another study, when the children of mothers who did not drink alcohol were compared with the children of mothers who consumed more than eight alcohol per week, a weak correlation was found between alcohol consumption during pregnancy and ADHD in children.11 In the present study, it was observed that the mean CPRS-48 score did not show a statistically significant difference compared to alcohol use during pregnancy. The reason why we reached such a result in the present study may be that almost none of the mothers participating in the study stated that they used alcohol during pregnancy, and that did not cause a statistically significant difference.

A total of 4.5% of the children were born preterm, 73.7% were born term and 4.1% were born postterm. Cak et al[12] found that children diagnosed with ADHD had shorter week of delivery and lower birth weights. In a meta-analysis study, when the cognitive status of preterm children was evaluated, it was reported that preterm new borns showed ADHD symptoms more than twice as often as the term ones. In the present study, it was found that the mean CPRS-48 score did not show a significant difference according to the week of delivery. The statistically insignificance might be due to the low number of preterm children.

Breast milk contains nutrients that have positive effects for the development of intelligence, such as peptides and essential long-chain fatty acids (LFA). It has been reported that there is a relationship between LFA intake and intelligence development in infants. When the intelligence development of babies who are breastfed and fed with formula that does not contain LFA, it has been reported that the intelligence scores of children who are breastfed are higher.[13,14] When the literature is examined, the results of studies on the duration of breastfeeding in children and ADHD are controversial. In a study by Ptacek et al[15], children with ADHD and controls were compared when breastfeeding duration was less than 3 months, and no significant difference was found between breastfeeding rates. However, when focusing on breastfeeding durations over 6 months, the rate of breastfeeding was found to be higher in controls compared to children with ADHD in the same study. In the study by Field.[16] breastfeeding only reduced the risk of ADHD in the absence of parental psychopathology, but posed a risk for ADHD if the mother had a history of psychopathology. In a meta-analysis of four studies that revealed the difference between the duration of breastfeeding in children with ADHD and the control group without ADHD, it was shown that the duration of breastfeeding in children with ADHD was shorter than in controls.[17] In the present study, it was found that the mean CPRS-48 scores of those who were breastfed for 0 to 2 months were statistically significantly higher than those who were fed for more than 6 months. Considering that breast milk intake affects the cognitive development of children, the

result of the present study is compatible with the general literature and with this important finding, it has once again demonstrated the importance of breastfeeding.

The status of skipping meals was questioned in order to determine the food consumption habits of children. In the study conducted by Kim et al[18], no significant difference was found between the food consumption habits of the normal and ADHD groups.[18] In the present study, the mean CPRS-48 score was determined by those who skip meals frequently, those who skip meals sometimes, and those who never skip; those who skip sometimes were found to be significantly higher than those who did not skip at all. This data we obtained showed us that children's skipping meals may pose a risk for ADHD. In this respect, it is a valuable finding.

Of all the meals of the day, breakfast has the highest dietary quality, but the frequency of having breakfast has decreased in recent years, according to studies. This has the potential to negatively affect cognitive function, and past studies have shown a positive association between breakfast consumption and cognitive function. It has been proven that eating breakfast regularly is associated with better cognitive performance and academic achievement.[19] In the present study, when the mean CPRS-48 scores of those who regularly eat breakfast and those who do not, were found to be significantly lower than those who did not. This finding shows us once again that breakfast is important for children's cognitive development.

A meta-analysis of studies on children's television viewing time revealed that electronic media use is particularly associated with ADHD's attention deficit symptoms. It is thought that the use of electronic media, especially in the first years of life, may have significant negative effects on the development of the child.[20] In the present study, in accordance with the literature findings, the mean CPRS-48 score of those who spend more than 4 hours a day in front of a computer/tablet was found to be significantly higher than those who spend between 1 and 2 hours and less than 1 hour. The mean CPRS-48 score of the children who watched television for 1 to 2 hours a day on mean was found to be significantly lower than those who watched television for a mean of 2 to 3 hours. Our finding is very important as it shows that limiting screen time in children reduces the risk of ADHD.

Sleeping difficulties often coexist with ADHD. About 25 to 50% of children and adolescents with ADHD also report sleep disturbances. Despite the high comorbidity between sleep disorders and ADHD, it is unclear whether sleep disturbance is a cause, consequence or comorbid problem associated with such disorders. Studies have examined the complex situation of the relationship between sleep disorders and ADHD, and it has been stated that there is a two-way relationship between them. It has been determined that sleep-related pathologies contribute to the increase in ADHD symptoms and ADHD causes worsening of sleep.[17-21] Gruber et al[21] evaluated the effect of cumulative sleep deprivation on the neurobehavioral functioning of both healthy developing children and children with ADHD. It has been found that sleep deprivation leads to a significant decrease in performance in the continuous performance task, which is a neurobehavioral task that requires constant attention and behavioural control, which is widely used in the assessment of inattention and impulsivity in children with ADHD.[22] The mean CPRS-48 score of the children who regularly sleep at night was found to be significantly lower than those of the others, and the mean score of those who slept an mean of 6 to 8 hours a day was found to be significantly higher than that of those who slept for 8 to 10 hours. More studies are needed to clearly determine the relationship between sleep and ADHD, but our result is very important as it finds a relationship between sleep duration and ADHD risk.

In the study of DuPaul et al, it was found that the parent-child relationship was problematic in families with a child with ADHD, and the stress level was higher than normal.[23] The mean CPRS-48 score of children who spend quality time with their parents at least 2 days a week was found to be significantly lower than that of other children. This result showed us that quality time spent with parents is important in reducing the risk of ADHD.

In the study conducted by Kim et al18, there was evidence that children with ADHD were less likely to participate in physical activity and organised sports compared to those without ADHD. The mean CPRS-48 score of children who are regularly involved in sports or hobbies was found to be significantly lower than those who did not have sports or hobbies. These data showing that regular exercise and hobbies reduce the risk of ADHD in children is very important.

Studies on the relationship between family history, twinning, and ADHD have shown that genetics play a strong role in the aetiology of ADHD. In a study, the risk of developing ADHD in first-degree relatives of people with ADHD is 2 to 8 times higher than relatives of healthy people. Twin studies in many different countries have shown high heritability rates of around 71 to 90% for ADHD.[24-26] Psychiatric pathologies in the family, especially in the mother, are stated to be more common in families with ADH.[27] In the present study, it was observed that the mean CPRS-48 score of the children did not show a significant difference according to the presence of ADHD in the family members other than the parents, and the mean CPRS-48 score did not differ statistically according to the presence of a psychiatric disease other than ADHD in the parents. It can be thought that the reason for these findings in the present study was that the reporting of psychiatric illness in parents and non-parent family members was less stated because it was dependent on the parents who answered the questions.

While the majority of children in the present study did not have a nutritional supplement that they used regularly, 32 (10.03%) of them were using omega-3 and 24 (7.53%) of them were using multivitamin supplements. When the literature is examined, it has been suggested that minerals such as zinc, iron and magnesium play a role in the pathogenesis of ADHD, and therefore it is thought that the supplementation of these minerals may be beneficial in the treatment of ADHD.[28,29] Studies in humans also show that omega-3 fatty acid deficiency causes an imbalance in the

omega-3/omega-6 PUFA ratio, thus affecting neurocognitive abilities and inducing behavioural disorders including ADHD.[30] In the present study, it was found that there was no significant difference when the mean CPRS-48 scores were compared according to whether or not children took nutritional supplements. This may be due to the fact that a low number of children included in the present study were using nutritional supplements.

It has been shown that 12% of children with ADHD use complementary or alternative medicines, including dietary supplements. Concerns about the adverse effects of pharmacotherapy have spurred research on alternative treatment strategies, including the use of dietary supplements, and the role of nutrition and nutritional supplements in the aetiopathophysiology and treatment of ADHD has become central to research. For example, ADHD has been associated with a Western-style diet high in fat and refined sugars and low in omega-3 fatty acids (omega-3 PUFAs) and fibre. It has been suggested that minerals such as iron, zinc and magnesium also play a role in ADHD pathology, and it is thought that supplementation of these minerals may be beneficial in the treatment of ADHD.[28-31] A recent case-control study evaluated the possible association between dietary patterns and ADHD risk. In the study, it was shown that there is a negative relationship between the fish and white meat diet model and the risk of ADHD. It has been said that a protein diet pattern rich in minerals such as protein and zinc is also inversely related to the risk of ADHD.[30,31] Although parents report an increase in hyperactive behaviour in their children after high intakes of foods such as candy or sugary drinks, studies cannot prove a significant negative effect of sucrose.[31] In a study conducted on adolescents with a 14-year follow-up, the relationship between dietary habits and ADHD was investigated. And two major diets have been identified: 'Western' and 'Healthy'. The higher the mean score, the higher the Western diet was associated with the diagnosis of ADHD. However, the diagnosis of ADHD was not found to be related to 'healthy' eating habits. This study shows us that a Western-style diet may be one of the risk factors for ADHD.[32] In the present study, no significant relationship was found in the correlation analysis of the mean frequency of unhealthy food consumption and the mean CPRS-48 score. When the correlation analysis of the mean healthy food consumption frequency score and the mean CPRS-48 score was made, a negative very weak statistically significant relationship was observed. More detailed and large-scale studies are needed to reveal the relationship of ADHD, whose incidence is increasing and the benefits of nutritional models in reducing its symptoms, are seen with food consumption habits.

In the questionnaire, there were several questions regarding healthy and unhealthy food consumption applied to the mothers of the participants. Each question in this group was like 'How often does your child consume this food?' for each kind of food. The responses were 'never', 'never', 'once a month or less frequently', '3 to 4 times a month', 'once a week', '3 to 4 times a week', 'once a day' and 'several times a day', and those responses were scored between 0 and 6 according to the frequency of food consumption. Then we summed all scores dividing the food into healthy and unhealthy groups. In this way, we prepared a survey that can be evaluated objectively, instead of asking mothers a general and subjective question about whether their children have a healthy or unhealthy diet in general. In addition, we asked mothers a total of 29 groups of foods without commenting on whether they were healthy or unhealthy, and thus we aimed to prevent the mothers' subjective opinions about whether that food was healthy or not from affecting the survey results. Furthermore, we asked mothers about these high numbers of food groups separately and scored them separately, thus creating a very detailed mapping of the child's food consumption. Thanks to this entire methodology, we have enabled children's food habits to be compared objectively and statistically with other factors. As a result of this entire application, we could not find a significant relationship between the child's CPRS-48 score, which indicates the child's hyperactivity status, and the child's 'unhealthy' food consumption score, but we found a weak, significant but inverse relationship between the CPRS-48 score and the 'healthy' food consumption score. All these findings indicate that there may be an inverse relationship between hyperactivity and healthy food consumption in children. However, this weak significance despite our large number of participants and the statistical insignificance in the analysis with unhealthy foods show that hyperactivity does not directly affect children's consumption of healthy or unhealthy food or is not the main factor affecting this consumption. From this perspective, for example, forcing children to eat foods that are offered to them by their parents may be a restrictive factor in terms of children's ability to choose food freely. These and similar factors may have limited the direct impact of children's hyperactivity levels on healthy or unhealthy food consumption.

It is known that the knowledge level of mothers about nutrition affects the nutritional habits of children.[33] Williams et al[33] drew attention to the effect of the knowledge level of mothers with low socio-economic status on their children's eating habits. In the present study, the mean of healthy food consumption frequency of children mothers' education level was primary school or undergraduates. When the mean scores of children's unhealthy food consumption frequency were compared according to the education level of the mother, there was no significant difference. More detailed studies are needed to better elucidate this issue.

There were some limitations in the present study. Since the study was based only on a questionnaire, the data were based only on the statements of the mother or father. In addition, variables such as the number of children in the family or the educational status of the parents may have affected the observation of children. The number of participants was kept high so that these situations do not cause statistical errors.

The findings of the present study show that the level of attention deficit and hyperactivity disorder in children is higher in males, in those whose mothers smoked during pregnancy, in those who did not receive breast milk at birth or in those who received it for less than 2 months, in those with disordered eating and sleep patterns, in those who spend a lot of time in front of a tablet/computer and television and with their families. Studies showed that it was higher in those who did not spend quality time for a long time.

CONCLUSION

The finding of the present study show that CPRS score in children is associated with some factors such as mother's habits in pregnancy, behaviours in having meals, daily habits and regular sleep. Although eating habits are a risk factor for ADHD, when the right eating habits are acquired, they can reduce the risk or symptoms of ADHD. However

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Comparison of outcomes in epithelial ovarian cancer, fallopian tube cancer and primary peritoneal serous carcinoma between a multidisciplinary and a single-speciality centre

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ABSTRACT

Introduction: Epithelial ovarian cancer (EOC) is the fourth most common malignancy among Malaysian women. This study aims to evaluate the outcomes of EOC, fallopian tube cancer and primary peritoneal serous carcinoma (PPSC) between a centre managed by both clinical oncologists and gynaecologic oncologists, Institut Kanser Negara (IKN) and a centre managed solely by gynaecologic oncologists, Hospital Ampang (HA).

Materials and Methods: This retrospective cohort study involved data review of all the newly diagnosed patients with EOC, fallopian tube cancer and PPSC who received treatment in IKN and HA from January 2015 to December 2019, with follow-up continuing until December 2022. The primary outcome is overall survival (OS) and the secondary outcome is progression free survival (PFS) rates; estimated using the Kaplan-Meier method and compared using the log-rank test. Another secondary outcome is to determine the prognostic factors affecting the OS of patients from these two cohorts using Cox regression analysis.

Results: A total of 256 patients from both centres were recruited (106 and 150 patients from IKN and HA respectively) and at the time of diagnosis, more than half of the patients were diagnosed with advanced stage disease (67.5% and 62% from IKN and HA respectively). The median OS for patients with EOC was significantly longer for HA compared to IKN (69 months vs 39 months, p < 0.042). There was no significant difference in the median PFS for both centres. Furthermore, when the comparison was made based on the disease staging, there was no difference in the median OS and median PFS. Multivariate analysis identified that patients aged between 41 and 60 years (Hazard ratio [HR]: 2.83; 95% CI: 1.11, 7.25, p = 0.030), patients with medical illness (HR 1.51; 95% CI: 1.04, 2.21, p = 0.033), patients with advanced-stage disease (HR: 3.63; 95% CI: 2.20, 6.00, p < 0.001) and patients with ECOG ≥ 1 (HR: 2.00; 95%CI: 1.38, 2.91, p < 0.001) as independent risk factors for adverse outcome. Meanwhile, optimal surgery is found to be a protective factor (HR 0.60; 95% CI: 0.41, 0.89, p = 0.011). Patients with optimal surgery had reduced the risk of adverse outcome.

Conclusion: Our findings confirmed that the median OS was significantly longer for patients with EOC in HA compared to IKN. However, there was no significant difference in the median OS based on the disease staging; therefore, we could not establish the non-inferiority outcome between the two centres. Furthermore, there was no significant difference in median PFS for both centres. This could be due to small sample size to be able to detect any difference. In addition, it could also be contributed by the different treatment options available and unequal volume of patients treated in both centres. Thus, further study with larger sample size and longer time period is needed to provide better guidance and treatments for the patients.

KEYWORDS:
Epithelial ovarian cancer, fallopian tube cancer, primary peritoneal serous carcinoma, clinical oncologist, gynaecologic oncologist

INTRODUCTION

Epithelial cancers of the ovary and fallopian tube, as well as primary peritoneal serous carcinoma (PPSC) have been shown to share similar clinical characteristics and behaviour. Therefore, they are frequently combined together and defined as epithelial ovarian cancer (EOC) in clinical trials and clinical practice.[1]

According to Malaysia national cancer registry, ovarian cancer is ranked as the fourth most common cancer among women in Malaysia, accounting for 5.6% of all female cancer cases; and among these patients, more than half (56.3%) were detected at an advanced stage (III and IV).[2] However, the registry report does not provide any information on the survival outcome of these patients. From the literature review, there is no published data or information available regarding the treatment outcome for patients with EOC in Malaysia. Currently in Malaysia, patients with EOC are being treated either by both clinical oncologists and gynaecologic oncologists or solely by gynaecologic oncologists, based on the services available at the respective centres (both in government and private centres).

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At the present moment, oncology services in government hospitals are mainly based in a number of state hospitals and university hospitals whilst gynaecologic oncology services are more widely available in all states and most major hospitals (including university hospitals).

This study is designed to evaluate the outcomes of EOC, fallopian tube cancer and PPSC between a centre managed by both clinical oncologists and gynaecologic oncologists, Institut Kanser Negara (IKN) versus a centre managed solely by gynaecologic oncologists, Hospital Ampang (HA).

The primary endpoint of this study is to compare the overall survival (OS) between the two centres (OS is calculated from the date of treatment initiation by the clinicians to the time of death from any cause). The secondary endpoints are to compare the progression-free survival (PFS) as calculated from date of treatment initiation by the clinicians to the time clinically defined disease progression or death from any cause, whichever occurred first; and to determine the prognostic factors affecting the OS of patients with EOC from these two cohorts.

The hypothesis of this study is that there is no difference in the outcome of EOC patients treated in both centres despite having different management structures. If the hypothesis is supported by the study findings, it could potentially streamline the patient care by allowing flexibility in choosing treatment centres based on factors such as accessibility or patient preference without compromising the clinical outcomes.

MATERIALS AND METHODS

Approval from the Medical Research and Ethics Committee (MREC) was obtained prior to the commencement of this study (NMRR ID-22-02823-XFS).

Study Design and Participants

This retrospective cohort study involved data review of all the newly diagnosed patients with EOC, fallopian tube cancer and PPSC who received treatment in IKN and HA from January 2015 to December 2019, with follow-up continuing until December 2022.

The eligible patients were aged 18 and older with newly diagnosed (histologically confirmed) EOC, fallopian tube cancer and PPSC that underwent surgical procedures, received chemotherapy and continued follow up in IKN and HA from the aforementioned dates. Exclusion criteria encompassed patients with borderline ovarian tumour, non-epithelial ovarian cancer, synchronous tumour or more than one primary cancer and those who did not complete the initial treatment (surgery with or without chemotherapy) at the respective centres.

Statistical Analyses

Continuous variables are expressed as mean ± standard deviations or as medians ± interquartile ranges (IQR) following normality testing, whereas categorical variables are presented as frequencies and percentages. Data were analysed using IBM SPSS statistics version 26. Survival was estimated using the Kaplan-Meier method and was compared using the log-rank test (for both OS and PFS). Statistical significance was set at two-sided $p < 0.05$. Cox proportional hazards models were used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs). The independent effects of the clinical prognostic factors on overall survival were analysed in multivariate Cox regression analysis.

RESULTS

Patient Demographics

Patient demographic characteristics are described in Table I. A total of 404 patient data records were reviewed (186 and 218 patients from IKN and HA, respectively) and 256 patients met the selection criteria (106 and 150 patients from IKN and HA, respectively) aged 21 to 84 years (mean 54.2 ± 11.7). The performance status was classified based on the Eastern Cooperative Oncology Group (ECOG) score, and the majority of the patients had ECOG 0 (59.4% from IKN and 72.7% from HA). One patient had ECOG score 2 from HA and for IKN, one patient had ECOG score 2 and one patient had ECOG score 3. Among all the patients, 53.8% from IKN and 47.3% from HA were recorded to have medical illness.

EOC is further subclassified into high-grade serous carcinoma (HGSC), low-grade serous carcinoma (LGSC), endometrioid, clear cell, mucinous, mixed carcinoma, undifferentiated and dedifferentiated carcinoma. HGSC comprises the highest number of histological subtypes in both centres (43.4% and 54% from IKN and HA respectively). For HGSC, the ovary was the most common site of origin. All patients were staged based on 2014 FIGO staging classification and at the time of diagnosis, more than half of the patients were diagnosed with advanced stage disease (67.5% and 62% from IKN and HA, respectively). The median follow-up period was 39 months (IQR 46.5) for IKN and 46 months (IQR 40.5) for HA. Patients' status at last follow-up is also included in Table I. For patients who have defaulted, their status (alive or dead) was confirmed via phone or through National Registration Department.

The surgery type and treatment regime received by patients are depicted in Table II. All patients had undergone some form of surgery, the majority of them having had a total abdominal hysterectomy with bilateral salphingo-opherectomy (TAHBSO), omentectomy with or without pelvic and/or para-aortic lymphadenectomy (PL/PAL) and also with or without tumour debulking (88.7% and 87.4% from IKN and HA, respectively). A small number of patients opted for fertility sparing surgery i.e., unilateral salphingo-opherectomy and omentectomy, with or without PL/PAL (8.5% and 9.3% from IKN and HA, respectively). About 72.6% patients from IKN and 80% patients from HA had optimal surgery (defined as residual disease of less than 1 cm).

More than 80.0% patients from both centres received first line chemotherapy either as neoadjuvant or adjuvant treatment. For patients with early-stage disease, 74.4% patients from IKN and 75.4% patients from HA, received adjuvant chemotherapy. For patients with advanced disease, 32.8% patients from IKN and 57.0% patients from HA received neoadjuvant chemotherapy prior to surgical treatment, while

Table I: Demographic, clinicopathologic, and patients' outcome characteristics for the entire patient cohorts and separately for Institut Kanser Negara versus Hospital Ampang

Characteristics	All patients, (n = 256) n (%)	IKN (n = 106) n (%)	HA (n = 256) n (%)	p-value
Age, mean (SD)	54.2 (11.7)	52.9 (11.1)	55.1 (12.0)	0.130[a]
ECOG score				
0	172 (67.2)	63 (59.4)	109 (72.7)	0.026
≥ 1	84 (32.8)	43 (40.6)	41 (27.3)	
Medical illness				
Yes	128 (50.0)	57 (53.8)	71 (47.3)	0.310
No	128 (50.0)	49 (46.2)	79 (52.7)	
Histology				
HGSC	127 (49.6)	46 (43.4)	81 (54.0)	0.076[b]
LGSC	6 (2.3)	4 (3.8)	2 (1.3)	
Endometrioid	33 (12.9)	12 (11.3)	21 (14.0)	
Clear cell	59 (23.0)	27 (25.5)	32 (21.3)	
Mucinous	25 (9.)	12 (11.3)	13 (8.7)	
Mixed carcinoma	4 (1.6)	4 (3.8)	0 (0.0)	
Undifferentiated	1 (0.4)	1 (0.9)	0 (0.0)	
Dedifferentiated	1 (0.4)	0 (0.0)	1 (0.7)	
HGSC -organ**, n = 127		n = 46	n = 81	
Ovary	98 (77.2)	35 (76.0)	63 (77.8)	0.005
Fallopian tube	15 (11.8)	8 (17.5)	7 (8.6)	
PPSC	14 (11.0)	3 (6.5)	11 (13.6)	
FIGO staging				
Early				0.485
Stage 1A	16 (6.3)	6 (5.7)	10 (6.7)	
Stage 1C	58 (22.7)	25 (23.6)	33 (22.0)	
Stage 2	21 (8.2)	7 (6.6)	14 (9.3)	
Advanced				
Stage 3	126 (49.2)	49 (46.2)	77 (51.3)	
Stage 4	35 (13.7)	19 (17.9)	16 (10.7)	
Status at last follow-up				
Died	130 (50.8)	61 (57.5)	69 (46.0)	0.132[b]
Alive	95 (37.1)	37 (34.9)	58 (38.7)	
Defaulted	28 (10.9)	8 (7.5)	20 (13.3)	
Unknown	3 (1.2)	0 (0.0)	3 (2.0)	
Follow up time (months)				
Overall, mean (SD)	42.1 (24.7)			
Median (interquartile range)		39.0 (46.5)	46.0 (40.5)	0.100[c]

Values are presented as number (percentage) unless otherwise indicated; SD: standard deviation; n: patient number; HA: Hospital Ampang, IKN: InstitutKanser Negara, ECOG: Eastern Cooperative Oncology Group, HGSC: High grade serous carcinoma, LGSC: Low grade serous carcinoma, PPSC: Primary peritoneal serous carcinoma; aIndependent t-test; b Fisher's exact test; otherwise by Pearson Chi-square test; cMann-Whitney test; **Denominator is the total no of patients in the subgroup; Bold P-values indicate statistically significant.

the remaining patients with advanced disease received adjuvant chemotherapy after primary surgery were 50.8% and 38.7% from IKN and HA, respectively. The majority of patients received platinum-based doublet (i.e., carboplatin and paclitaxel) as the first line chemotherapy. After primary surgery, the average time for patients to receive the first dose of adjuvant chemotherapy was 5 weeks and 8 weeks for HA and IKN, respectively.

About 68.9% and 61.3% patients had recurrent disease or disease progression from IKN and HA, respectively. The treatment following the events for these patients were determined by the assessment and discretion of the attending doctors, after which the majority of the patients received chemotherapy (61.6% and 78.2% from IKN and HA, respectively). The type and course of chemotherapy received by patients were determined by multiple factors, which include the duration from the previous line of chemotherapy (platinum sensitivity), side effects from previous chemotherapy exposure, clinical symptoms and performance status. The drugs used include single agent regime such as carboplatin, gemcitabine, pegylated liposomal doxorubicin (Caelyx) or double agents regime such as carboplatin/paclitaxel, carboplatin/gemcitabine, carboplatin/Caelyx and cisplatin/paclitaxel. Other treatment modalities offered to a small number of patients with recurrent or progressive disease include secondary surgery, poly ADP-ribose polymerase inhibitors (PARP-i), radiotherapy (for metastatic extra abdominal disease such as the brain, spine, thorax etc) and transarterial chemoembolisation (TACE). Another additional treatment received patients with advanced disease in HA (10%) was bevacizumab (BEV) which was used in combination with chemotherapy and continued as maintenance therapy in the first line setting or recurrent disease.

Survival Outcomes

The Kaplan-Meier curves depicting median OS and median PFS between IKN and HA are illustrated in Figure 1. The comparison was made between all patients, early stage and

Table II: Surgery and treatment regime for Institut Kanser Negara versus Hospital Ampang

Characteristics		IKN (n = 106) n (%)	HA (n = 150) n (%)	p-value
Surgery type				
TAHBSO, Omentectomy +/- PL/PAL, tumour debulking		94 (88.7)	131 (87.4)	0.864
SO, omentectomy +/- PL/PAL		9 (8.5)	14 (9.3)	
Completion surgery, omentectomy +/- PL/PAL		2 (1.9)	5 (3.3)	
Laparotomy and biopsy		1 (0.9)	0 (0.0)	
Surgery outcome				
Optimal		77 (72.6)	120 (80.0)	0.168
Suboptimal		29 (27.4)	30 (20.0)	
Chemotherapy regime				
Early stage **, n = 95		n = 38	n = 57	
Adjuvant	NA	6 (15.4)	9 (15.8)	0.954b
	Yes	29 (74.4)	43 (75.4)	
	Refused	4 (10.3)	5 (8.8)	
Advanced stage		n = 68	n = 93	
Neoadjuvant**, n = 77		25 (36.8)	52 (55.9)	0.006
Adjuvant**, n = 84				
	Yes	34 (50.0)	36 (38.7)	
	Refused	7 (10.3)	4 (4.3)	
	Other****	2 (2.9)	1 (1.1)	
Type of chemotherapy**, n = 217		n = 86	n = 131	
Carboplatin		19 (22.1)	18 (13.7)	0.110
Carboplatin + Paclitaxel		67 (77.9)	113 (86.3)	
Recurrent/disease progression**		n = 73	n = 92	
2nd line***		45 (61.6)	72 (78.3)	Nilc
3rd line***		24 (32.9)	27 (29.3)	
4th line or higher***		11 (15.1)	14 (15.2)	
Secondary surgery***		1 (1.4)	14 (15.2)	
Yes**		n =1	n = 14	
Optimal		1 (100.0)	11 (78.6)	> 0.950b
Suboptimal		0 (0.0)	3 (21.4)	
Other treatment				
PARP-I, n = 9		0 (0.0)	9 (6.0)	Nilc
Radiotherapy, n = 8		3 (2.8)	5 (3.3)	
TACE, n = 1		1(0.9)	0 (0.0)	
BEV, n = 15		0 (0.0)	15 (10.0)	

HA: Hospital Ampang, IKN: Institut Kanser Negara ; TAHBSO: Total abdominal hysterectomy bilateral salpingo-oophorectomy, SO: salpingo-oophorectomy, PL: pelvic lymphadenectomy; PAL: para-aortic lymphadenectomy, NA: Not applicable, PARP-i: PARP inhibitor, BEV: Bevacizumab, TACE: Transarterialchemoembolisation; n: patient number; a Independent t-test; b Fisher's exact test; otherwise by Pearson Chi-square test;cNot comparing for the differences; **Denominator is the total no of patients in the subgroup; ***Total number is different as the same patient might go for subsequent line of therapy; Patient number and percentages based on total number of cases for recurrent disease in both centres; ****Patients died before the initiation of chemotherapy; Bold P-values indicate statistically significant.

advanced stage diseases from each centre. The median OS for all patients was significantly longer for HA compared to IKN (69 months vs 39 months, $p < 0.042$) (Figure 1(A) and Table III). However, when the comparison was made according to the stage of disease, there was no significant difference of median OS between these two centres (Figure 1 (B, C) and Table III). For the median PFS, there were no significant difference between IKN and HA for all patients and for disease staging as presented in Figure 1(D-F) and Table III.

Prognostic Factors

Table IV depicted the prognostic factors for OS of all patients with EOC from the two cohorts using univariate and multivariate Cox regression analyses. During the multivariate analysis, all except, neoadjuvant chemotherapy variables, were significant in predicting the OS in this study. Patients aged between 41 and 60 years old had 2.8 times higher risk of dying compared to age ≤ 40 years old (HR: 2.83; 95% CI: 1.11, 7.25, $p = 0.030$), patients with medical illness had 51% higher risk of dying compared to those without medical illness (HR 1.51; 95% CI: 1.04, 2.21, $p = 0.033$), patients with advanced-stage disease had 3.6 times higher risk of dying compared to those with early-stage disease (HR: 3.63; 95% CI: 2.20, 6.00, $p < 0.001$) and patients with ECOG ≥ 1 had 2 times higher risk of dying compare to those with ECOG = 0 (HR: 2.00; 95% CI: 1.38, 2.91, $p < 0.001$). Meanwhile, optimal surgery is found to be a protective factor as patients with optimal surgery had reduced risk of dying by 40% compared to those with suboptimal surgery (HR 0.60; 95% CI: 0.41, 0.89, $p = 0.011$)

DISCUSSION

Hospital Ampang and IKN are both government hospitals which are located in urban areas and the services offered are largely subsidised. The gynaecologic oncology service was

Table IV: Prognostic factors for overall survival of ovarian cancer (EOC), fallopian tube cancer, and primary peritoneal serous carcinoma (PPSC) by univariate and multivariate Cox regression analyses

Variables	Univariate		Multivariate	
	Crude HR (95% CI)	p-value	Adjusted HR (95% CI)	p-value
Age group				
≤ 40 years	1 (Reference)		1 (Reference)	
41 – 60 years	3.80 (1.54, 9.41)	0.004	2.83 (1.11, 7.25)	0.030
≥ 61 years	5.97 (2.38, 15.00)	< 0.001	2.60 (0.97, 6.95)	0.056
Medical illness				
No	1 (Reference)		1 (Reference)	
Yes	2.15 (1.51, 3.06)	< 0.001	1.51 (1.04, 2.21)	0.033
Optimal surgery*				
No	1 (Reference)			
Yes	0.319 (0.22, 0.46)	< 0.001	0.60 (0.41, 0.89)	0.011
Neoadjuvant chemotherapy				
No	1 (Reference)			
Yes	2.09 (1.47, 2.96)	< 0.001	NS	NS
Figo staging				
Early disease	1 (Reference)		1 (Reference)	
Advanced disease	5.09 (3.12, 8.30)	< 0.001	3.63 (2.20, 6.00)	< 0.001
ECOG				
0	1 (Reference)		1 (Reference)	
≥ 1	2.91 (2.05, 4.11)	< 0.001	2.00 (1.38, 2.91)	< 0.001

HR: Hazard ratio; CI: Confidence interval; Backward stepwise was applied; Two-way interaction and multicollinearity problem were checked and not detected. Proportional hazard assumptions were fulfilled (hazard function plot and hazard function plots were checked); Bold P-values indicate statistically significant; NS: Not selected during multivariable variable selection; *protective factor.

Table III: Comparison of median overall survival and progression free survival time between IKN and HA

Characteristics	Median overall survival time (95% CI)		Log-rank statistics (df)	p-value	Median progression free survival time (df)		Log-Rank statistics	p-value
	IKN	HA			IKN	HA		
All patients, n = 256	39.00 (21.58, 56.42)	69.00 (52.67, 85.33)	4.13 (1)	0.042	22.00 (8.50, 35.50)	Nil (Nil, Nil)	3.79 (1)	0.052
Early disease, n = 95	Nil (Nil, Nil)	Nil (Nil, Nil)	1.36 (1)	0.244	Nil (Nil, Nil)	Nil (Nil, Nil)	1.89 (1)	0.241
Advanced disease, n = 161	27.00 (18.92, 35.08)	32.00 (19.25, 44.76)	2.85 (1)	0.092	12.00 (10.79, 13.21)	18.00 (14.88, 21.12)	2.97 (1)	0.085

CI: Confidence interval; Nil: Median survival time not reach; Bold p-values indicate statistically significant.

established in Hospital Ampang in the year of 2009 while for IKN, the service only started in 2015. This explains the difference in the number of patients between the two centres as IKN only started to receive more referrals from other health centres in the later years of this study. Even though IKN was a new centre at that point of time, the departments were established and led by experienced clinical consultants. This would reduce the risk of comparative bias between the two centres.

In addition to that, patients who have had surgeries in other health centres and referred directly to the clinical oncologists were also excluded from this study as it was difficult to ascertain whether or not a complete surgical staging had been performed by trained gynaecologic oncologists. This is a paramount factor in subsequent staging and management as even in apparent stage I EOC, comprehensive surgical staging is found to upstage one third of the patients; and one third of these upstaged patients had altered treatment plans.[3] The outcomes for patients with early stage EOC have also been shown to improve if the surgery is performed by gynaecologic oncologists.[4] By having only patients that were operated from these two centres as one of the inclusion criteria of this study, the homogeneity of the subjects could be preserved.

Similar to published data, the majority of the patients in these two centres had advanced disease at diagnosis.[5] The disease was surgically staged based on 2014 FIGO staging and the operative findings determined the precise histologic diagnosis and therefore the prognosis.[6] In terms of the histological subtype, high grade serous carcinoma (HGSC) is the most common subtype encountered in this study, followed by clear cell, endometrioid, mucinous, low grade serous carcinoma and others. The distribution is also in line with other published data.[6,7] Almost all patients in this cohort had good performance score prior to surgery, except for one patient from IKN who had ECOG 3 which was due to her underlying physical disability.

Patients with medical illness as comorbidities are found to have higher risk of poor outcomes. In this study, the medical illness encompasses mostly non-communicable diseases such as hypertension, diabetes, dyslipidaemia, chronic kidney

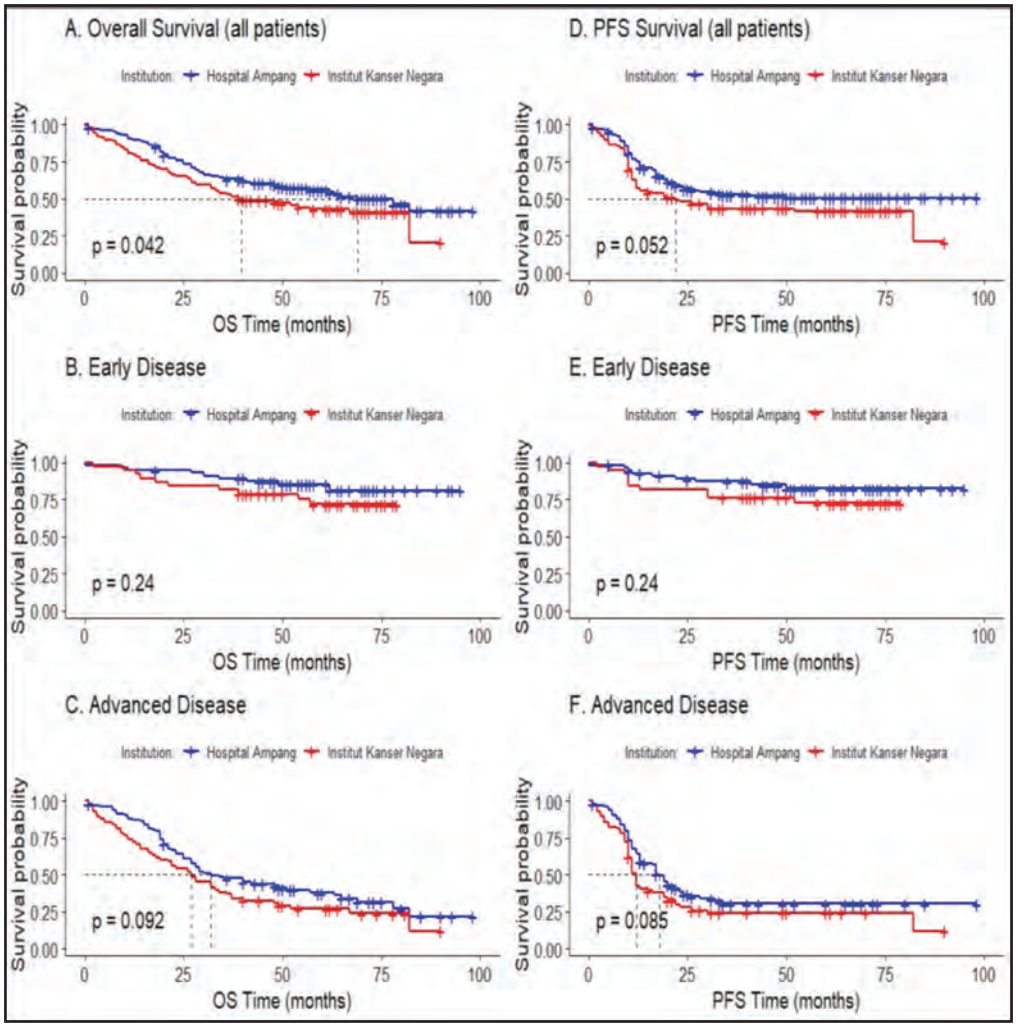

Fig. 1: Kaplan Meier curves for OS (A-C) and PFS (D-F) based on two institutions. (A) Probability of OS according to the institutions (all patients), (B) Probability of OS according to the early-stage disease patients, (C) Probability of OS according to the of advanced stage disease patients, (D) Probability of PFS according to the institutions (all patients), (E) Probability of PFS according to the early-stage disease patients, and (F) Probability of PFS according to the advanced stage disease patients.

disease, heart disease, bronchial asthma, autoimmune diseases (systemic lupus erythematosus, rheumatoid arthritis), cerebrovascular disease etc. A few patients had communicable disease such as active tuberculosis, HIV and hepatitis carrier status. The individual's medical illness and overall comorbidity burden has an impact on the cancer outcome.[8] This is in line with the study finding in which patients with medical illness had 51.0% higher risk of dying compared to those without medical illness (Table IV).

A complete cytoreduction surgery by gynaecologic oncologists has been established to be one of the paramount treatments in EOC.[9,10] For apparent early stage ovarian cancer, primary surgery with systematic pelvic and para-aortic lymphadenectomy is advocated.[11,12] Meanwhile, in the case of advanced EOC, the cytoreduction surgery can be performed as primary surgery followed by adjuvant chemotherapy or as interval debulking surgery (IDS) in between chemotherapy. Trials have shown similar outcomes with respect to OS and PFS for both groups, but with better perioperative outcomes for the patients who received neoadjuvant chemotherapy and IDS.[13,14] With regards to systematic pelvic and paraaortic lymphadenectomy in patients with advanced EOC, studies have demonstrated that routine systemic pelvic and para aortic lymphadenectomy does not improve overall survival and results in increased perioperative morbidity.[15,16] In this study, majority of patients from both centres had undergone cytoreductive surgery with comparable optimal outcome (p = 0.168). With regard to patients with advanced disease, more patients in Hospital Ampang received neoadjuvant chemotherapy prior to surgery compared to IKN (p = 0.006) (Table II). However this did not change the median OS and PFS of the two groups, which concurs with the available evidence.

Chemotherapy has also been established as an integral part in the treatment of EOC. However, this is an exception for those with EOC confined to the ovary (stage IA and IB) and/or well differentiated (grade 1) tumours as the survival of this group is at least 90% following surgery alone.[17,18] For

high-risk early stage disease, defined as Stage IC or stage II, clear cell histology, and high grade tumour (grade 3), systemic reviews have shown the benefits of adjuvant chemotherapy in terms of PFS and OS.[19,20] The preferred choice of chemotherapy is a platinum-based doublet (i.e., carboplatin and paclitaxel) and this is based upon its efficacy in the adjuvant therapy of women with advanced stage EOC.[21,22]

The use of platinum-based doublet (carboplatin and paclitaxel) in adjuvant setting for advanced stage EOC has been shown to improve the OS and PFS.[23,24] Based on Table II, all patients that required chemotherapy received at least a platinum-based drug (carboplatin) and the majority of them received a platinum-based doublet drugs. The difference in the average time taken for patients to receive adjuvant chemotherapy following surgery between the two centres did not appear to affect the comparison median OS and PFS of patients with early and advance disease EOC (Figure 1). The addition of BEV, a vascular endothelial growth factor inhibitor as part of the front-line treatment for advanced EOC was evaluated in two trials (GOG 218 and ICON 7). Their post hoc subgroup analysis indicated statistically significant OS benefit in patients with stage IV disease in GOG 218 and in patients at high risk of progression in the ICON 7 trial.[25,26] Despite the combination of optimal surgery and the use of standard first line chemotherapy, approximately 70% of patients will relapse within 3 years.[27,28] The subsequent platinum-based treatments would lead to disease control for shorter periods.[29,30] The treatment approach for relapsed disease would be based on the multiple factors which include the performance status, clinical symptoms, site of metastasis and response towards platinum (the time elapsed between the completion of treatment and the detection of relapse; platinum sensitive are those who relapsed 6 months or longer after initial treatment while platinum resistance are those who relapsed in less than 6 months).

Patients with platinum-sensitive recurrent EOC could be offered secondary cytoreduction (if complete gross resection is predicted to be achievable) plus chemotherapy with the aim to prolong survival.[31] However this option is limited to selected group of patients especially to those with isolated nodal disease or isolated peritoneal disease. Patients with peritoneal carcinomatosis are mostly treated with chemotherapy with or without BEV. In most cases, combination therapy is preferred to single agent chemotherapy as it is associated with superior objective response and PFS.[32,33] There are a few combination options which include carboplatin plus paclitaxel, carboplatin plus gemcitabine and carboplatin plus pegylated liposomal doxorubicin.[34-36] However there is no ideal combination therapy and the use of single agent chemotherapy might be preferred for medically frail patients or those who had hypersensitivity reaction or persistent toxicities from previous treatment.

The use of PARP-i as maintenance therapy after platinum-based therapy in the first line and recurrent setting for patients with BRCA mutations and homologous recombinant deficiency (HRD) has been well established to improve OS and PFS.[37-40] At the time of this writing, Olaparib is the only PARP-i available in Malaysia but because of its high price, the medication is not subsidised. Due to this, the use of PARP-i is very limited in government hospital setting and the uptake for BRCA and HRD testing is still low as it is also not subsidised. The comparison between the two centres showed that both centres are able to provide surgery and chemotherapy as per recommendations; however, both centres are not able to provide routine maintenance therapy of advanced ovarian cancer such as BEV and PARP-i due to cost and availability of these drugs in the government settings.

We noted that when we stratified based on disease staging, there was no significant difference in the median OS and PFS. The discrepancy between median OS for all patients and median OS based on the disease stage could be contributed by the additional treatment received by patients in HA i.e., more patients underwent secondary surgery (15.2% vs 1.4%) and more patients received BEV (10.0% vs 0.0%) and poly (ADP-ribose) polymerase inhibitors (PARP-i) (6.0% vs 0.0%). Another contributing factor would be small sample size and unequal number of patients between the two centres which could have also contributed to the different outcomes of this study. Suggestions for future studies include a longer study period to obtain a larger sample size and the recruitment of patients could be started in the later years when the gynaecologic oncology service in IKN has been well established. Moreover, further study could be conducted looking into patients' preferences and outcomes in terms of quality of life between these two centres.

CONCLUSION

Our findings confirmed that the median overall survival (OS) was significantly longer for patients with epithelial ovarian cancer (EOC) in Hospital Ampang (HA) compared to Institut Kanser Negara (IKN). However, there was no significant difference in the median OS based on the disease staging; therefore, we could not establish the non-inferiority outcome between the two centres. Furthermore, there was no significant difference in median PFS for both centres. This could be due to small sample size to be able to detect any difference. In addition, it could also be contributed by the different treatment options available and unequal volume of patients treated in both centres. Thus, further study with larger sample size and longer time period is needed to provide better guidance and treatments for the patients. As the majority of patients present in advanced stage of disease, the use of PARP-i as maintenance in those with BRCA mutations and HRD could prove to be beneficial in the improvement of the OS and PFS of EOC patients in Malaysia; thus, strategies to ensure the availability of genetic testing and the medications should be implemented in the public hospital settings.

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CONFLICT OF INTEREST
None

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ORIGINAL ARTICLE

Predictors of duodenal eosinophil counts among subjects undergoing diagnostic endoscopy

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ABSTRACT

Introduction: Duodenal eosinophilia has been implicated in the pathophysiology of functional dyspepsia. In a retrospective observational study, we previously reported that duodenal eosinophilia (as defined by a mucosal count of greater than 15 eosinophils per 5 high power fields), was associated with symptomatic erosive gastroesophageal reflux disease (GERD), concomitant co-morbidities and Chinese ethnicity but not functional dyspepsia among 289 multiracial subjects undergoing diagnostic endoscopy in 2019 before the COVID-19 pandemic. We tested the reproducibility of those findings on a larger sample that included the original cohort and another 221 subjects who underwent endoscopy in 2022 after the easing of pandemic restrictions.

Materials and Methods: Archived duodenal histology slides were assessed by a pathologist blind to demographic and clinical data gleamed retrospectively from clinical chart review. Logistic regression analysis was used to explore associations between duodenal eosinophilia and the variables age, gender, ethnicity, year of sampling (2019 vs 2022), concomitant co-morbidities, functional dyspepsia, symptomatic erosive GERD (Los Angeles Grades A to D), endoscopic oesophagitis, gallstone disease, Helicobacter pylori infection, irritable bowel syndrome and NSAID consumption. Three different thresholds for defining duodenal eosinophilia (>15, >22 and >30 eosinophils per 5 high power fields) were tested.

Results: Year of sampling (2019, pre-pandemic) strongly predicted duodenal eosinophilia across all thresholds (OR 11.76, 13.11 and 21.41 respectively; p = 0.000). The presence of concomitant co-morbidities was a modest predictor across all thresholds whereas Chinese ethnicity only predicted at the lowest threshold. Absolute duodenal eosinophil counts predicted symptomatic erosive GERD (OR 1.03; p = 0.015) but not functional dyspepsia (OR 1.00; p = 0.896) after adjusting for age, gender, ethnicity, concomitant comorbidities and year of endoscopy. None of the subjects reached the threshold for the diagnosis of eosinophilic duodenitis.

Conclusion: The cumulative impact of environmental exposures on duodenal eosinophil counts may be much greater than of putative factors linked to functional dyspepsia. A signal linking duodenal eosinophil counts and symptomatic erosive GERD was detected.

KEYWORDS:
Duodenal eosinophilia, GERD, functional dyspepsia

INTRODUCTION

There has been much interest recently in duodenal mucosal eosinophil counts; an interest that has been driven by two main considerations. Firstly, the postulation that duodenal microinflammation is a key factor in the pathogenesis of functional dyspepsia and secondly that eosinophilic gastrointestinal disorders as a cause of abdominal symptoms may be underdiagnosed.[1-4] Furthermore, duodenal eosinophil counts are relatively easily determined in most histopathology laboratories and is a potentially attractive biomarker of duodenal microinflammation. In a previously published study, we retrospectively audited the duodenal mucosal biopsies of 289 patients who underwent elective diagnostic oesphagogastroduodenoscopy (OGD) in a Malaysian tertiary hospital in the year 2019 with a view to identifying the relative strength of the associations between duodenal eosinophilia and several demographic variables and clinical conditions.[5] We found that the presence of symptomatic erosive gastroesophageal reflux disease (GERD), the presence of comorbidities and Chinese ethnicity were each independently associated with duodenal eosinophilia as defined by a duodenal mucosal eosinophil count of greater than 15 eosinophils per 5 high power field (eos/5hpf). However, we failed to detect an association between duodenal eosinophilia and undifferentiated functional dyspepsia.[5] In the current study, we aimed to assess the reproducibility of our previous findings by expanding the sample size to include a similar cohort of 221 patients who underwent elective diagnostic OGD in the year 2022. The analysis was conducted on a consolidated sample that consisted of both the 2019 and 2022 cohorts.

MATERIALS AND METHODS

The cohort of the year 2019 consisted of 289 subjects as previously described.[5] The 2022 cohort consisted of 221 consecutive subjects who underwent elective diagnostic OGD between January and August of 2022 for a variety of indications performed by a single gastroenterologist (SMR). As in our previously reported study, we excluded patients in whom the OGD was primarily therapeutic or undertaken in an emergency setting, as well as patients who had a bleeding diathesis or who were on anticoagulants and/or antiplatelet agents. Four patients who had undergone diagnostic OGD in

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both 2019 and 2022 were included in the 2019 cohort but were excluded from the 2022 sample. Helicobacter pylori infection was routinely determined by the rapid urease test on biopsies taken from both the gastric antrum and body. It was routine practice for at least a single mucosal biopsy to be taken from the second part of the duodenum in all subjects. The clinical and endoscopic data were gleamed from the clinical charts by the gastroenterologist (SMR) who was blind to the results of the histology review. The definitions of functional dyspepsia, irritable bowel syndrome (IBS), symptomatic GERD, gallstone disease and comorbidities were as previously described.[5] Reflux oesophagitis on endoscopy was defined as the presence of erosive changes (grade A to D) as described by the Los Angeles classification.[6]

The archived histology slides were examined and reported by the pathologist (SR) who was blind to the clinical data. The histology protocol was as previously reported.[5] The eosinophils were counted in 5 random high-power fields at X40 magnification and field diameter of 0.55 mm. The duodenal mucosal eosinophil counts were expressed as the number of eosinophils per 5 high power fields (eos/5 hpf).

Statistical Analysis and Definition of Duodenal Eosinophilia
Statistical analyses were performed with the Epi InfoTM version 7.2 statistical software package available from the Centres for Disease Control and Prevention (CDC) website. Logistic regression analysis was used to determine the independent association between multiple explanatory variables and a dichotomous response variable. Association was expressed in terms of odd ratios (OR) and 95% confidence intervals (CI). Differences in the rates of categorical variables between groups were tested using the Chi-square test while differences in numerical variables were tested with the non-parametric Kruskal-Wallis test.

Logistic regression analysis was undertaken using three different thresholds to define duodenal eosinophilia. In the first analysis, duodenal eosinophilia was defined as more than 15 eos/5 hpf as proposed by Chaudhari et al[7] and was the definition used in our previous publication.[5] The second threshold was >22 eos/5 hpf as suggested in previous studies exploring the association between functional dyspepsia and duodenal eosinophilia.[8,9] The third cut off was arbitrarily set at >30 eos/5 hpf, a level twice as high as the initial threshold. Logistic regression models were also constructed to determine if the absolute eosinophil count was independently predictive of functional dyspepsia and/or symptomatic erosive GERD after adjusting for age, gender, ethnicity, presence of comorbidities and year of endoscopy (2019 or 2022).

Ethical Approval
This retrospective observational study was approved by the hospital research and ethics committee (PHKL-EC-2023-0002) in accordance with the ethical standards laid down by the 1964 Helsinki Declaration.

RESULTS

Demographic and Clinical Data
The median age of the total sample was 50 years (14 to 90). There were 255 male subjects and an equal number of female subjects. In terms of ethnicity, 79 were Malay, 162 were Chinese, 193 were Indian and 76 were of other ethnicities. Compared to the 2019 cohort, the mean age was slightly higher, the proportion of Malay subjects was lower and the proportions of subjects of Indian and 'other ethnicity' were higher in the 2022 cohort (Table I). There were also significantly more subjects with comorbidities and symptomatic erosive GERD in the 2022 cohort (Table I).

Logistic Regression Analyses to Assess the Independent Association Between Duodenal Eosinophilia and Several Variables
As shown in Table II, duodenal eosinophilia as defined by more than 15 eos/hpf was independently associated with having undergone OGD in the year 2019 (as opposed to 2022), the presence of comorbidities and Chinese ethnicity (as opposed to Malay or Indian ethnicity). There was no statistically significant association between duodenal eosinophilia and either symptomatic erosive GERD, reflux oesophagitis (irrespective of symptoms), functional dyspepsia, gallstone disease IBS or the consumption of NSAIDs. Undergoing OGD in 2019 (as opposed to 2022) was the strongest predictor of duodenal eosinophilia (OR 11.76; 95% CI 7.24–19.12).

On repeating the analysis after redefining duodenal eosinophilia at a higher threshold (>22 eos/5hpf) the independent association between duodenal eosinophilia and undergoing OGD in 2019 (OR 13.11; 95% CI 6.61 26.04, p = 0.000) as well as the association between duodenal eosinophilia and the presence of comorbidities (OR 2.46; 95% CI 1.43 4.24, p = 0.001) were preserved. However, Chinese ethnicity was no longer associated with duodenal eosinophilia. None of the other variables significantly predicted duodenal eosinophilia.

At an even higher cut off (>30 eos/5hpf), undergoing OGD in 2019 (OR 21.41; 95% CI 6.41 71.43, p = 0.000) and the presence of comorbidities (OR 2.28; 95% CI 1.13 4.58, p = 0.021) remained statistically significant predictors of duodenal eosinophilia. At this highest cut off, male gender was associated with duodenal eosinophilia (OR 1.95; 95% CI 1.03 3.70, p = 0.041). In addition, an association between functional dyspepsia and duodenal eosinophilia that approached statistical significance was also detected (OR 2.20; 95% CI 0.95-5.12, p = 0.067). None of the other variables significantly predicted duodenal eosinophilia.

Logistic Regression Analysis to test if Absolute Duodenal Eosinophil Counts were Independently Predictive of Functional Dyspepsia or Symptomatic Erosive GERD
After adjusting for age, gender, ethnicity, year of endoscopy and the presence of comorbidities, the absolute duodenal eosinophil count was independently predictive of symptomatic erosive GERD (OR 1.03; 95% CI 1.01 1.05, p = 0.015) but not functional dyspepsia (OR 1.00; 95% CI 0.98 1.02, p = 0.896).

Comparison of Duodenal Eosinophil Counts Between the 2019 and 2022 Cohorts
The duodenal eosinophil counts per hpf in the 2019 cohort was significantly higher than in the 2022 cohort (median 18 [range 1 85] vs median 7 [range 1 35]; p = 0.000]. The duodenal eosinophil count was greater than 30 eos/5hpf in

Table I: Comparison of demographic and clinical variables between the 2019 and 2022 cohorts

	2019 cohort (n = 289)	2022 cohort (n = 221)	p-value
Median age (range) at time of OGD in years	48 (15 88)	53 (14 90)	0.002[a]
Number of males: females	137:152	118:103	0.211
Ethnicity: Number (% of total in the cohort)			
Malay	56 (19.3)	23 (10.4)	
Chinese	93 (32.2)	69 (31.2)	0.029[a]
Indian	102 (35.3)	91 (41.2)	
Others	38 (13.2)	38 ((17.2)	
Number of subjects (%) with:			
Co-morbidities	105 (36.3)	115 (52.0)	0.000[a]
Helicobacter pylori infection	27 (9.3)	19 (8.6)	0.892
Functional dyspepsia	45 (15.6)	36 (16.3)	0.922
Irritable bowel syndrome[b]	53 (18.3)	35 (15.8)	0.533
Gallstone disease	17 (5.9)	11(5.0)	0.804
Symptomatic erosive GERD	29 (10.0)	44(19.9)	0.002[a]
Endoscopic evidence of oesophagitisc	81 (28.0)	76(34.4)	0.148
Recent consumption of NSAIDs	16 (5.5)	9(4.1)	0.581

[a]Statistically significant difference ($p < 0.05$). [b]Denotes all subjects with irritable bowel syndrome symptoms including those with other coexisting or overlapping conditions. In our original publication5 the denoted number was of subjects in whom irritable bowel syndrome was the predominant cause of symptoms. [c]Includes subjects with visible oesophageal erosive changes on endoscopy irrespective of symptoms

Table II: Logistic regression model of predictors of duodenal eosinophilia defined as >15 cells per 5 high power fields

	Odds ratio (95% confidence interval)	p-value
Age	0.99 (0.98 - 1.01)	0.383
Female gender	1.15 (0.75 - 1.76)	0.525
Year of endoscopy (2019 compared to 2022)	11.76 (7.24 – 19.12)	0.000[b]
Ethnicity: Chinese compared to Malay	2.03 (1.06 – 3.90)	0.033[b]
Chinese compared to Indian	1.71 (1.03 – 2.85)	0.038[b]
Chinese compared to Other	1.30 (0.67 – 2.52)	0.442
Presence of co-morbidities	1.76 (1.09 – 2.86)	0.021[b]
Helicobacter pylori infection	0.76 (0.36 – 1.60)	0.471
Functional dyspepsia	0.79 (0.43 – 1.43)	0.433
Irritable bowel syndrome	0.86 (0.49 -1.50)	0.590
Gall stone disease	1.00 (0.39 – 2.53)	0.998
Symptomatic erosive GERD	1.86 (0.86 – 4.01)	0.115
Endoscopic evidence of reflux oesophagitis[a]	0.87 (0.49 – 1.52)	0.615
Recent consumption of NSAIDs	2.23 (0.86 – 5.82)	0.100

[a]Includes subjects with visible oesophageal erosive changes on endoscopy irrespective of symptoms. [b]Statistically significant difference ($p<0.05$)

TableIII: Proportion of duodenal eosinophilia in various subsets of subjects

Subject subset	Proportion of subjects with duodenal eosinophilia as defined by an eosinophil count of:		
	>15/HPF	>22/HPF	>30/HPF
Co-morbidities	92/220 (41.8%)	54/220 (24.5%)	27/220 (12.3%)
Helicobacter pylori infection	17/46 (37.0%)	8/46 (17.4%)	5/46 (10.9%)
Functional dyspepsia	28/81 (34.6%)	19/81 (23.5%)	11/81 (13.6%)
Irritable bowel syndrome	34/88 (38.6%)	18/88 (20.5%)	7/88 (8.0%)
Gallstone disease	12/28 (42.9%)	9/28 (32.1%)	5/28 (17.9%)
Symptomatic erosive GERD	30/73 (41.1%)	15/73 (20.5%)	8/73 (11.0%)
Endoscopic evidence of oesophagitis	64/157 (40.8%)	38/157 (24.2%)	19/157(12.1%)
Recent consumption of NSAIDs	15/25 (60.0%)	6/25 (24.0%)	4/25 (16.0%)

HPF:– High power fields

53 (18.3%) of the subjects in the 2019 cohort and in only three (1.4%) of the 2022 cohort. Counts of greater than 22 eos/5hpf were found in 101(35.0%) and 11(5.0%) of the 2019 and 2022 cohorts, respectively. Counts of greater than 15 eos/5 hpf were found in 177(61.3%) and 32(14.5%) of the 2019 and 2022 cohorts respectively.

Proportion of Duodenal Eosinophilia in Subsets of the Subjects

For the sake of perspective, the proportions of duodenal eosinophilia using the three different thresholds in subsets of subjects with functional dyspepsia, symptomatic GERD, endoscopic evidence of reflux oesophagitis, IBS, gall stone disease, Helicobacter pylori infection and comorbidities respectively are shown in Table III. It should be noted that there would be obvious reasons for there to be overlap between the subsets as many subjects fall into more than one subset.

DISCUSSION

The key finding in our study is that among patients undergoing elective diagnostic OGD, duodenal mucosal eosinophilia was independently associated with having the OGD done in 2019 (as opposed to 2022) and the presence of co-morbidities. These associations were observed irrespective of whether duodenal eosinophilia was defined as greater than 15, 22 or 30 eos/5hpf. The association with having the OGD done in 2019 as opposed to 2022, was particularly strong with odds ratios of 11.76, 13.11 and 21.41 at thresholds of >15, >22 and >30 eos/5hpf, respectively. The association with co-morbidities was modest but consistent with odds ratios in the range of 1.76 2.38 at the three different thresholds. There was a weaker association between Chinese ethnicity and duodenal eosinophilia that was detected only at the lowest threshold of >15 eos/hpf.

The striking observation that the year of sampling (2019 as opposed to 2022) was the strongest predictor of duodenal eosinophilia is intriguing and any explanation for this would admittedly be speculative. It could be more than a coincidence that 2019 was the year before the onset of the COVID-19 pandemic while 2022 was when the world was starting to emerge from the worst of the pandemic. The years 2020 and 2021 in Malaysia were characterised by strictly enforced public health measures to prevent transmission of the virus that included social distancing and restrictions on travelling. There was a significant easing of these restrictions from 2022 onwards. It is conceivable that the public health measures designed to prevent viral transmission caused a significant reduction of environmental exposure to a myriad of agents including microbes and dietary constituents resulting in a reduced state of immune activation in the duodenal mucosa.

The modest but statistically significant association between duodenal eosinophilia and the presence of co-morbidities was consistent with our previous findings and is compatible with the notion that systemic disease is associated with intestinal inflammation and increased intestinal permeability.[10] It is acknowledged however that the co-morbidities represented a heterogenous group of conditions and it is quite possible that some conditions influence duodenal eosinophil counts more than others.

There are limitations to the conclusions that can be made in our study with respect to the possible association between duodenal eosinophilia and specific clinical entities such as functional dyspepsia and symptomatic erosive GERD predominantly because of the absence of truly healthy controls in our sample. In addition, the diagnosis of these clinical entities was based on practice based clinical impressions rather than validated questionnaires and therefore carries risks of subjectivity and bias. There were also gaps in information that are almost inevitable in retrospective observational studies such as ours. For instance, data on history of allergies was not complete enough to be included and it was not possible to subtype cases of functional dyspepsia based on the information in the case records. Finally, almost all subjects only had single biopsies from the second part of the duodenum. This could have resulted in some degree of under-detection as eosinophilic infiltration may have been patchy. A retrospective heterogenous sample such as in our study raises the possibility of confounding variables. We have mitigated this limitation by using logistic regression to adjust for confounding variables.

Despite these limitations and the absence of direct clinical implications, the results do provide some insight into the determinants of duodenal eosinophil counts. Our previous observation of an association between symptomatic GERD and duodenal eosinophilia (defined as >15 eos/5hpf) was not reproducible on this larger sample. Nor was there any association between duodenal eosinophilia and the presence of endoscopically visible reflux oesophagitis regardless of symptoms. However, it is notable that the absolute duodenal eosinophil count did independently predict symptomatic erosive GERD, providing a signal that duodenal eosinophilia may well be linked to symptomatic erosive GERD. This is concordant with the observations of a large population-based study in which the presence of eosinophilia in the second part of the duodenum among subjects with functional dyspepsia predicted the onset of GERD 10 years later, suggesting that functional dyspepsia and GERD may be part of a spectrum of which duodenal eosinophilia is a link.[11] Our findings lend credence to that hypothesis. It is conceivable that in our study there was an intrinsic bias to label dyspeptic patients with endoscopic signs of oesophagitis as having GERD rather than functional dyspepsia. This could have been amplified by the fact that we accepted Los Angeles grade A oesophagitis as a criteria of reflux oesophagitis. Hence, subjects with overlapping GERD and functional dyspepsia may have been more likely to be labelled as GERD, perhaps explaining why duodenal eosinophil counts significantly predicted symptomatic GERD but not functional dyspepsia. It is also tempting to postulate that many subjects with functional dyspepsia and duodenal eosinophilia in previous studies may in fact have had GERD as the primary problem. The proposed hypothesis of duodenal microinflammation causing functional dyspepsia is based on the premise that duodenal stimulation plays an important role in controlling gastric motility and visceral hypersensitivity.[1] It is conceivable that this applies equally to GERD if indeed subsets of functional dyspepsia and GERD are part of the same spectrum.[1,11]

The limitations notwithstanding, our data would be compatible with a hypothesis that the cumulative impact of the various environmental exposures on duodenal eosinophil

counts is much larger than that of putative factors linked to individual clinical entities such as functional dyspepsia. The effect of these putative factors on the eosinophil density may be even further diluted by the influence of other factors such as the presence of co-morbidities and even ethnicity or gender. This could well explain the discordant findings of case control studies designed to detect an association between duodenal eosinophilia and functional dyspepsia. A recent meta-analysis and systematic review concluded that the evidence for a link between microinflammation and functional dyspepsia was of very low quality due to unexplained heterogeneity and possible publication bias.[12] It is possible of course that duodenal eosinophil count is a poorer marker of duodenal microinflammation than degranulated eosinophils as has been suggested by a number of studies.[12] Our results also expose the challenges and pitfalls in attempting to define normal duodenal eosinophil counts given the potential for marked variation in relation to time frames alone.

It is also noteworthy that none of the subjects in the sample had eosinophil counts that approached the levels compatible with the diagnosis of eosinophilic duodenitis. The widely accepted criterion for eosinophilic duodenitis is 30 eosinophils per high powered field.[4,13] The highest eosinophil count among our subjects was 85 eos/5 hpf that crudely translates to only 17 eos/hpf. Indeed, it is lower than even the 20 eos/hpf that has been suggested as the upper end of normal in a US population.[14] This is in sharp contrast to the findings of a recent multisite study in the US that found duodenal eosinophil counts of greater than 30 eos/hpf in 45% of subjects with unexplained moderate to severe abdominal symptoms.[4] Although the subjects in our study are unlikely to be comparable to that of the US study and the number of biopsies taken in our study may not have been enough to have detected patchy eosinophilia, it is nonetheless significant that not even a single subject in our sample reached the threshold for the diagnosis of eosinophilic duodenitis.

CONCLUSION

Among the variables investigated, sampling in the year 2019 (before the COVID-19 pandemic) was the strongest predictor of duodenal eosinophilia while the presence of comorbidities was a modest but statistically significant predictor. These results suggest that the cumulative impact of multiple exposures on duodenal eosinophil counts is much greater than that of putative factors linked to individual clinical entities such as functional dyspepsia. A signal suggesting a link between symptomatic GERD and duodenal eosinophil counts was detected.

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The benefits of early pulmonary rehabilitation with incentive spirometer among chronic obstructive pulmonary disease patients with exacerbation of chronic obstructive pulmonary disease

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ABSTRACT

Introduction: Inspiratory muscle dysfunction is prevalent in chronic obstructive pulmonary disease (COPD). This study aimed to compare the benefits of adding volume incentive spirometry (VIS) to active-cycle-breathing technique (ACBT) and ground-based walking (GBW) training in patients hospitalised for COPD exacerbations. The objectives were to evaluate the impact of early initiation of VIS on respiratory muscle strength, measured by maximum inspiratory pressure (MIP), maximum expiratory pressure (MEP) and the 6-minute walk test (6-MWT), as well as on symptoms, as assessed by the COPD assessment test (CAT) score.

Materials and Methods: This randomised, prospective study was conducted among COPD subjects admitted with exacerbation between June 2021 and August 2022. Subjects were randomly assigned to either the VIS (interventional group) or the control group. Baseline assessments, including spirometry, MIP, CAT score, and the 6-minute walk test (6MWT), were performed. Both groups commenced active cycle of breathing techniques (ACBT) and ground-based walking (GBW) training within 72 hours of admission, with daily sessions involving three repetitions of each phase to complete one cycle, repeated three times daily. The intervention group received VIS. Upon discharge, subjects were provided with a diary and instructed to continue a home-based pulmonary exercise regimen, performed for at least 15 minutes per day, 3 days a week, with compliance monitored through weekly phone calls. At the 4-week follow-up, repeat assessments of spirometry, MIP, maximal expiratory pressure (MEP), CAT score and 6MWT were conducted to evaluate the outcomes.

Results: A total of 34 subjects with a median age of 68 years (interquartile range [IQR] 65–74.3 years). The cohort predominantly males (32 subjects, 94%). The distribution of disease severity was as follows: GOLD 2 in 15 subjects (44%) and GOLD 3 in 14 subjects (41%). Additionally, 17 subjects (50%) had experienced three or more exacerbations in the preceding year. The majority of patients (29 out of 34, 85%) had a length of stay of less than 7 days. In the interventional group, the median MIP improved from 50 cm H2O (IQR 40.5–70.5) to 59 cm H2O (IQR 39–76.5), though this was not statistically significant (p = 0.407). The control group saw an improvement from 58 cm H2O (IQR 36.5–85) to 60 cm H2O (IQR 33–88), also not statistically significant (p = 0.112). The 6MWT distance improved in the interventional group from 220 meters (IQR 118–275) to 260 meters (IQR 195–327) (p = 0.002) and in the control group from 250 meters (IQR 144–294) to 280 meters (IQR 213–359.5) (p = 0.001). The median CAT score decreased significantly in the interventional group from 22 (IQR 16–28) to 11 (IQR 7.5–13) (p < 0.001) and in the control group from 21 (IQR 14–24.5) to 10 (IQR 8–12.5) (p < 0.001).

Conclusion: Early initiation of pulmonary rehabilitation in patients with acute exacerbations, characterised by poor muscle strength and a history of exacerbations, resulted in significant improvements in patient-reported symptoms and 6MWT outcomes. Although there was only a numerical improvement in MIP and MEP, the intervention did not extend the length of hospital stay, highlighting its safety and efficacy in the acute care setting.

KEYWORDS:
COPD, pulmonary rehabilitation, ACBT, incentive spirometer

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a preventable and treatable disease characterised by persistent airflow limitation and respiratory symptoms. It is usually caused by significant exposure to tobacco smoking and pollutants. Host factors that may predispose to the development of COPD include genetic abnormalities, abnormal lung development and ageing.[1]

COPD exacerbations are episodes of worsening symptoms associated with increased airway inflammation and physiological changes. Symptom recovery generally improves over the first 14 days after an exacerbation of COPD; however, it varies between studies and individuals.[2]

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Systematic review has shown that prior exacerbation history is an important predictor for future moderate to severe exacerbations.[3]

Patients with COPD are frequently disabled because of dyspnoea as a result of a decreased capacity of the respiratory muscles. In stable COPD, respiratory muscles, in particular the inspiratory muscle function, are altered. Following an exacerbation of COPD, there is a decrease in external intercostal muscle strength and hyperinflation of the lungs, resulting in a decline in forced expiratory volume at 1 second (FEV1) and maximal inspiratory pressure (MIP).[4]

MIP is a non-invasive parameter used to assess respiratory muscle strength. In the early stages of COPD, MIP declines with the reduction of diaphragmatic contractility, and in later stages, further reduction of MIP is caused by hyperinflation of the lungs and reduced inspiratory muscle strength.[5] This decline is important as MIP appears to be a distinct predictor of survival.

Pulmonary rehabilitation (PR) is an accepted non-pharmacological treatment for COPD, proven to improve quality of life and exercise capacity.[6] Volume-oriented incentive spirometer (VIS) is a device used in PR that measures the volume of inspired air to assess patient's inspiratory effort with visual feedback. It has been shown to be effective in improving lung function and functional capacity.[7] Hosseini et al. reported a significant increase in MIP in moderate COPD patients admitted with an exacerbation following 4-weeks of VIS training.[8] Faster improvement in physical performance with early PR has been seen after acute exacerbation of COPD.[9]

The benefits of early inpatient PR with VIS during peri and post-exacerbation of COPD have not been widely studied. The objectives were to evaluate the impact of early initiation of VIS on respiratory muscle strength, measured by MIP, maximum expiratory pressure (MEP) and the 6-minute walk test (6-MWT), as well as on symptoms, as assessed by the COPD assessment test (CAT) score.

MATERIALS AND METHODS

Study Design and Participants

This was a randomised, prospective interventional single-centre study of COPD patients admitted with exacerbation to Universiti Kebangsaan Malaysia Medical Centre (UKMMC), conducted between June 2021 and August 2022. The Research Ethics Committee, Universiti Kebangsaan Malaysia, FF-2020-444 approved the study protocol.

We included COPD patients with a documented spirometry result with an FEV1/FVC ratio of less than 70%, aged more than 40 years who were admitted with a diagnosis of acute exacerbation of COPD (AECOPD). AECOPD was defined as sustained worsening of a patient's baseline respiratory symptoms, lasting for at least 48 hours and requiring the addition or increase of bronchodilators, corticosteroids or antibiotics.

Patients were excluded if they had a diagnosis of bronchial asthma, were on long-term oxygen therapy (LTOT), or had uncontrolled hypertension. Additional exclusion criteria included unstable cardiac conditions such as congestive heart failure, recurrent pneumothorax, neuromuscular disorders, cerebrovascular accident with a modified Rankin Scale (mRS) score >3, prior completion of pulmonary rehabilitation, recent eye surgery, inability to tolerate upright sitting, cognitive impairments that precluded comprehension of instructions, or the presence of pain that interfered with the performance of forceful breathing manoeuvres.

Subjects were assigned to either the intervention group (VIS) or the control group (non-VIS) using block randomisation with a 1:1 ratio. Both groups received the same standard interventions, including active cycle breathing technique (ACBT) and ground-based walking training (GBW). Blinding of the investigators was not feasible due to the distinct nature of the intervention. Consequently, the investigators were not blinded during the analysis.

Subjects were recruited within 72 hours of admission. Upon admission, all participants underwent laboratory screening, and baseline demographic data were collected. A review of exacerbation history, current medications and medical records, including the number of hospitalisations and emergency department visits, was conducted.

Baseline spirometry, including pre-bronchodilator FEV1/FVC, MIP, and MEP, was performed by a trained technician using the Plethysmography Bodybox System (CareFusion) model VMAX E22. According to ATS criteria, subjects were required to perform the spirometry test by exhaling for at least 6 seconds, with a minimum of three attempts and a maximum of eight, depending on test quality. Results were deemed acceptable if the difference between the two best readings was less than 5% and 150 mL. Additionally, subjects completed a COVID-19 antigen rapid test (RTK-Ag) within 72 hours prior to the procedure. Technicians adhered to level three personal protective equipment (PPE) protocols, and disposable, single-patient mouthpieces were used to minimise infection transmission.

The CAT was utilised to evaluate the impact of COPD on health status. This instrument comprises eight domains, with a total score ranging from 0 to 40. The scores are categorised into four levels: low, medium, high and very high. The CAT is a single-dimensional tool available in multiple languages. Depending on the subject's language preference, the questionnaire was administered in Malay, English or Chinese.

6MWT is a simple, self-paced walking test to assess the level of functional exercise capacity. It was done by a trained physiotherapist. The walking track was a flat, hard-surfaced, continuous point-to-point 15-meter tract. Portable pulse oximetry was used to monitor patients' oxygen saturation throughout the test, and it was recorded every minute. Blood pressure was recorded pre-and post-test.

All subjects were required to perform both active cycle of breathing technique (ACBT) and ground-based walking (GBW). ACBT is a breathing technique that combines three different phases of breathing techniques to loosen airway secretions. It involves breathing control (tidal breathing

using the lower chest with shoulders and upper chest relax), chest expansion (breathe in deeply and hold the breath for 5-seconds followed by passive relaxed expiration) exercises and forced expiration technique (huffing -inhaling and active exhaling). Subjects were required to repeat each phase 3 times to complete one cycle of ACBT and to do three cycles at different times in a day. Subjects were trained at least twice during admission to ensure their understanding of the steps and techniques of ACBT. The teach-back method was employed during one-to-one sessions to confirm the effectiveness of the interventions used.

GBW training was conducted by a trained physiotherapist. Subjects were instructed to walk at their own pace on a flat surface for 15 minutes per day, three times a week. Rest breaks were permitted during the walking sessions if patients experienced shortness of breath, light-headedness, or other intolerable symptoms.

In the interventional group, subjects received VIS in addition to ACBT and GBW training. VIS is a therapeutic tool designed to enhance lung function by promoting deep breathing. It utilises a hand-held device, specifically the B-Spiro 5000 as shown in Fig.1 which includes a low resistance filter and measures inhaled air volume while providing visual feedback. Patients are instructed to sit upright, seal the mouthpiece properly, and breathe in forcefully to maintain the piston between two lines for at least 3 seconds. Subjects were required to perform 15 breaths three times a day. The use of VIS aids in lung expansion, helps prevent complications such as atelectasis and supports overall respiratory health.

All subjects were provided with a diary to document their at-home pulmonary rehabilitation (PR) activities to ensure adherence. Weekly telephone follow-ups were conducted to evaluate symptoms, remind subjects of their PR regimen, and verify diary documentation. At week 4, a comprehensive assessment was performed, including a review of symptoms, and spirometry with MIP, MEP, CAT score, and 6MWT were repeated.

Statistical Analysis

The sample size calculation was performed using Cohen's d Formula of effect size (Cohen 1988). The sample size was based on a study by Goswami et al. using 6MWT pre- and post-forced expiratory techniques in chronic bronchitis patients.10 The calculated sample size was 92 (46 subjects in each group), allowing a 10% drop-out rate. The power of the study was designed at a level of 80%. Enrolment was interrupted by the COVID-19 pandemic in March 2020 when UKMMC became a hybrid hospital accepting COVID-19 cases. This resulted in fewer COPD hospital admissions, which slowed down recruitment. The final sample size was 34, and the last subject was recruited in August 2022.

All statistical analyses were performed using Statistical Package for Social Sciences version 27.0 (SPSS Inc, Chicago, IL, USA). Variables were expressed in median (interquartile) and range. Continuous variables were analysed using the Mann–Whitney U test while comparing the two groups: interventional and non-interventional groups. The categorical data was tested with the Wilcoxon signed-rank test. Spearman's rank correlation coefficient was used to determine the relationship between MIP and FEV1, as well as the CAT score and 6MWT. All p-values were two-sided, and values below 0.05 were considered statistically significant.

RESULTS

A total of 34 participants were randomised into two groups: 17 in the intervention group and 17 in the control group. The study design and CONSORT flow diagram are presented in Figure 2. The demographic and baseline characteristics were similar across the groups (Table I). The median age in the intervention group was 71 years (IQR 65–75), while in the control group it was 67 years (IQR 64.8–73). The participants were predominantly male, accounting for 94% of the group. Ethnic distribution was predominantly Malay (70.6%), followed by Chinese (23.5%) and Indian (5.9%). The majority of participants were ex-smokers (27, 79.4%), with five (14.7%) being active smokers and two (5.9%) passive smokers.

Most subjects, 23 (67.6%), had at least one comorbidity, with nine (26.5%) having two, and seven (20.6%) having three or more comorbidities. The distribution according to GOLD classification was: 15 subjects (44.1%) in GOLD II, 14 (41.2%) in GOLD III, 4 (11.8%) in GOLD IV, and 1 (2.9%) in GOLD I. There was no difference in the number of exacerbations between the groups. Two subjects (5.9%) experienced exacerbations once a year, 15 (44%) had exacerbations twice a year, and 17 (50%) had three or more exacerbations annually.

Seven subjects (20%) did not require any supplemental oxygen. Nasal prongs were needed by 41%, 20% required NIV, 11% used a Venturi mask and only 1(2%) required intubation.

The median baseline MIP was 55 cm H_2O, with the control group exhibiting a baseline MIP of 60 cm H_2O and the intervention group a baseline MIP of 50 cm H_2O. The MEP was 65 cm H_2O, with the control group having a baseline MEP of 64 cm H_2O and the intervention group a baseline MEP of 66 cm H_2O.

There was no difference between the interventional group and control group in baseline MIP and MEP (Table II). MIP showed an improvement in both groups at week 4. In the interventional group, the median baseline MIP was 50 cmH_2O (IQR 40.5–70.5) and 59 cmH_2O (39–76.5) at week 4 (p=0.407). In the control group, the median MIP improved from 58 cmH_2O (36.5–85) to 60 cmH_2O (33–88) (p = 0.112).

Approximately 50% (17) of the participants did not record the interventions in the provided diary. However, follow-up phone calls revealed that they were, in fact, adhering to the prescribed pulmonary rehabilitation regimen.

The median 6MWT distance for the overall study population was 235 meters (IQR 126–282). The addition of VIS significantly improved exercise capacity, increasing from 220 meters (IQR 118–275) to 260 meters (IQR 195–327) (p =

Table I: Demographic and baseline characteristics between Interventional and non-interventional groups (n = 34)

Demographic variables	COPD patients admitted for COPD exacerbation n = 34		U	p-value
	Interventional group n = 17	Control group n = 17		
Age (years)	71(65–75)	67 (64.5–73)	113.5	0.284[a]
BMI (kg/m^2), n (%)				
<18.5	2 (11.8)	3 (17.6)	125.5	0.487[a]
18.5–22.9	4 (23.5)	6 (35.3)		
23–24.9	3 (17.6)	1 (5.9)		
≥25	8 (47.1)	7 (41.2)		
Gender, n (%)				
Male	15 (88.2)	17 (100)	127.5	0.151[a]
Female	2 (11.8)	0 (0)		
Ethnicity, n (%)				
Malay	12 (70.6)	6 (35.5)	88.5	0.033[a]
Chinese	4 (23.5)	7 (41.2)		
Indian	1 (5.9)	3 (17.6)		
Others	0 (0)	1 (5.9)		
Smoking status, n (%)			133	0.574a
Non-smoker	0 (0)	0 (0)		
Active smoker	2 (11.8)	3 (17.6)		
Ex-smoker	13 (76.5)	14 (82.4)		
Passive smoker	2 (11.8)	0 (0)		
Co-morbidities, n (%)				
DM	4 (23.5)	5 (29.4)	136	0.702[a]
HTN	10 (58.8)	7 (41.2)	119	0.311[a]
HPL	7 (41.2)	9 (52.9)	127.5	0.498[a]
IHD	2 (11.8)	3 (17.6)	136	0.633[a]
GOLD stages, n (%)				
1	1 (5.9)	0 (0)	126	0.488[a]
2	8 (47.1)	7 (41.2)		
3	6 (35.3)	8 (47.1)		
4	2 (11.8)	2 (11.8)		
Inhalers, n (%)				
SABA	16(9.4)	17 (100)	136	0.317[a]
LABA	0 (0)	0 (0)	144.5	1.000[a]
SAMA	0 (0)	0 (0)	144.5	1.000[a]
LAMA	4 (23.5)	4 (23.5)	144.5	1.000[a]
SAMA/SABA	1 (5.9)	4 (23.5)	119	0.152[a]
ICS	0 (0)	1(5.9)	136	1.000[a]
LAMA/LABA	13(76.4)	13(76.4)	144.5	0.317[a]
LABA/ICS	2 (11.8)	0 (0)	127.5	0.151[a]
LAMA/LABA/ICS	0 (0)	0 (0)	144.5	1.000[a]
Number of exacerbation past 1 year, n (%)				
1	1 (5.9)	1 (5.9)	104.5	0. 121[a]
2	5 (29.4)	10 (58.8)		
≥3	11 (64.7)	6 (35.3)		
Length of hospital stay (days), n (%)				
<7	14 (82.4)	15 (88.2)	136.5	0.654[a]
7–10	2 (11.8)	1 (5.9)		
≥11	1 (5.9)	1 (5.9)		
Highest oxygen requirement during admission, n (%)				
Room air	1 (5.9)	6 (35.3)	106.5	0.170[a]
Nasal prong	8 (47.1)	6 (35.3)		
Face mask	1 (5.9)	0 (0)		
Venturi mask	3 (17.6)	1 (5.9)		
High flow mask	0 (0)	0 (0)		
NIV**	4 (23.5)	3 (17.6)		
Mechanical ventilation	0 (0)	1 (5.9)		
MIP (cmH_20)	50 (40.5–70.5)	60(33–88)	119.5	0.389[a]
MEP (cmH_20)	66 (43–88)	64(35.5–81)	137	0.796[a]
FEV1 (Liter)	1.28(0.88–1.56)	1.26 (0.84–1.55)	133	0.904[a]
FEV1 (%)	51(36.5–62.5)	48 (39–56)	141	0.962[a]
6MWT				
Distance (meters)	220 (118–275)	250(144–294)	126	0.524[a]
Lowest saturation (%)	92(88–94.5)	92(90.5–94)	121	0.413[a]
CAT Score	22(16–26)	21(24)	137.5	0.809[a]

*DM: Diabetes mellitus, HTN: Hypertension, HPL: Hyperlipidaemia, IHD: Ischemic heart disease:
**NIV: Non-invasive ventilation
a : Mann-Whitney U test; p-value < 0.05 is significant

Table II: Comparison of MIP score, CAT score and 6MWT within interventional and non-interventional group (n = 34)

Variables	Interventional group (n = 17)			Control group (n = 17)		
	Before	After	p-value	Before	After	p-value
MIP (cmH20)	50(40.5–70.5)	59(39–76.5)	0.407	58(36.5–85)	60(33–88)	0.112
MEP (cmH20)	66 (43–88)	69(51.5–77)	0.356	64(35.5–81)	63(50.5–101)	0.014
FEV1 (Litres)	1.28(0.88–1.56)	1.1(0.95–1.71)	0.023	1.26(0.84–1.55)	1.19(0.95–1.74)	0.055
FEV1 (%)	51(36.5–62.5)	57(40.5–68.5)	0.017	48(39–56)	51(39–63.5)	0.044
CAT Score						
6MWT	22(16–26)	11(7.5–13)	<0.001	21(14–24.5)	10(8–12.5)	<0.001
Distance(metres)	220(118–275)	260(195–327)	0.002	250(144–294)	280(213–359.5)	0.001
Lowest SpO_2 (%)	92(88–94.5)	95(91–95)	0.002	92(90.5–94)	95(93.5–96)	0.004

Note: Data are presented as median (IQR) unless otherwise stated.
MIP: Maximal inspiratory pressure, CAT: COPD assessment test, 6-MWT: 6 minutes walking test
a Wilcoxon signed-rank test; p-value < 0.05 is significant

Table III: Association of the mean difference (baseline and at week 4) of MIP, CAT score and 6 MWT between the two groups

Variables	Interventional group	Control group	U	p-value
Δ mean MIP (cmH20)	9.0 (20.0)	5.0 (9.5)	128.0	0.569[a]
Δ mean MEP (cmH20)	5.0 (13.0)	4.0 (12.5)	136.5	0.783[a]
Δ mean FEV1 (Litres)	0.06 (0.14)	0.08 (0.16)	142.5	0.945[a]
Δ mean FEV1(%)	3 (5.5)	3 (7.3)	139.5	0.863[a]
Δ mean CAT Score	–9.0 (6)	–10.0 (8.5)	124.5	0.490[a]
Δ mean 6 MWT				
Distance (metres)	40 (57)	36 (83)	134.0	0.717[a]
Lowest SPo2 (%)	2 (2.5)	3 (3)	121.0	0.413[a]

MIP: Maximal inspiratory pressure, CAT: COPD assessment test, 6 MWT: 6 minutes walk test
a: Mann-Whitney U test; p-value < 0.05 is significant

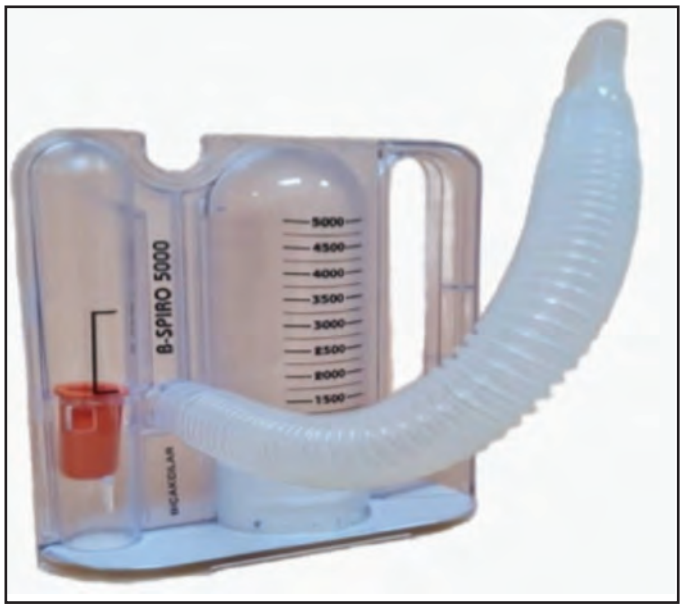

Fig. 1: Volume-oriented (B-Spiro 5000) incentive spirometer.

0.002). This improvement was also observed in the control group, where the distance increased from 250 meters (IQR 144–294) to 280 meters (IQR 213–359.5) (p = 0.001).

The baseline median CAT score for the overall study population was 21.5 (IQR 15.8–25). In the intervention group, the median CAT score was 22 (IQR 16–26) at baseline and decreased to 11 (IQR 7.5–13) at week 4 (p < 0.001). A similar result was seen in the control group: 21 (14–24.5) to 10 (8–12.5) (p = <0.001). Comparison between the two groups in MIP, MEP, FEV1, CAT score and 6MWT is shown in Table III.

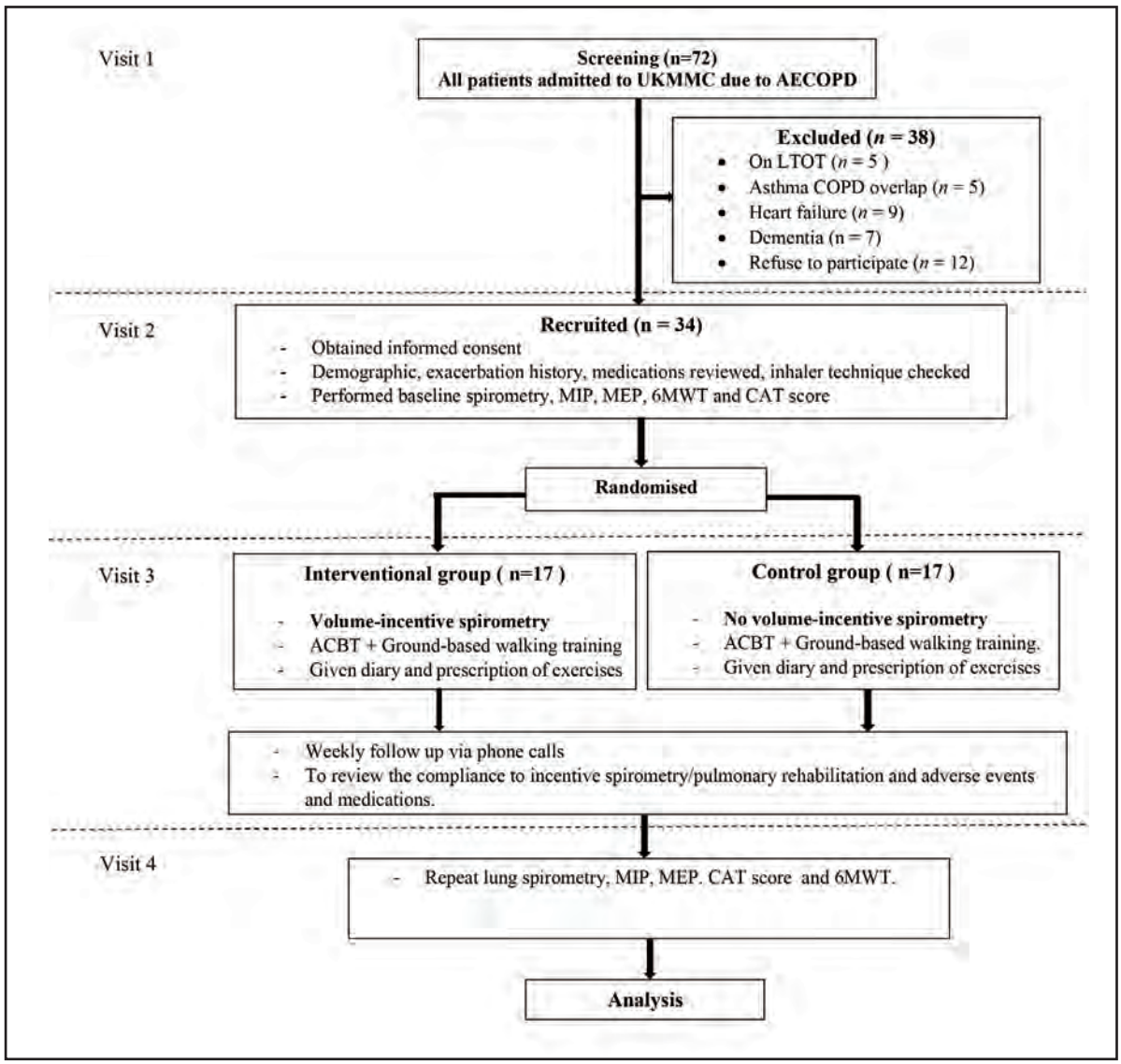

Fig. 2: Study design and flow diagram

DISCUSSION

During the first 6 months of the study, from June 2021 to December 2021, a movement control order (MCO) was in effect due to the COVID-19 pandemic. This period saw a significant reduction in patient mobility and healthcare facility visits. Following the relaxation of the MCO in January 2022, there was a noticeable decrease in hospital admissions for exacerbations of COPD.

The majority of subjects in this study were male (94%), and 14.7% of the participants were active smokers (Table I). These are consistent with known higher prevalence of COPD among males and smokers.[11,12]

COPD patients are typically not obese.[13] In our study, over half of the subjects were classified as overweight. This observation reflects the broader trend of rising obesity rates in Malaysia, where approximately one or two individuals is overweight.[14] Obesity in COPD has demonstrated mixed effects; reduced 6 minute-walk distance, worse dyspnoea, poor quality of life and an increased risk for hospitalisation for exacerbations but also lower mortality and higher lung functions.[15,16] While one study in Taiwan and another in China suggest COPD patients who are obese may have a lower exacerbation rate than leaner COPD patients.[17,18]

Exacerbations play a significant role in the clinical course of COPD. In our study, 94.11% of patients had a history of at least two exacerbations in the past year. This figure exceeds those reported in other studies of inpatient pulmonary rehabilitation, which typically showed improvement over 12 weeks.[19,20] The frequency of exacerbations is associated with a progressively higher risk of mortality; each additional moderate exacerbation further elevates the risk of death, with the risk increasing substantially with severe exacerbations.[21]

In COPD patients, lower MIP and MEP typically indicate reduced respiratory muscle strength and can contribute to

increased respiratory symptoms and reduced exercise tolerance. COPD patients hospitalised for exacerbations have been reported to have low MIP.[22] In our study, the baseline MEP and MIP values were lower compared to those reported in other studies, which documented higher baseline MEP and MIP values.[19]

In our study, a higher proportion of patients were on supplemental oxygen therapy, including NIV, whereas other studies included patients who did not require oxygen therapy.[19,20] This is likely attributable to the lower MIP and MEP values observed.

Early rehabilitation during hospital admission for chronic respiratory diseases has not been shown to reduce subsequent readmission rates or improve physical function recovery over 12 months, with higher mortality observed in the intervention group.[22] These results suggest that progressive exercise rehabilitation may not offer additional benefits beyond standard physiotherapy in the early stages of an acute illness. However, our study found that initiating inpatient pulmonary rehabilitation at 48 hours post-admission is safe, indicating that while early rehabilitation may not enhance long-term outcomes, it does not compromise patient safety when carefully managed.

In our study, we utilised a specific approach by combining VIS with the active-cycle-breathing technique (ACBT), distinguishing it from other inpatient pulmonary rehabilitation (PR) designs. VIS focuses on enhancing lung volumes and inspiratory muscle strength, while ACBT targets mucus clearance and improved ventilation. The combined approach aimed to address multiple aspects of respiratory function simultaneously.[23] In our study, the addition of VIS to ACBT and ground-based walking training resulted in a significant improvement in the 6MWT.

There was a numerical improvement in both MEP and MIP after the intervention, although the changes were not statistically significant. This may be attributed to the study population's higher history of exacerbations and lower baseline MIP and MEP values, indicating poorer muscle strength. Oliveira et al. reported significant changes in MIP after 45 days of COPD exacerbation. Our study, which had a shorter duration of 4 weeks, may have been too brief to detect significant changes. A longer duration might be necessary to demonstrate the significance of such improvements.[24]

The CAT is a questionnaire designed to evaluate the impact of COPD on a patient's health status and quality of life with higher scores indicating greater disease impact and poorer health status. Studies have shown that higher CAT score categories are associated with a significantly shorter time to first exacerbation and higher exacerbation risk.[25] In our study, at baseline, the median CAT score was high (Table I). This is an expected finding as all subjects were in exacerbation.

In the intervention group, the mean CAT score decreased from 22 to 11, while in the control group, it decreased from 21 to 10; both changes were statistically significant. These reductions signify substantial improvements in the impact of COPD on patients' health status and quality of life. The findings suggest that both treatment approaches, whether the intervention or standard care, effectively alleviated symptoms and enhanced overall well-being, demonstrating the effectiveness of these strategies in managing COPD and improving patient outcomes.

Study Limitation

The study had several limitations. The small sample size suggests that a longer follow-up period might have provided more robust data. Additionally, the lack of supervision could have led to suboptimal use of VIS techniques by the subjects. Future prospective studies are needed to compare the effectiveness of VIS in stable versus acute exacerbations of COPD.

CONCLUSION

Early initiation of pulmonary rehabilitation in patients with acute exacerbations, characterised by poor muscle strength and a history of exacerbations, resulted in significant improvements in patient-reported symptoms and 6-minute walk test (6MWT) outcomes. Although there was only a numerical improvement in maximum inspiratory pressure (MIP) and maximum expiratory pressure (MEP), the intervention did not extend the length of hospital stay, highlighting its safety and efficacy in the acute care setting.

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ETHICS DECLARATIONS

Ethics approval and consent to participate

This study was approved by the Medical Ethics Committee of Universiti Kebangsaan Malaysia Medical Centre (FF-2020-444), and it is in accordance with the Helsinki Declaration (IV adaptation). Written informed consent was obtained from all participants.

COMPETING INTERESTS

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

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Organisms causing community-acquired bloodstream infection in medical department: A single centre retrospective observational study

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ABSTRACT

Introduction: Community acquired bloodstream infection (CA-BSI) is positive blood culture obtained within 48 hours of hospital admission. Bloodstream infections need to be treated with antibiotics. Inappropriate choice of antibiotics will lead to antimicrobial resistance. This is an observational retrospective study to look at the antimicrobial resistance of organisms causing bloodstream infections in patients admitted to the medical wards in our centre. The aim of the study is to determine the appropriate choice of empirical antibiotics for suspected CA-BSI in our hospital.

Materials and Methods: All patients admitted to medical wards with blood stream infection during the period January 2021 to June 2021 were enrolled. Identification of organisms and antimicrobial susceptibility testing were obtained. Information regarding the severity of the bacteremia was collected by assessing if the patient needed inotropes, mechanical ventilation or renal replacement therapy. Data on comorbidities which were the presence of end-stage renal failure, diabetic mellitus and immunosuppression were collected.

Results: Total of 269 cases were screened. Out of these 104 communities acquired cases were included. The pathogens frequently isolated were gram negative organisms most commonly *Escherichia coli* (43%) and Klebsiella species (30%). *Staphylococcus aureus* accounts for the majority of gram-positive organisms. Only two out of 20 *Staphylococcus aureus* were methicillin resistant. *Bulkholderia pseudomallei* accounts for 7.8% cases. All *Burkholderia pseudomallei* isolates were sensitive to cotrimoxazole. *Escherichia coli* (46%) isolates demonstrated a higher resistance pattern to Augmentin compared to *klebsiella species* (17.4%). The overall mortality rate was 22%, with higher rates for those critically ill (39%). Patients with Enterobacteriaceae infection showed no difference in outcome between the groups of patients according to sensitivity to Augmentin and cefotaxime. These groups of patients who were critically ill did not demonstrate any significant difference in terms of resistance pattern to Augmentin (p = 0.3) and cefotaxime (p = 0.7). Patients who are aged 65 or older have a significantly more resistant pattern to Augmentin and cefotaxime.

Conclusion: Antibiogram serves as a guide for clinicians to choose appropriate choices of antibiotics based on local data. Empirical antibiotics of choice for patients with sepsis should be narrow-spectrum beta lactam/beta lactamase inhibitors. Broad spectrum beta lactam/beta lactamase inhibitors such as piperacillin tazobactam should be reserved for patients who are critically ill and elderly patients over 65 years. The antibiotics should be deescalated once the organisms and sensitivity of the antibiotics are known.

INTRODUCTION

Bloodstream infections are a common cause of morbidity and mortality in many countries in the world. The mortality rate ranges from 15.2% up to 40.8% depending on severity and clinical risk factors.[1] Bloodstream infections can be subdivided based on the timing of presentation. Based on the Centre for Disease Control and Prevention (CDC) definition, community acquired bloodstream infection (CA-BSI) is positive blood culture obtained within 48 hours of hospital admission and hospital acquired bloodstream infection (HA-BSI) is positive blood culture obtained after 48 hours of admission. It is important to differentiate CA-BSI from HA-BSI as the causative organisms and sensitivity of the bacterias are different. Bacteria such as *Escherichia coli, Klebsiella pneumonia, Pseudomonas aeruginosa* and *Staphylococcus aureus* frequently cause bloodstream infections. Bloodstream infections are treated with antibiotics. However, inappropriate use of antibiotics has been shown to cause antimicrobial resistance.

Antimicrobial resistance is a global problem because it leads to increased morbidity and mortality.[2] Antimicrobial resistance can be attributed to many factors. Michael et al.,[3] divided these causes into microbiological and human causes.[3] Microbiological causes include the ability to acquire resistance either via mutations or plasmids. Human causes include a large and growing population, and overuse of antimicrobials either due to prescription in a clinical setting or in agriculture.[6,7] Antimicrobial overprescription may occur when the antibiotic is used in an empirical setting where tests to identify the causative organism to allow de-escalation is not done. Failure to identify the causative organisms may also lead to treatment failure necessitating more visits or a

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prolonged stay. Antibiotic overprescription may also occur when antibiotics are prescribed in conditions where they are not needed.[8,9] Multiple studies have shown that increasing antibiotic usage will increase the resistance of bacteria in the environment.[8,9]

The causative organisms in a patient presenting with sepsis will not be known until 24 to 72 hours after cultures are taken.[10] During this time, clinicians usually initiate empirical antibiotics. The selection of empirical antibiotics is guided by clinical guidelines, antibiograms and previous microbiological results of the patient or the physician's experience. Antibiograms are created from microbiological data obtained from lab results.[11] However, the disadvantage is that the cultures are not stratified into community or hospital-acquired infections. Many organisms causing community-acquired bloodstream infections are more sensitive to narrow-spectrum antibiotics compared to hospital-acquired organisms. This may give a false appearance that empirical antibiotics selected to treat community-acquired infections appear to have a higher-than-expected resistance rate. Another limitation of this method is these calculations are made based on the culture sent rather than based on individual patients. The epidemiology of BSI and antimicrobial resistance patterns are always evolving and vary between different institutions. As such, we conducted an observational retrospective study to look at the antimicrobial resistance of organisms causing community-acquired bloodstream infections in patients admitted to the medical wards in our hospital. The aim of the study is to determine the appropriate choice of empirical antibiotics for suspected community-acquired bloodstream infections in our hospital.

MATERIALS AND METHODS

This study was performed at Hospital Tuanku Ja'afar Seremban, a tertiary referral and teaching hospital in Negeri Sembilan. All patients admitted to medical wards in our hospital with bloodstream infections from January 2021 to June 2021 were enrolled. Exclusion criteria include patients who had positive blood cultures taken after 48 hours of admission, blood cultures growing contaminant, fungal organisms, blood cultures taken within 30 days of previous admission or the source of infection was a catheter-related bloodstream infection. Catheter-related bloodstream infections were excluded because they were more likely due to hospital-acquired organisms.

All peripheral blood culture results were collected from the microbiology laboratory using the WHONET 2022 database (expanded version of WHONET 5.6). Information about the patient identifiers, date of blood culture collection, identification of organisms, and antimicrobial susceptibility testing were obtained from this system. Organisms which were skin colonisers or yeast were removed. Reports were matched to their individual cases. Each case was assessed to determine if the bloodstream infection was community acquired. Cases that were determined to be community acquired were included in the analysis. Information regarding the severity of the bacteremia was collected by assessing if the patient needed inotropes, mechanical ventilation, or renal replacement therapy. Although the severity of bacteremia is usually assessed with more robust scores such as SOFA scores, collecting the details needed to assess these scorings were deemed difficult for the investigating team. Other data that were collected included the presence of diabetic mellitus and immunosuppression.

For this study, blood culture bottles (BACTEC Plus Aerobic/F bottles, BACTEC Anaerobic Lytic/F) were incubated in BACTEC FX system (Becton Dickinson Microbiology System, BMS Diagnostics), and flagged positive blood culture bottles were gram-stained and cultured onto blood agar, Mac Conkey agar, chocolate agar, and Sabouraud Dextrose agar. Preliminary antimicrobial susceptibility testing was done according to the microbiology laboratory standard operating protocol. All culture plates were incubated for 16-18 hours. Colony of organisms that were isolated were identified by matrix-assisted laser desorption/ionisation time-of-flight mass spectrometry (MALDI-TOF MS) Biotyper platform (Bruker Daltonics MALDI Biotyper, BMS DIagnostics). Final antimicrobial susceptibility testing was performed and interpreted according to the Clinical and Laboratory Standard Institute (CLSI) guidelines (CLSI M100 32nd Edition 2022, CLSI M45 3rd Edition 2016, CLSI M24-A2 2011) or European Committee on Antimicrobial Susceptibility Testing (EUCAST) 2022 guideline. Immunocompromised status is defined as patients with haematological malignancy, human immunodeficiency virus with a CD4 less than 200, patients receiving chemotherapy within the last 30 days and patients taking immunosuppressants.

The protocol was approved by the human research ethics committee of the National Medical Research Register (NMRR ID-23-00783-TRL). The study was conducted in compliance with ethical principles outlined in the Declaration of Helsinki and the Malaysian Good Clinical Practice Guideline. Due to the retrospective observation nature of the study, the MREC waived the need for informed consent. Data analysis was done using the Rstudio version (2023.09.1+494). Continuous variables will be expressed as mean and standard deviation (SD) unless otherwise stated. Binary variables will be expressed as percentages. Inferential analysis of categorical data will use Chi-square or Fisher's exact test. A value of $p < 0.05$ is considered statistically significant.

RESULTS

During the study period from January 2021 to June 2021, a total of 269 cases of bloodstream infections were screened. Out of these, 99 (36.8%) were considered clinically significant community-acquired organisms, 143 (53.1%) were hospital-acquired organisms, 5 (1.9%) were healthcare-associated bloodstream infections and the rest were classified as contaminants.

Patient Characteristics

The demographics, severity, and comorbidities of patients with bloodstream infections are summarised in Table I. There were almost equal proportions of male and female patients in our study. Of note, 68 patients (69%) were diabetic. However only a small proportion of patients were immunocompromised. About 17.2% of these patients were critically ill requiring inotropic support, mechanical ventilation, and/or renal replacement therapy.

Table I: Characteristics of patients with community acquired bacteremia at medical wards Hospital Tuanku Ja'afar Seremban, January to June 2021

Variables	Patients no. (%)
Age, year (mean,SD)	
Male	62.2 ± 21.0
Female	64.3 ± 16.7
Sex	
Male	53 (54%)
Female	46 (46%)
Comorbidities	
Diabetes mellitus	68 (69%)
Immunocompromised	7 (7.1%)
Critically ill	
Mechanical ventilation	12 (12%)
Renal replacement therapy	2 (2.0%)
Inotropic support	15 (15%)

Table II: Organisms isolated from the blood of patients at medical wards Hospital Tuanku Ja'afar Seremban, January to June 2022

Organism	Total number (%)
Escherichia coli	42 (38)
Klebsiella sp.	22 (20)
Staphylococcus aureus	16 (15)
Burkholderia pseudomallei	9 (8)
Streptococcus sp.	7 (6)
Others	14 (13)

Table III : Outcome according to patient characteristics

Characteristics	Survivor	Non survivor	p-value
Sex			0.3
Male	37 (50%)	13 (62%)	
Female	37 (50%)	8 (38%)	
Age	61 ± 18	68 ± 20	0.075
Critically Ill	10 (14%)	7 (33%)	0.052
Comorbids			
Diabetes mellitus	54 (73%)	12 (57%)	0.2
Immunocompromised state	5 (6.8%)	2 (9.5%)	0.6

Table IV : Characteristics of Enterobacteriaceae bacteremia according to sensitivity of antibiotics

Characteristics	Augmentin		p-value
	Sensitive	Resistant	
Age			
< 65 years old	23 (88%)	3 (12%)	0.006
> 65 years old	19 (56%)	15 (44%)	
Gender			
Male	13 (54%)	11 (46%)	0.029
Female	29 (81%)	7 (19%)	
Diabetes mellitus	31 (76%)	10 (24%)	0.2
Critically Ill	8 (89%)	1 (11%)	0.3
Outcome			
Alive	34 (71%)	14 (29%)	0.3
Dead	8 (80%)	2 (20%)	

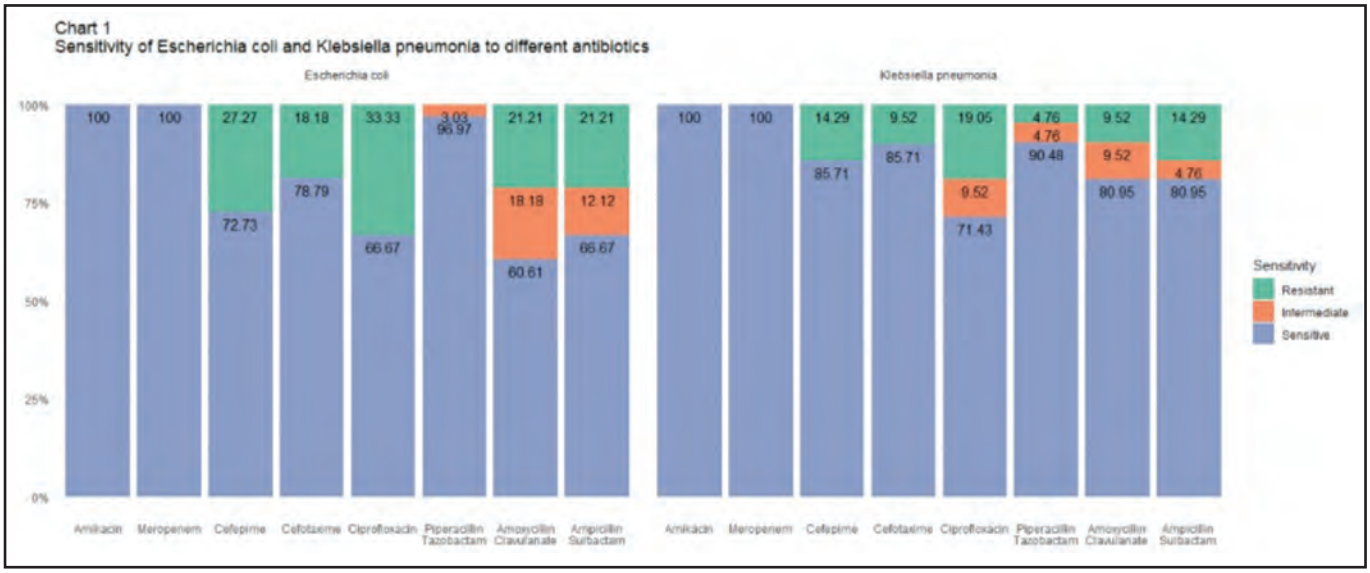

Fig. 1:

Blood Culture Isolates

Gram-negative organisms were isolated in 79% of blood cultures. The pathogens most commonly found were *Escherichia coli* and *Klebsiella species*, which accounted for 48% and 25% of gram-negative episodes respectively. Out of 21% of episodes caused by gram-positive microorganisms, two-thirds were due to *Staphylococcus aureus*. Of note, *Burkholderia pseudomallei*, the causative agent of melioidosis, was isolated in 8.2% of community-acquired bacteremias. 89% of the patients with *Burkholderia pseudomallei* bacteremia have a history of diabetes mellitus. Other organisms isolated in smaller numbers were *Streptococcus sp* (6.4%), *Salmonella sp* (3.6%), *Pseudomonas aeruginosa* (3.6%), *Enterococcus sp* (1.8%), *Enterobacter sp* (1.8%) and *Proteus sp* (1.8%).

Antimicrobial Susceptibility Patterns

Antibiotic sensitivity patterns of the four main organisms isolated were analysed. Antibiotic disk diffusion susceptibility testing of *Escherichia coli* isolates demonstrated that 39.4% were resistant to Augmentin, 18.2% resistant to cefotaxime and 33.3% resistant to ciprofloxacin, while 97% were sensitive to piperacillin tazobactam and none were resistant to meropenem. Comparatively, Klebsiella isolates demonstrated a less resistant pattern, 19% were resistant to Augmentin, 9.5% were resistant to cefotaxime and 28.6% were resistant to ciprofloxacin. Only 2 out of 20 *Staphylococcus aureus* were methicillin-resistant. All *Burkholderia pseudomallei* isolates were sensitive to cotrimoxazole.

Outcome

Of 99 patients with clinically significant community acquired bacteremia, the mortality rate is 21% (21), excluding a small proportion of 4.0% (4) unknown outcome. Critically ill patients did not demonstrate any significant difference in mortality rate. There are also no statistical differences between genders, comorbidities, and age predisposition for mortality. We did a further analysis looking into the patient groups with *Enterobacteriaceae* infection. No difference in outcome was seen between the groups of patients according to sensitivity to Augmentin and cefotaxime. The patients with *Enterobacteriaceae bacteremia* who were critically ill did not demonstrate any significant difference in terms of resistance pattern to Augmentin ($p = 0.3$) and cefotaxime ($p = 0.7$). However, our analysis has shown that patients who are aged above 65 years have significantly more resistance to Augmentin and cefotaxime.

DISCUSSION

Hospital Tuanku Ja'afar Seremban (HTJS) is a 968 bedded hospital. Medical department makes up about 28% of these beds. It is located in a tropical environment in an upper middle-income nation. In our sample, the majority of bloodstream infections are caused by gram-negative organisms. The two most common organisms that were isolated are *Escherichia coli* and *Klebsiella pneumonia*. These organisms are expected to be common in our setting due to the high prevalence of diabetes mellitus.[12] In our data, female patients were more likely to develop *E. coli* bacteremia. *E. coli* is a more common pathogen in females because they are more prone to urinary tract infections.

Comparing our findings with other studies shows some interesting differences. Laos, a country from South East Asia showed that the most commonly cultured organism was Salmonella typhi.[13] The resistance rates of *E.coli* and *K. pneumonia* to ceftriaxone were 8% and 0% respectively. This was lower than the rates we encountered in our centre. Another study by Kanoksil et al.,[14] which was done in northeast Thailand showed some different findings. Here the most common organisms were *Escherichia coli* (23.1%), *Burkholderia pseudomallei* (19.3%), and *Staphylococcus aureus* (8.2%). This study was conducted from 2004 to 2010 and showed an increase in the proportion of extended spectrum beta-lactamases (ESBL) producing *E. coli* and *Klebsiella pneumoniae* over time.

In our study, resistance to narrower-spectrum antibiotics was predominant in patients above 65 years of age. Evidence for

this trend has been demonstrated by Pop-Vicas et al.[15] They have demonstrated that there is a 16-fold increase in the rates of resistant organisms for community-acquired bloodstream infections in elderly patients. The elderly are more likely to be from long-term care facilities. Hujer et al have shown that resistant organisms are more likely to colonize patients from these facilities.[16] Causes for the increase in resistant organisms colonization in this population are the presence of devices, frequent admissions, repeated courses of antibiotics, and the spread of resistant organisms from one patient to another. However, our findings show no difference in the resistance patterns and severity of the presentation.

Our study does not show an association between resistance patterns of Enterobacteriaceae and mortality. We found that there is no significant association between patients who presented with more severe disease and mortality, but this could be due to very small numbers in the subset. Older age was associated with higher mortality in our study. Similar findings were demonstrated by de Lastours et al who studied E. coli bacteremia.[17] These findings are important as they can determine the choice of empirical antibiotics for a centre.

Hence, we recommend that empirical antibiotics for patients with sepsis who are not critically ill, narrow-spectrum beta-lactam/beta-lactamase inhibitors should be selected. Broad-spectrum beta-lactam/beta-lactamase inhibitors such as piperacillin tazobactam should be selected for patients who are elderly above 65 years of age. We should consider broad spectrum antibiotics for patients who are critically ill as they tend to deteriorate rapidly. Our centre avoids the use of third-generation cephalosporins as empirical therapy except for central nervous system infections. Third-generation cephalosporins over-usage has been shown to increase rates of extended-spectrum beta-lactamase-producing organisms.[9] Third-generation cephalosporins are useful in the setting of drug-resistant *Salmonella typhi*. However, from our data, this organism is not encountered. Once the organisms and sensitivity has been identified, the antibiotics should be de-escalated to the narrowest possible spectrum.

The limitations of this study include firstly, the complete physical case notes were not reviewed. This was done to reduce the manpower needed and save time. Rather the abbreviated electronic discharge summary was reviewed. This may have caused some risk factors of resistant organisms to be underestimated, such as residence in long-term care facilities. This may explain why older patients were more likely to have resistance than younger patients. We had a lack of information on proper cultures and imaging to support clinical diagnosis for the study population. Hence, we could not be able to analyse the relationship between antibiotic sensitivity and clinical diagnosis further. The small sample size caused the lower power when subgroups were analysed. This study is the first study in Malaysia to review the antibiogram of community-acquired bloodstream infections.

CONCLUSION

Antibiogram serves as a guide for clinicians to choose appropriate choices of antibiotics based on local data. Empirical antibiotics of choice for patients with sepsis should be narrow-spectrum beta lactam/beta lactamase inhibitors. Broader spectrum antibiotics should be selected for older or patients in critically ill. Further studies will be required to assess the relationship between antibiotic sensitivity, clinical diagnosis, and clinical outcomes.

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Eating disorders among physically disabled national athletes in Malaysia

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ABSTRACT

Introduction: Eating disorders are becoming a cause of concern amongst athletes in recent times. The objective of this study was to determine the prevalence of eating disorders amongst physically disabled athletes in Malaysia. Athletes were sampled and screened for eating disorders utilising the Eating Disorder Examination-Questionnaire 6.0 (EDE-Q-for females) and the Eating Disorder Assessment in Males (EDAM-for males).

Materials and Methods: Athletes were approached individually, and they responded via an online questionnaire. A total of 271 athletes responded (sample needed 269) from the total of 700 athletes (38.7%).

Results: From the total, 14.4% (n = 39, 95% CI = 10.56–19.28) of the athletes had eating disorders (14.4% of the male athletes and 14.5% of female athletes). The final model of a binary logistic regression was conducted and found that the higher the body weight (AOR: 1.02, 95% CI: 1.00–1.04, p = 0.03), the higher the income (AOR: 0.992, 95% CI: 0.990–0.994, p = 0.02), the more athlete suffered from coaches intimidating behaviours(AOR: 1.17, 95% CI: 1.03–1.33, p = 0.02), a perception of having stress (AOR: 7.61, 95% CI: 1.69–34.39, p = 0.01) and having stress (AOR: 3.70, 95% CI: 1.02–9.68, p = 0.04) were common factors seen in athletes with eating disorders.

Conclusion: About two in every 10 disabled athletes suffered from eating disorders.

KEYWORDS:
Eating disorders, disabled athletes, athletes, eating disorder examination questionnaire, eating disorder assessment in males, Malaysia

INTRODUCTION

Eating disorders have been discussed since the early 80s and in South East Asia- since the 90s.[1,2] Eating disorders have always been linked to the female gender- with many initial and early studies only showing that the problem was prevalent among females.[1,3] However, that has been attributed to the fact that many of the screening scales have been validated amongst females only, and questions that are used to screen lacked male outlooks on eating patterns as well as body image perceptions.[3–5] The prevalence of eating disorders among females is between 5.5–17.9% and 0.6–2.4% amongst males.[6] The yearly incidence among females is eight in 100,000 population and five in 1,000,000 population.[7] In Malaysia, though limited, research published in 2022 reported that 0.8% had anorexia nervosa, 1.4% had bulimia nervosa, 0.1% had binge eating disorders and 51.4% of them had Other Specified Feeding and Eating Disorders (OSFED).[8]

Eating disorders are not strangers in the field of sports athletes. Athletes have been prone to eating disorders for some time now due to different reasons- such as competing in weight-sensitive sports, body weight, gender, genetics, mental health issues and many others.[3,9–13] Disabled athletes are also at risk if not even at higher rates, compared to ordinaryathletes.[10,14] Disabled athletes might be more at risk as some disabilities are linked to specific co-morbidities like diabetes especially if they are physically disabled and/or are suffering from genetical disorders.[15,16] However, little is known about their prevalence of eating disorders.

In Malaysia, there were a few research papers that studied eating disorders among athletes and disabled athletes. Generally, the prevalence of eating disorders in Malaysia (from previous studies) was between 13.9 to 18.2% and the sample population were mostly from the female population.[1,8,17–19] A study in 2009 looking at the female athlete triad (menstrual dysfunction, bone density reduction and low energy availability) amongst female athletes in Malaysia reported that 1.9% of female athletes suffered from it.[20] In 2011, a Malaysian study that sampled both males and females reported that female athletes were more prone to eating disorders and body dissatisfaction than their male colleagues.[21] A general study conducted in 2019 sampling disabled Malaysian athletes concluded that 37.6% had eating disorders due to changing emotions (emotional eating disorder), 34.3% had uncontrolled eating and 28% had restrained eating disorders due to cognition impairment.[14]

Studies worldwide reported that the associated factors of eating disorders amongst athletes without disabilities and disabled athletes were about the same.[22]

Eating disorders have been known to increase the rate of injuries among athletes, especially those that involve the musculoskeletal system.[23] The situation may be made worse that many injured athletes with eating disorders tend to either get repeated injuries or risk not recovering from recent injuries.[23] Poor general health, especially that involving anaemia, bone health and the irregularity of menstrual

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cycles in female athletes, are among the consequences that can be seen from eating disorders.[20,23–25] Picking up eating disorders early might help rehabilitate the athlete so that they do not suffer further from the after-effects of eating disorders like injuries.[26]

Eating disorders and disordered eating are often used interchangeably but do not refer to the same thing. Eating disorders can be diagnosed via the classification of anorexia nervosa, bulimia nervosa, binge eating disorder or OSFED.[27] For it to be an eating disorder, it must meet the criteria set by the DSM-5 manual.[3] On the other hand, disordered eating is described as a spectrum of abnormal or harmful eating behaviours that might be linked in an attempt to alter weight.[27] However, it must be understood that all screening tools that have been used in the past are to screen for eating disorders and not disordered eating, though they might not be able to pinpoint a specific eating disorder.[3,5,27] In this research, the term eating disorder is used in the context of the ability of screening tools to pick up eating disorders among those who answer it. Though it might not be specific to the type of eating disorder suffered, it is used as a screening tool to detect the presence of an eating disorder.

The main objective of this study was to identify the prevalence of eating disorders amongst disabled national athletes in Malaysia. It was also the objective to identify factors associated with eating disorders among them.

In this study, we defined disabled athletes as physically disabled athletes who have represented the country at least once. Eating disorders were defined as having an eating disorder that the final score of the EDE-Q 6.0 (global score >2.3) and EDAM (Scale ≥2) indicated.[5]

MATERIALS AND METHODS

We conducted a cross-sectional study from October 2021 to May 2022 amongst Malaysian paralympic athletes to identify the prevalence of eating disorders. We obtained the database of athletes from the central repository kept by the Paralympic Athletes' Division in the Ministry of Youth and Sports. We then approached the athletes via short messaging or electronic mail, inviting them to participate in the study. We included Malaysian national athletes who were above the age of 18 and were still competing professionally. We excluded those already with an eating disorder (to calculate factors affecting unknown eating disorders) or those who were on long sabbatical leave. The athletes had an option to either answer the questionnaire in Malay (local language) or English. The consent and data collection was done online (due to the COVID-19 pandemic) that was accessible via any electronic device that had access to the internet. They were provided a link to read and understand this study's objectives before giving their electronic informed consent. They were then asked about their brief demographic details such as age, gender, sport they were involved in, their level of representation and other relevant details. Then, the female athletes were automatically directed (based on their answers for their birth gender) to the EDE-Q 6.0 questionnaire, and the males were directed to the EDAM questionnaire. After answering them, the male and female athletes answered the DASS-21 questionnaire (to screen for depression, anxiety and stress), the CAREMS questionnaire (to screen for coach-athlete relationship emotional maltreatment scale, to identify if they were suffering from any emotional issues with their coaches) and the CRAFFT 2.1 (a questionnaire to detect substance use and abuse). The time taken to complete the questionnaire was estimated to be about an hour. Once the questions were answered, the respondents clicked 'Send,' their answers were stored in a database accessible to the researchers only. Data was later imported and analysed in the SPSS v21.0 software.

Sample Size

We calculated the sample size with multiple objectives given. To calculate the sample size, we calculated all the objectives for identifying the prevalence in general, by gender, by levels of depression, anxiety and stress, by coach relationship, and by addiction. The largest sample size was yielded by using the precision formula in the EpiCalc Calculator v1.01 (2000)- by setting the prevalence of coach-athlete emotional maltreatment at 22.4% (from the study of Coker-Craney & Reel, 2015), the final sample needed was 267 athletes.[28] For the gender sample, it was calculated that the minimum required male athletes for this study was 58, and the female athletes needed were 33 (a total of 91).[29] There were about 700 athletes in the database and all were approached via social media.

Tools Used

We utilised the EDE-Q 6.0 and Eating Disorder Assessment in Males (EDAM) questionnaires (in English and the translated Malay version (a local native language) to identify the prevalence of eating disorders. The EDE-Q 6.0 questionnaire was used amongst the female athletes, and the EDAM was used amongst the male athletes.[4,5] To identify the coach-athlete relationship and emotional maltreatment relationship, the researchers utilised the Coach-Athlete Relationship Emotional Maltreatment Scale (CAREMS).[30]

To identify if the athlete was having any depressive, anxiety or stress symptoms- the DASS-21 scale was used.[31] To identify substance abuse, CRAFFT 2.1 was used.[32] Except for the DASS-21 (already translated to Malay before this), forward and backward translation was done for all the questionnaires. The reliability (Cronbach alpha) obtained for the Malay language was as follows:

- EDAM = 0.87 (original in English: 0.91)[4]
- EDE-Q = 0.95 (original in English: 0.93)[5]
- CAREMS = 0.97 (original in English: 0.96)[30]
- CRAFFT 2.1 = 0.79 (original in English: 0.73)[33]

All necessary permissions to utilise the EDAM and CAREMS questionnaire were obtained. The CRAFFT 2.1 and EDE-Q questionnaires were openly available. All data was entered and analysed via SPSS v21.0.

Perceived Depression, Anxiety and Stress

From the demographic variables, the researchers enquired from the participants if they generally felt depressed, anxious or stressed. This was solely the perception by the participant without a formal medical diagnosis.

EDAM

The EDAM questionnaire has a specific section (from 4) to identify eating disorders. The questions of interest are 5, 10, 12, 26, 30, 40, 41, 42, 45, 47 and 50. The responses to these questions are in the form of a Likert scale with 'Never' scored as 0, 'Rarely' as 1, 'Sometimes' as 2, 'Often' as 3, and 'Always' as 4. These scoring for the eating disorder domain were then totalled, with scores 0-11 given the 'scale of 1', 12–17 as the 'scale of 2', 18–22 as the 'scale of 3', 23–28 as the 'scale of 4', 29–33 as the 'scale of 5', 34–38 as the 'scale of 6' and 39–44 as the 'scale of 7'. The 'scale of 1' was interpreted as 'Little or No Concern', 'scale of 2–3' as 'Slight concern', 'scale of 4 – 5' as 'Moderate concern' and 'scale of 6–7' as 'Significant concern'. This was according to the analysis and cut-off suggested for using the EDAM questionnaire.4 This was later put into a binary form: 'scale of 1' as 'Not having an eating disorder' and scales 2–7 as 'Having an eating disorder'. This scale was used for male athletes only.

EDE-Q 6.0

The EDE-Q questionnaire was analysed using the Global Score- the mean of the scores obtained from each athlete. This was later categorized as 'having an eating disorder' for scores of 2.3 or above, and those below 2.3 were classified as 'Not having an eating disorder'. This followed the recommendation of Mond et al. (2004).[34] This scale was utilised amongst female athletes only.

CAREMS

The CAREMS questionnaire was utilised, looking at the five domains.[30] The domains were: 'Performance-based disparagement', 'direct personal disparagement', 'embarrassing behaviours', 'indirect personal disparagement' and 'intimidating behaviours'. Responses were given in the form of a 5-point Likert scale, and the scores ranged from 'Never' = 1 to 'Always' = 5.[30] The higher the score, the more the relationship-emotional maltreatment between the coach and athlete.[30] This scale was used to compare those with eating disorders and those without. The mean and standard deviations were used to compare the 'eating disorders' and 'no eating disorders' groups.

DASS-21

The DASS-21 questionnaire responses were calculated based on the categories Gomez gave in 2016.[35] Depression scores from 0–9, anxiety from 0–7, and stress from 0–14 were considered normal. The outcomes were further made binary- anything higher than the scores previously mentioned was deemed to be having depression, anxiety or stress (based on the domain).

CRAFFT 2.1

The CRAFFT 2.1 questionnaire was used to identify if there was substance abuse amongst the respondents. The identification of abuse was made based on 'does not have a substance issue' for a score of 0 for questions 1 to 3, and anything above is considered 'may have a substance issue'. This was per the CABHRE 2018 manual.[36]

Statistical Analysis

A binary logistic regression analysis was conducted to identify factors affecting the eating disorders of disabled athletes. The outcome variable was then compared to those with eating disorders against those who do not have eating disorders.

A univariate analysis was conducted by comparing one variable with the outcome variable. The variables yielding a p-value of ≤0.3 were deemed significant and included in the final analysis of the multivariate binary logistic regression.
A multivariate analysis was conducted, including all variables that yielded a p-value of ≤0.3 in the univariate analysis.[37] The final model with factors affecting eating disorders will be determined with variables that yield a p-value of <0.05.

Ethical Approval

The researchers applied for an ethical approval within the *Universiti Kebangsaan Malaysia* medical ethics committee and were provided with the ethical approval (Malaysia (FF-2020-468; JEP-2020-594). No identifiers were collected for the purpose of analysis and all data remained anonymous as well as confidential. The database containing data collected was only accessible by researchers through password mechanisms.

RESULTS

The researchers obtained 271 physically disabled athletes (38.7% of the number listed in the database) to participate in the survey (there were no athletes that had a known history of eating disorder and none of them were on long sabbatical leave). Of the total, 195 (72.0%) athletes were male, and 76 (28.0%) were female.

Of the 271 athletes sampled, 14.4% (n = 39, 95% CI = 10.56–19.28) had eating disorders. When calculated according to the athletes' gender, 14.4% (n = 28, 95% CI = 9.94–20.30) were male athletes, and 14.5% (n = 11, 95% CI = 7.81–24.88) were female athletes.

The participants were described and separated into those with eating disorders and those without eating disorders. From the total, the majority had answered the questionnaires in the Malay language, were of the Malay race, were male, involved in athletics, were not involved in weight-sensitive sports, competed mainly at the state level, were mainly for the state of Perak, were of the normal body mass index (BMI) category, mainly clerical support staff, did not perceive to have an eating disorder, did not perceive to have a family history of eating disorders, perceived that they did not have depression, perceived not to have anxiety, perceived not to have stress, were non-diabetics, were non-smokers, had no active substance abuse, had no previous history of substance abuse and did not consume alcohol.

A statistical comparison between those with an eating disorder and those without an eating disorder showed that the only statistical significance found was the difference in the distribution of BMI between the two groups (p = 0.03), those who perceived to have stress (p = 0.01). These categorical variables were compared via a Chi-square.

Table I: Description of the participants by their eating disorder status

Categorical variables	With an eating disorder N (%) (n = 39)	Without an eating disorder (n = 232)	p-value
Language answered in			
Malay language	36 (14.8)	208 (85.2)	0.78*
English	3 (11.1)	24 (89.9)	
Race			
Malay	33 (15.1)	186 (84.9)	0.48*
Chinese	1 (6.7)	14 (93.3)	
Indian	0	9 (100)	
Others	5 (17.9)	23 (82.1)	
Gender			
Male	28 (14.4)	167 (85.6)	0.98
Female	11 (14.5)	65 (85.5)	
Sports involved in			
Athletics	11 (14.7)	64 (85.3)	0.65*
Bowling	6 (21.4)	22 (78.6)	
Lawn bowls	4 (25.0)	12 (75.0)	
Archery	8 (18.2)	36 (81.8)	
Ping-pong	2 (6.5)	29 (93.5)	
Weightlifting	2 (20.0)	8 (80.0)	
Swimming	1 (5.9)	16 (84.1)	
Boccia	1 (11.1)	8 (88.9)	
Badminton	3 (13.6)	19 (86.4)	
Cycling	0	11 (100)	
Others	1 (12.5)	7 (87.5)	
Involved in weight-sensitive sports			
Yes	2 (20.0)	8 (80.0)	0.64*
No	37 (14.2)	224 (85.8)	
Common level of representation			
State	28 (15.1)	158 (84.9)	0.97*
South East Asia	5 (14.3)	30 (85.7)	
Asia	2 (13.3)	13 (86.7)	
World	4 (11.4)	31 (88.6)	
State represented			
Perlis	1 (20.0)	4 (80.0)	0.76*
Kedah	0	5 (100)	
Pulau Pinang	1 (16.7)	5 (83.3)	
Perak	7 (17.5)	33 (82.5)	
Pahang	9 (30.0)	21 (70.0)	
Kelantan	2(14.3)	12 (85.7)	
Terengganu	2 (8.3)	22 (91.7)	
Selangor	2 (12.5)	14 (87.5)	
Negeri Sembilan	1 (10.0)	9 (90.0)	
Melaka	2 (12.5)	14 (87.5)	
Johor	2 (7.4)	25 (92.6)	
Sarawak	3 (18.8)	13 (81.3)	
Sabah	5 (15.6)	27 (84.4)	
WP Labuan	0	1 (100)	
WP Kuala Lumpur	1 (7.4)	13 (92.9)	
National representation only	1 (7.1)	13 (92.9)	
BMI status			
<18.5- underweight	4 (11.8)	30 (88.2)	0.03*
18.5 -<25- normal weight	11 (9.8)	101 (0.2)	
25 -<30 – overweight	12 (18.5)	53 (81.5)	
30 -<35 – Class I obesity	8 (25.0)	24 (75.0)	
35 -<40 – Class II obesity	0	16 (100)	
40 and above- Class III obesity	4 (33.3)	8 (66.7)	
Working status			
Not working	14 (19.2)	59 (80.8)	0.18*
Clerical support staff	17 (18.3)	76 (81.7)	
Technical and certified workers	3 (6.0)	47 (94.0)	
Trade and services	4 (12.9)	27 (87.1)	
Professional workers	1 (5.3)	18 (94.7)	
Civil service workers	0	5 (100)	

Table I: Description of the participants by their eating disorder status

Categorical variables	With an eating disorder n (%) (n = 39)	Without an eating disorder (n = 232)	p-value
Perceived to have an eating disorder			
Yes	7 (14.6)	41 (85.4)	0.97
No	32 (14.3)	191 (85.7)	
Perceived to have a family history of eating disorder			
Yes	6 (20.7)	23 (79.3)	0.31
No	33 (13.6)	209 (86.4)	
Perceived to have depression			
Yes	3 (10.3)	26 (89.7)	0.59*
No	36 (14.9)	206 (85.1)	
Perceived to have anxiety			
Yes	3 (7.9)	35 (92.1)	0.30*
No	36 (15.5)	197 (84.5)	
Perceived to have stress			
Yes	3 (4.4)	65 (95.6)	0.01*
No	36 (17.7)	167 (82.3)	
Diagnosed as a diabetic			
Yes	1 (6.7)	14 (93.3)	0.49*
No	38 (14.8)	218 (85.2)	
Smoking status			
Yes	5 (12.5)	35 (87.5)	0.53*
No	30 (15.9)	159 (84.1)	
Smoked before and stopped	4 (9.5)	38 (90.5)	
Addiction status (Marijuana, Elicit drugs, Cocaine etc)			
Yes	0	0	-
No	39 (14.4)	232 (85.6)	
Previously addicted (Marijuana, Elicit drugs, Cocaine etc)			
Yes	0	4 (100)	0.54*
No	39 (14.6)	228 (85.4)	
Alcohol consumption			
Yes or consumed previously	1 (5.9)	16 (94.1)	0.48*
No	38 (15.0)	216 (85.0)	
Continuous variables	Mean (SD)	Mean (SD)	p value
Age (in years)	30.67 (8.79)	30.65 (9.67)	0.99
Weight (in kilograms)	68.69 (18.67)	63.91 (16.72)	0.10
Continuous variables	Median (IQR)	Median (IQR)	p value
Height (in meters)	1.60 (0.20)	1.63 (0.18)	0.54
BMI (kg/m2)	26.72 (9.93)	24.08 (8.31)	0.06
Staying alone (in months)	1.00 (2.00)	2.00 (4.00)	0.27
Monthly income (RM)	800 (900)	1100 (1700)	0.08

*Fisher-exact or Exact test was applied

For the continuous variables that were normally distributed (age in years and weight in kilograms), an independent t-test was conducted. A Mann-Whitney U test was applied for the continuous variables that were not normally distributed (height, BMI, months stayed alone and income in Ringgit Malaysia). There was no statistically significant difference when comparing those with and without eating disorders (Table I).

Analytical Analysis

The DASS-21, CRAFFT 2.1 and CAREMS variables were calculated as stipulated in the mode of analysis section. The analysis comparing those with eating disorders and those without eating disorders found that the majority had no depression, anxiety or stress. The majority also did not have any substance abuse. However, when a Chi-square statistical analysis was applied, there was a statistically significant difference between the groups where stress was concerned (p = 0.03).

Comparing the CAREMS score to identify the Coach-Athlete relationship with emotional maltreatment, a Mann-Whitney U test showed no statistically significant difference between the two groups (Table II).

Statistical Analysis

Before moving on to the binary logistic regression with the outcome of looking at those with eating disorders against those without, we examined the possible interactions between all independent variables. This was also done for the final model.

Upon review, there was a high interaction between 'monthly income' and 'working status'. There was also an interaction

Table II: Comparison of the DASS-21, CRAFFT 2.1, and CAREMS scale between those with eating disorders and those without

Categorical variables			With an eating disorder n (%) (n = 39)	Without an eating disorder n (%) (n = 232)	p-value
DASS-21	Depression	Yes	15 (20.8)	57 (79.2)	0.07
		No	24 (12.1)	175 (87.9)	
	Anxiety	Yes	15 (18.1)	68 (81.9)	0.25
		No	24 (12.8)	164 (87.2)	
	Stress	Yes	9 (26.5)	25 (73.5)	0.03
		No	30 (12.7)	207 (87.3)	
CRAFFT 2.1		May have a substance issue	1 (8.3)	11 (91.7)	0.70*
		Does not have a substance issue	38 (14.7)	221 (85.3)	
Continuous variables			**Mean (SD)**	**Mean (SD)**	**p-value**
CAREMS		Performance-based disparagement	9.82 (5.10)	10.56 (5.97)	0.47
		Direct personal disparagement	5.72 (2.91)	5.89 (3.43)	0.77
		Embarrassing behaviours	4.74 (2.84)	4.70 (2.8()	0.93
		Indirect personal disparagement	4.51 (2.62)	4.37 (2.41)	0.73
		Intimidating behaviours	5.21 (3.04)	4.67 (2.60)	0.17

*Fisher-exact or Exact test was applied

Table III: Univariate and multivariate analysis table

Variables		Univariate analysis			Multivariate analysis		
		OR	95%CI	p	AOR	95%CI	p
Perceived to have anxiety	Yes	Reference		0.30	Reference		0.83
	No	2.13	0.62–7.31		1.19	0.23–6.18	
Perceived to have stress	Yes	Reference		0.01	Reference		0.01
	No	4.67	1.39–15.71		7.61	1.69–34.39	
Weight in kilograms		1.02	1.00–1.04	0.10	1.02	1.00–1.04	0.03
Stayed alone (in months)		0.96	0.89–1.03	0.27	0.96	0.88–1.05	0.37
Monthly income (RM)		1.00	0.99–1.00	0.08	0.992	0.990–0.994	0.02
Depression status	No	Reference		0.07	Reference		0.13
	Yes	1.91	0.94–3.91		2.66	0.76–9.37	
Anxiety status	No	Reference		0.25	Reference		0.32
	Yes	1.51	0.75–3.05		1.86	0.55–6.34	
Stress status	No	Reference		0.03	Reference		0.04
	Yes	2.48	1.06–5.83		3.70	1.02–9.68	
CAREMS	Intimidating behaviours	1.08	0.97–1.21	0.17	1.17	1.03–1.33	0.02

between the BMI with the variables 'weight' and 'height'. For these interactions and variables- the researchers picked 'monthly income', 'weight,' and 'height' as they provided the best model value. BMI and 'Working status' were removed from the regressional model. A model for Goodness-of-fit was conducted for the binary logistic regression.

A Hosmer-Lemeshow test was done, and the value obtained was p = 0.38. A correctly classified percentage was conducted, and it showed 86.3%, and the Nagelkarke R^2 done was 0.202. This interpreted that the dataset for the binary logistic regression was good and acceptable.

The researchers conducted a univariate and a multivariate logistic regression with the outcome of 'With an eating disorder' being compared with 'Without an eating disorder'. The univariate analysis was conducted, comparing the independent variables with the outcome. All variables that yielded a p-value of less than 0.3 in the univariate analysis were included in the multivariate regression. The odds in the univariate were reported as odds ratio (OR). For the multivariate analysis, independent variables with a p value <0.05 were deemed statistically significant. The multivariate analysis was reported with an adjusted odds ratio (AOR).

From the univariate analysis (Table I analysis), we found that 'Perceived to have anxiety', 'Perceived to have stress', 'Weight in kilograms', 'Stayed alone', 'Monthly income', and 'Depression status'. Anxiety status', 'Stress status,' and the 'CAREMS score for intimidating behaviours' all yielded a p-value of ≤0.3. These variables were included in the multivariate analysis (Table III).

The independent variables that yielded p ≤ 0.3 from the univariate analysis were included.37 The final model showed that "Perceived to have stressed" (AOR: 7.61; 95% CI: 1.69–34.39, p = 0.01), "Having stress" (AOR: 3.70; 95%CI: 1.02–9.68, p = 0.04), an increase in weight (AOR: 1.02, 95%CI: 1.00–1.04, p = 0.01), an increase in income (AOR: 0.992, 95%CI: 0.990–0.994, p = 0.02) and an increase in the CAREMS score for 'Intimidating behaviour' (AOR: 1.17, 95% CI: 1.03–1.33, p = 0.02) were factors that were related to those athletes with an "eating disorder" when compared to those "Without an eating disorder". Independent variables of "Perceived to have anxiety", "Staying alone", "Depression status," and "Anxiety status" were deemed to be confounders. Full details are available in Table III.

Summary of results

(1) Athletes who perceived stress were eight times more likely to have an eating disorder than those who did not.
(2) Athletes who are stressed are four times more likely to have an eating disorder than those who do not.
(3) For every rise in 1 kg, there is a 1.02 times likelihood that the athlete might have eating disorders compared to those who do not.
(4) For every 1 Ringgit Malaysia extra income earned, athletes are likelier to have an eating disorder than those who do not.
(5) For every 1.00-point increase in the CAREMS score for intimidating behaviour, there is 1.17 times increase in an athlete having an eating disorder compared to those who do not.

DISCUSSION

Prevalence of Eating Disorders Amongst Athletes

The prevalence of eating disorders among Malaysian athletes can range anywhere between 13.9% to 18.2%.[1,8,17–19] The prevalence in other countries might differ because some differentiate between eating disorders and disordered eating. A similar prevalence study conducted in Spain during the 2016 period, reported that among the 60 disabled athletes sampled, 1.67% of them were deemed to have eating disorders. This differs from the prevalence of the current study discussed perhaps due to a different screening tool utilised and the sample of athletes used were smaller.

In a 2013 Norwegian study, it was reported that 7% of athletes had an eating disorder compared to the control group (2.3%).[38] It was also reported that more female athletes had eating disorders (14.0%) compared to male athletes (3.2%).[38] It must be understood that the screening process from the Norwegian study picked up 25% of athletes suspected to have an eating disorder, it was only 7% of them who finally had an actual eating disorder (after a clinical interview).[38] Thus, the prevalence of eating disorders might differ from study to study- because of the different tools used to screen and diagnose eating disorders among athletes.[3,5]

Compared with a published paper on eating disorders in South East Asia in 2015, it was reported that eating disorders had been actively picked up ever since the 90s, especially in Singapore, Malaysia, and Hong Kong.[1] Though it was reported that the prevalence of eating disorders in this region was low, it might be underdiagnosed and is expected to increase in the future.[1]

Research conducted in 2019 amongst 150 female, non-disabled athletes in Sarawak (a state in the East of Malaysia) reported that less active and non-weight sensitive sports exhibited higher eating disorder issues. The current study did not obtain that, but it might have been due to the different sample populations (disabled athletes). A study published in 2023 in Malaysia regarding relative energy deficiency in sports reported that most sampled athletes (non-disabled) were at medium risk.[23] Of the 192 athletes sampled by Marzuki et al, 64.7% were worried about what they consumed, and 69.3% thought about burning calories while exercising.[23] This can be related to the 'Binge eating disorder,' explaining that the prevalence in Malaysia could be much more than what was found.

Factors that Affected Eating Disorders

Before moving into the details of factors that affect eating disorders in disabled athletes, attention must be paid to a paper that was published amongst Australian athletes in 2018 that reported that there was no statistically significant difference between non-disabled and disabled athletes when it comes to mental health issues except for alcohol consumption habits and the level of self-confidence.[22] Therefore, the researcher for this paper deduced that since eating disorders are considered a mental health issue, factors that affected non-disabled athletes in this instance would not be different from those affecting disabled athletes.

In research conducted amongst 93 disabled Malaysian athletes in 2020, it was reported that 37.6% of the athletes had eating disorders due to emotional stress, 34.3% had uncontrolled eating, and 28% had cognitive restraint.[14] One of the reasons reported that affected emotional eating was the athlete being obese.[14] This might explain why eating disorders were linked with increased weight and stress, as found in the current study.

A study conducted in 2015 mentioned that coaches often utilise intimidating and pressure modalities to get the best out of their athletes.[39] This might have efficacy in terms of performances, but as it was found in this study, it might affect the mentality of athletes, causing them to be more prone to eating disorders.

Other factors that might lead to eating disorders are other associated mental health issues like stress and perceived stress. Some of them are linked to participation prior to big-staged events, especially regarding thoughts on injuries.[40] It was also stated in the same study that factors that play a role in injuries and recovery are eating habits.[40] This might mean that eating disorders, injuries, and stress might be a vicious cycle that must be intervened early to prevent prolonged periods of being out of competitive fitness.

A previous study conducted during the year 2016 in the United States reported that one of the factors that increases eating disorders is having a higher income.[41] Similarly, a study in China (2008) reported that higher-income houses were more likely to be where eating disorders were more commonly seen.[42] An increase in weight might also indicate a possibility of suffering from an eating disorder, especially where binge eating disorders are concerned.[3,5]

Strengths and Limitations

Amongst the strengths of this study was that it was one of the few studies conducted with a large sample size of disabled national athletes compared to previously published work. The study also utilised forward and backward-translated questionnaires to obtain the data from a Malay language (a locally preferred language) version of the questionnaires. Some of the limitations are that there might have been an under or over-estimation of the prevalence as the list of athletes obtained might be incomplete as it might not have been updated from the system – not allowing the researchers

to sample new athletes. Due to the limited local data, the sampling was not done by different sports.

CONCLUSION

It was found that the prevalence of eating disorders amongst Malaysian disabled athletes was 14.4%. Factors that affected the eating disorders were perceived to be stressed, being stressed, an increase in weight, an increase in income, and an increased score for the CAREMS intimidating behaviour scale. The researchers would recommend that future studies look at screening for eating disorders amongst disabled athletes by sports (proportionate sampling) so that eating disorders can be more screened in a targeted manner. It might be useful for stakeholders to screen for eating disorders amongst disabled athletes so that the repercussions that can arise will be minimal.

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CONFLICT OF INTEREST

The authors do not have any conflicts of interest to declare.

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ORIGINAL ARTICLE

The prevalence, risk factors and coping strategies of low back pain among nurses in public hospitals in Kota Kinabalu, Sabah: A cross-sectional study

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ABSTRACT

Introduction: Healthcare workers are recognised to have a high prevalence of musculoskeletal disorders and nursing profession are well known with high prevalence of low back pain (LBP). There is a widespread consensus that low back discomfort is a major contributor to both inabilities to work and illness. Absenteeism is frequently employed as a proxy for the presence of a handicap. Aim: The purpose of this study was to determine the prevalence of LBP among nurses in six different wards in three general hospitals in Kota Kinabalu, Sabah as well as the associated workplace risk factors and coping strategies implemented by nurses in ward.

Materials and Methods: A cross-sectional study involved 420 nurses from three public hospitals in Kota Kinabalu, Sabah, was carried out. The respondents were carefully selected by proportionate stratified random sampling method. Nurses sociodemographic and occupational details, occupational health in nursing practice, seventeen work risk variables and nine coping techniques were collected via a self-administered questionnaire.

Results: Among the 420 participants, 57 did not report any discomfort. In the previous 12 months, 44.5% (95.0% CI: 39.74,49.25) of nurses experienced low back discomfort lasting longer than three days. The results of a simple logistic regression analysis revealed that gender and years of working experience were significantly associated with LBP. The department of intensive care unit nurses had the highest OR value of 2.4 (p = 0.03). There were no statistically significant association with age, marital status and body mass index (p > 0.05). Adjusting plinth or bed height (68.4%) was the top coping mechanism cited by respondents in the clinical context to reduce the risk of LBP, and working with perplexed or agitated patients posed the greatest occupational risk.

Conclusion: LBP is still a major work-related issue among nurses, with a high prevalence rate. To mitigate these impacts, multidisciplinary efforts are required. The outcomes of this study may help policy makers to allocate resources to reduce LBP among nurses.

KEYWORDS:
Musculoskeletal disorders, low back pain, healthcare workers, coping strategies, job risk factors

INTRODUCTION

People from all over the world suffer from low back pain (LBP), a condition that is not only common but also debilitating, burdensome and incapacitating. Strains and sprains of the lumbar region, as well as injuries to the tendons, ligaments, or muscles in the lower back, are the most common causes of acute and chronic LBP, respectively. Back injuries can be caused by trauma, improper use or overuse, as well as the act of lifting a heavy object, twisting, bending, or extending the muscles, all of which result in strain and stretching. Back injuries may additionally be triggered by back overuse.[1] The location of LBP, also known as lumbago or lumbosacral pain, lies below the 12th rib and above the gluteal folds. Lumbago and lumbosacral pain are more correct terms for LBP. This discomfort is typically localised to the lower part of the back, and it can frequently be traced to a wide variety of underlying causes and disorders.[2]

According to the Global Burden of Disease Study 2015 (GBD), LBP is one of the top 10 conditions that causes disease and disability. It has an estimated number of disabilities adjusted life years higher than that of Hepatitis C, motor vehicle accidents, tuberculosis, lung cancer, chronic obstructive pulmonary disease and preterm birth complications.[3] There is a widespread consensus that low back discomfort is a major contributor to both inabilities to work and illness. It is projected that 116 million production days were lost in the United Kingdom as a result of work incapability caused by LBP in the year 1994–1995.[4] It is the primary factor in activity restriction and missed work across the globe, and imposes an enormous economic burden on people households, neighbourhoods, businesses and governments. Despite significant primary preventive efforts made in several nations throughout the years, a high prevalence of back pain among healthcare professionals has persisted.[5]

It has been found that the prevalence of LBP among nurses varies from country to country, with England having the

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highest rate (85.7%), followed by Hong Kong (80.9%) and Italy (62%). According to the findings of the research carried out in Africa, 70 % of nurses suffered with LBP. In 2015, research carried out in Qatar indicated that the prevalence of LBP among nurses was 54.3%. As is the case in a great number of other nations, LBP is a significant cause for worry among healthcare workers in the Kingdom of Saudi Arabia, particularly among registered nurses. In past cross-sectional studies, the prevalence of LBP in Saudi Arabia was shown to range from 48.41% in the Taif region, to 61% in the Sudayr region, and to 75 % in the capital of Riyadh.[3]

According to the World Health Organisation (WHO), musculoskeletal illnesses are the major cause of years lived with disability (YLDs) worldwide, accounting for approximately 149 million YLDs, which is equivalent to 17% of all YLDs. In addition, workplace musculoskeletal health policies, such as regulations for hard physical work and lifting, are frequently lacking or poorly monitored. This can lead to a variety of musculoskeletal injuries.6 Although self-reported work-related musculoskeletal disorders (WRMSDs) appear to be on the decline, the Labour Force Survey (LFS) estimates that there were roughly 480,000 WRMSD cases with a prevalence rate of 1420 per 100,000 employees in 2019/2020.[7] Variables that may affect the prognosis of musculoskeletal pain have lately received increased attention, with a focus on the role of coping mechanisms and the opportunity for change to improve outcomes.[8] There is a significant relationship between the prevalence of back pain and some coping strategies used by respondents, such as asking for help when performing patient handling activities, using height and or angle adjustable work surfaces, resting and sitting after a long period of work, pausing regularly to stretch or use different body parts to administer procedures, avoiding monotonous or awkward body positions and taking sick leave when necessary.[9]

The Social Security Organisation Malaysia (SOCSO), has documented a rising trend in the amount of money paid out to employees for occupational diseases (including permanent and temporary benefits), going from RM2.65 million in 2009 to RM14.05 million in 2014. The compensation for MSDs makes up a sizeable share of the total compensation for occupational disorders, and from 2009 to 2014, it also increased generally.[10] Government healthcare facilities in Malaysia are among the busiest workplaces in comparison to those in other countries that need their personnel to be physically active and exposed to different occupational risks that enhance the risk of accidents and musculoskeletal ailments.[1] Unfortunately, not many published statistics on MSDs among those healthcare workers exist. Only information pertaining to private companies that pay contributions to the compensation systems that SOCSO oversees is made available online by the SOCSO. The aim of this study is to investigate the prevalence, risk factors and explore on coping strategies of LBP among nurses working at public hospitals in Kota Kinabalu Sabah.

MATERIALS AND METHODS

Study Design and Population

This cross-sectional study took place from October 2022 to June 2023 in Kota Kinabalu, Sabah, and included nurses from three public hospitals: Queen Elizabeth Hospital, Queen Elizabeth II Hospital, and Sabah Women and Children Hospital (HWKKS). Out of 712 eligible nurses, 420 were selected through proportionate stratified random sampling, which considered various inclusion and exclusion criteria. The study encompassed nurses working across six different departments within these hospitals. Participants ranged in age from 20 to 60 years old and had at least 1 year of experience in a public hospital. Exclusions were made for nurses who were on maternity leave, pregnant, on unrecorded leave, or had previous trauma or congenital spine issues. The prevalence of LBP, which was found to be 79.4% in a prior study conducted in Port Dickson, Malaysia, was employed to establish the sample size using a single proportion and dichotomous outcome.[12] Formula $n = z^2 (1-\alpha/2)\ p(1-p)/d2$ was used with a 95% confidence level. This results in the requirement for 252 participants, and the final sample size (n = 420) after accounting for a 40% non-response rate adjustment.

Variables

The variables studies consist of independent variables, mainly on the sociodemographic aspects and important variables such working experience in years, marital status, working department, body mass index, total number of children and work-related pain experience. As for the dependent variable is the dichotomous outcome of LBP (yes/no). As the survey instrument, a self-administered questionnaire that had been validated in the past was used to collect data on sociodemographic characteristics, the prevalence and pattern of work-related musculoskeletal disorders (WMSDs), associated employment risk factors, and coping techniques. A previously validated questionnaire on WMSDs among physical therapists served as the basis for this study's questionnaire, which was developed from that questionnaire. There were four sections, section A described information on respondents' demographic, section B on component of the occupational health in nursing practice. It was a modified form of the Standardized Nordic Questionnaire, and consisted of inquiries regarding nine different body sites.[13]

Statistical Analysis

All data obtained was entered into Microsoft Excel, then filtered and reviewed for any missing or incomplete data before being entered into IBM Statistical Package for Social Sciences (SPSS) version 28.0. The findings of this research have been summed up in tables, graphs, frequency and percentage distributions as part of the descriptive presentation of the findings. As for Inferential analysis the association of self-reported LBP symptoms with sociodemographic and occupational characteristics were determined with simple logistic regression, odds ratios (OR) and upper and lower 95.0% confidence intervals (CI) were calculated to determine the risk of LBP.

RESULTS

Demographic and Characteristics of Participants

The sociodemographic and occupational characteristics of the participants were presented in Table I, majority of the

Table I: Sociodemographic and occupational characteristics (n = 420)

Variables	Frequency (n)	Percentages (%)	Mean ± SD
Age (in years)			35.7 ± 6.4
Less than 30	47	11.2	
31-40	281	66.9	
More than 41	92	21.9	
Gender			
Female	386	91.9	
Male	34	8.1	
Marital status			
Single	84	20.0	
Married	336	80.0	
BMI (kg/m2)			26.9 ± 9.8
Underweight	4	1.0	
Normal	102	24.3	
Overweight	85	20.2	
Obesity	229	54.5	
No. of children			
0	141	33.6	
1-2	169	40.2	
3-4	95	22.6	
More than 4	15	3.6	
Highest education			
Diploma	395	94.0	
Degree	25	6.0	
Working department			
Intensive care unit (ICU)	113	26.9	
Medical	105	25.0	
Obstetrics & gynaecology	32	7.6	
Orthopaedics	40	9.5	
Paediatrics	44	10.5	
Surgical	86	20.5	
Working experience (years)			
1-5	43	10.2	
6-10	210	50.2	
11-20	122	29.0	
More than 20	45	10.7	
Nursing rank/cadre			
Community nurse	30	7.1	
Staff nurse	333	79.3	
Chief nurse	57	13.6	

respondents were between the age of 31 and 40 years old, with a mean age of 35.7 ± 6.4 and mainly female (91.9%). The nurses body mass index (BMI) ranged from 15.8 kg/m^2 to 43.56 kg/m^2, with a mean BMI of 26.9 kg/m^2 ± 9.8. In terms of the participants current line of work, the intensive care unit (ICU) department where the vast majority of the participants in this study were employed (26.9%), followed by medical department (25%). About half of the respondents had worked in the nursing profession for between six and ten years and those worked less than five years and more than twenty years were 10.2% and 10.7% respectively. Out of 420 respondents, 48.6% had training on ergonomics. In terms of the educational background, 94 % of nurses have at least a diploma, and 25 nurses have pursued degrees in nursing. Most of the registered nurses, or approximately 79.3%, work as staff nurses. Another 7.1% were community nurses, while the remaining 13.6% were chief nurses.

Figure 1 shows the percentage of respondents who reported on coping strategies they used to reduce their risk of developing LBP. Adjusting the height of the plinth or bed, requesting assistance in managing heavy patients, and modifying the position of the patient or nurse were the top three coping techniques stated by the respondents in the clinical context to decrease the risk of low back discomfort. Figure 2 displays the 12-month prevalence rates of WMSDs in the various body regions of 363 respondents who complain of pain at any site of their body part, respondents were allowed to specify only one body area that has the most frequent or severe pain.

The association between LBP with sociodemographic and occupational factors was studied to identify risk factors causing the condition. The results from simple logistic regression conveyed in Table II. No statistically significant associations ($p > 0.05$) were found between age, marital status and BMI. Gender was statistically significant; woman have 2.38 times higher in odd compared to male. The vast majority of the study's nurses were obese and overweight accounted for about 75 % of all participants. Even though the proportion was high, noted that there is no significant association between BMI and LBP. Group with more than three children was significantly associated with LBP, $p < 0.01$, suggests that people with more than three children were 2.48

Table II: Simple logistic regression of sociodemographic factors and low back pain

Risk factors	Low back pain n (%)		p-value	Odds ratio (95% CI)
	Yes	No		
Socio-demographic				
Age				
Less than 30	23 (9.8)	24 (12.8)		ref
31-40	152 (65.2)	129 (69.0)	0.51	0.81 (0.44,1.51)
More than 41	58 (24.9)	34 (18.2)	0.11	0.56 (0.28,1.14)
Gender				
Male	25 (10.7)	9 (4.8)		ref
Female	208 (89.3)	178 (95.2)	0.03	2.38 (1.08,5.23)
Marital status				
Married	183 (78.5)	153 (81.8)		ref
Single	50 (21.5)	34 (18.2)	0.40	0.81 (0.50,1.32)
BMI (kg/m2)				
Normal	54 (23.1x)	47 (25.1)		ref
High	177 (75.9)	140 (74.9)	0.67	0.91 (0.58,1.42)
No. of children				
0	89 (38.2)	52 (27.8)		ref
1-2	99 (42.5)	70 (37.4)	0.42	1.21 (0.75,1.92)
More than 3	45 (19.3)	65 (34.8)	<0.01	2.48 (1.48,4.12)

p < 0.05 consider statistically significant
ref; reference category of the risk factor

Table III: Simple logistic regression of occupational characteristics and low back pain

Risk factors	Low back pain n (%)		p-value	Odds ratio (95% CI)
	Yes	No		
Occupational characteristics				
Working department				
Paediatrics	56 (65.1)	30 (34.9)		ref
Intensive Care Unit (ICU)	49 (43.4)	64 (56.6)	0.03	2.44 (1.37,4.35)
Medical	50 (47.6)	55 (52.4)	0.02	2.05 (1.14,3.69)
Obstetrics & Gynaecology	23 (71.9)	9 (28.1)	0.49	0.73 (0.30,1.78)
Orthopaedics	23 (57.5)	17 (42.5)	0.41	1.38 (0.64,2.97)
Surgical	32 (72.7)	12 (27.3)	0.38	0.70 (0.315,1.56)
Working experience (years)				
>20	32(71.1)	13(28.9)		ref
1-5	22(51.2)	21(48.4)	0.05	2.35 (0.97.5.66)
6-10	112(53.3)	98 46.7)	0.05	2.15 (1.07,4.33)
11-20	67 (54.9)	55(45.1)	0.06	2.02 (0.97,4.22)

p-value <0.05 consider statistically significant
ref; reference category of the risk factor

times more likely to experience LBP than people without children.

The association between the occupational characteristics and LBP were investigated and presented in Table III. The reported p-value=0.03 suggests statistical significance, indicating that the link between working in ICU and LBP is unlikely to have happened by chance. The odds ratio of 2.44 (95% CI: 1.37,4.35) indicated that nurses in the ICU are more likely than those in the paediatric department to experience LBP. Similarly, there is a stronger association between LBP and nurses working in the medical department. Nurses in the medical department are 2.05 times more likely to experience LBP than nurses in the paediatric department. This study also found that, working experience in years was significant associated with LBP among nurses. Based on the results, nurses who have experience working below 10 years were found to be associated with LBP. This working experience can be further categorized into two groups, those working in between 1-5 years, 2.35 (95% CI: 0.97,5.66, p = 0.05) and working in between 6-10 years, 2.15 (95% CI: 1.07,4.33, p = 0.05).

DISCUSSION

According to the research conducted at three public hospitals in Kota Kinabalu, 86.4% of workers experienced musculoskeletal disorders related to their jobs within a 12-month period, with 51.5% of the instances involving LBP. The 95% confidence interval (CI) indicated that the true prevalence of LBP in the population falls between 45.96% and 56.64%. Consistent with previous research from Malaysia and elsewhere, this study found that LBP was the most common MSD-related symptom overall. The prevalence

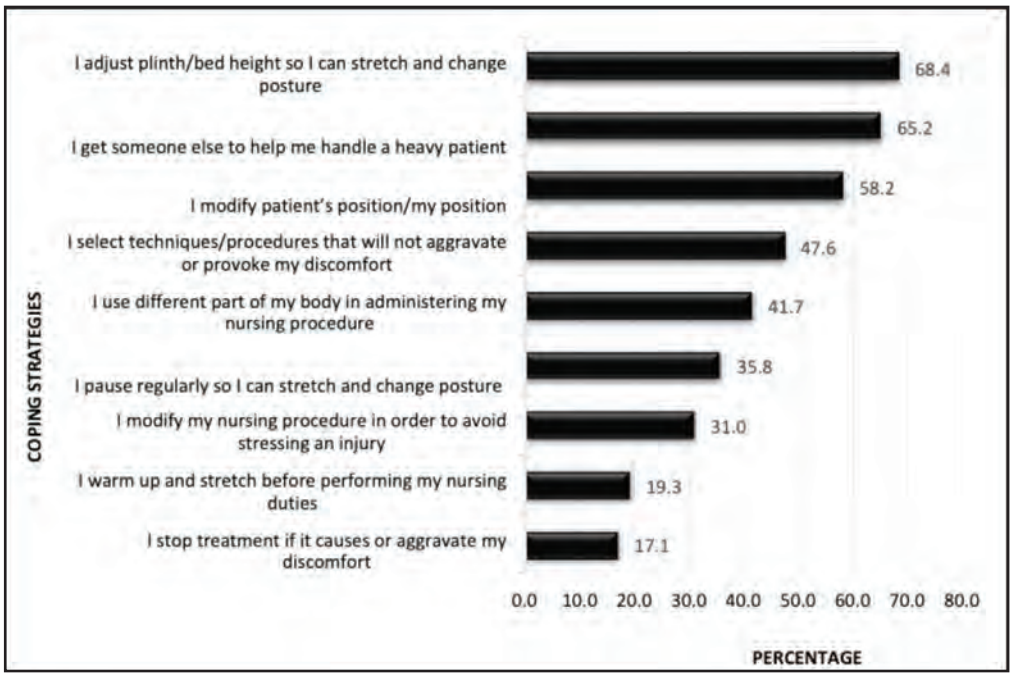

Fig. 1: Low back pain coping strategies adopted by respondents (almost always in the scale).

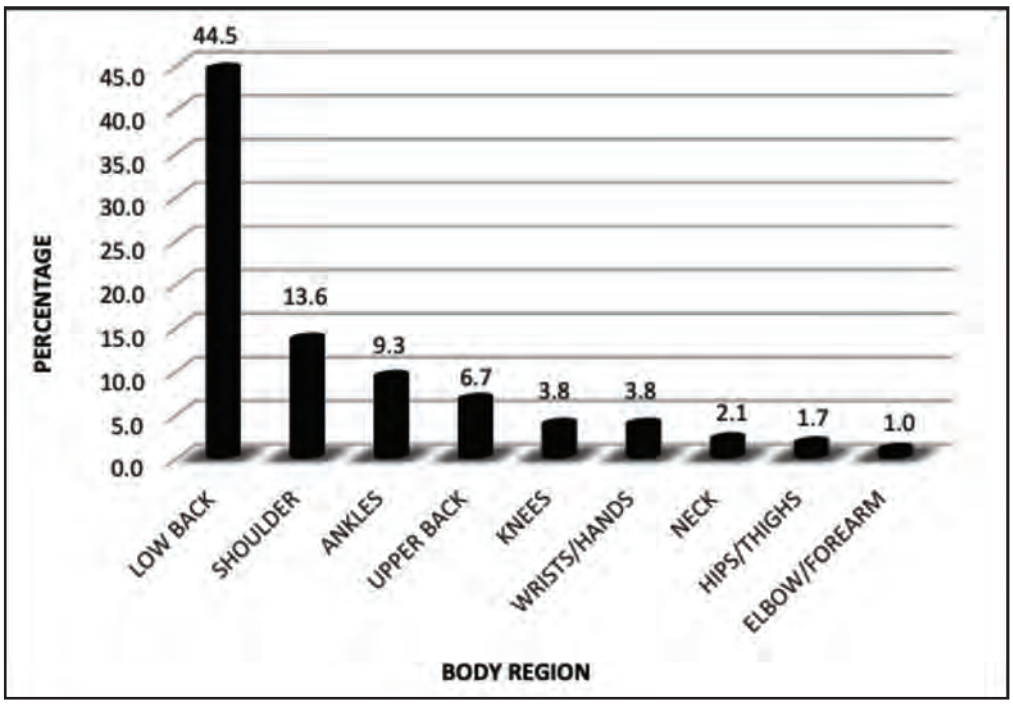

Fig. 2: Prevalence of work-related musculoskeletal disorders in the different body regions of all respondents.

of LBP among adults in the last 12 months was reported to be 56.9% in a study conducted in Sibu, Sarawak.[12] The frequency of LBP among nurses was found to be 58.8% in another study conducted at a medical centre in Pahang.[13] Similar studies conducted in public hospitals around Bangkok found a prevalence of 47.6% of LBP, therefore our study complements those findings.[14] Another study conducted in Jeddah found that the annual prevalence rate of LBP was 85.5%.[15] The 12-month prevalence of LBP among nurses in a multi-centre research done in rural Maharashtra, India, was 48%.[16]

The group with more than three children has higher risk of LBP, 2.5 times more likely to experience LBP compare to other subgroup with children less than three. This is not out of place with other studies conducted in several other countries such as in Nigeria and Egypt.[8,17] It is essential to point out that

the mechanisms that underlie the link between the number of children and LBP are not completely known. This is especially crucial given the correlation between the two factors. It is possible that the higher occurrence of LBP in women who have had children is caused by hormonal shifts that occur during pregnancy as well as the physical demands of childrearing, such as lifting and carrying newborns.[18]

Another interesting study was conducted in Hospital University Sains Malaysia (HUSM), presented that younger nurse with the age range between 20-30 years old had higher risk of LBP. Junior nurses were more likely to experience back pain because they did perform more manual work, whereas senior professionals were more responsible for organisational and management activities. Junior nurses were also less proficient in proper lifting and body mechanics techniques while senior nurses may have established suitable coping mechanisms over time. Younger nurses also reported higher levels of occupational stress than older nurses.[19]

Nurses working in the ICU department had the highest odd of LBP when compared to other wards. This could be due to the increased physical effort and work pressure caused by preoperative and postoperative patients. They need additional assistance in the ICU when transferring and moving in and out of bed. These results are in line with earlier studies that showed that nurses working in intensive care units had a higher incidence of LBP. Low back discomfort is more common in this context due to the physical demands of caring for critically sick patients, which include bending forward, lifting and relocating patients, and standing for long periods of time.[20] On the other hand, workers working in the orthopaedic ward were more frequently subjected to significant levels of physical pressure when managing and transporting patients who were suffering from serious fractures. Patient handling chores in the orthopaedic ward, such as holding a patient's extremities and prepping a limb, transferring a patient from a chair to a bed, and transferring a patient between a bed and a stretcher, can lead to awkward postures and an increased physical effort. Other patient-handling tasks include transporting a patient between a bed and a stretcher. Research done in the past has also revealed that tasks involving the care of patients can result in a higher proportion of awkward postures than duties that do not involve the handling of patients.[21]

Supporting patients in their everyday lives, placing them on beds, carrying and lifting them, transporting medical tools of varied weights and sizes, and tidying beds of varying heights all increase the risk of a low back injury for nurses. According to the American Nurses Association (ANA), nursing duties that include carrying patients are linked to LBP. LBP has been associated to receiving assistance or support during nursing care practices. A study discovered that performing particular nursing practices without assistance/support from equipment increases the frequency and intensity of LBP.[22] Prolonged durations of standing, leaning over, sitting, or kneeling can put undue strain on the lower back, resulting in back pain. Maintaining the same position for lengthy periods of time without proper breaks or postural adjustments might lead to the development of pain. A study conducted in Ethiopia supports this.[23] Another study conducted in Port Dickson found that carrying heavy loads among nurses is a major factor associated with low back discomfort.[12]

Top three coping methods in minimising the risk of low back discomfort were modifying bed heights (68.4%), receiving aid or support personnel in handling heavier patients (65.2%), and changing the patient's or nurse's position (58.2%). These coping methods among current study nurses appear to be consistent with another study in Ibadan.[17] The disparities in ways of coping may be due to the various facilities that can be provided to nurses in their workplace to lower the chance of developing work-related musculoskeletal condition in the various nations and types of hospitals included in this research. As we can concluded that, hospitals in Kota Kinabalu mostly equipped with semi-electric or fully-electric medical bed, easily the height of the bed can be adjusted. Whereby to move or carry a heavier patient, there are no proper equipment and still need to it manually so in this case definitely nurses to work in a team and seeking for support. In the case of changing the position, examples are like shifting weight from one leg to another or alternating between siting and standing positions. These changes help distribute the load and reduce the risk of overloading specific muscles or structures in the lower back.

Current study revealed that more than half of the participants (56.2%) had training on ergonomic. However, this could lead to an important critical thinking why the prevalence of LBP still high even though the nurses had been trained. In the nursing profession, "ergonomic training" refers to the instruction and implementation of ergonomic concepts and practices to increase safety, efficiency, and well-being among those who work in the nursing field. There is a high risk of musculoskeletal disorders (MSDs) and work-related accidents for nurses because their jobs require them to perform physically taxing duties and work in surroundings that can exacerbate these risks. Nurses in developing nations have minimal understanding of ergonomic concepts at work and are not trained to prevent and control occupational hazards. Knowledge of ergonomics can assist nurses in avoiding specific risk factors that can lead to the development of musculoskeletal illnesses and can improve workplace health and safety. Musculoskeletal diseases are more common in nurses who have received little or no training. Many elements in the workplace could contribute to nurses being exposed to physical danger.[25]

CONCLUSION

The reported 12-month prevalence rate of work-related musculoskeletal problem at any of the body areas was 86.4%, while the prevalence of (LBP) among nurses working in public hospitals in Kota Kinabalu was 44.5%. Almost half of the nurses who participated in this study received training on ergonomics. It is clear from the results that musculoskeletal issues, most notably LBP, continue to be a significant issue for nurses over the years may due to the cause of the specifics of their line of work, in contrast to those of other industries. Therefore, it is possible to argue that LBP follows a recurrent rather than an aggravating course, which is something that needs to be taken into consideration in the future

management of LBP in the healthcare sector. These assessments will make it possible to conduct an exhaustive study of the ergonomic elements of the workplace and the participants potential effects on their health and well-being as a result of those factors. An organisation can provide a more secure and comforting working environment for its employees by conducting an ergonomic risk assessment and addressing any issues that are discovered. This may include forming partnerships with professionals in the field of ergonomics, employing assessment instruments that have been vetted, and including ergonomic considerations into the process of survey design and data analysis.

CONFLICT OF INTEREST

The authors declare they have no conflicts of interest.

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Navigating Do-Not-Attempt-Resuscitation decisions in emergency department in Malaysia: A retrospective study

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ABSTRACT

Introduction: The practice of Do-Not-Attempt-Resuscitation (DNAR) aims to respect patient autonomy and acknowledge medical futility. Despite its global acceptance, there is limited research on DNAR in many Asian countries, including Malaysia. This study addressed this gap by exploring DNAR decision-making processes in a Malaysian tertiary hospital.

Materials and Methods: A mixed-method retrospective study was conducted in the emergency and trauma department (ETD) of Sarawak General Hospital, Malaysia, from February to July 2023. Data were collected from 115 DNAR cases using a surveillance form to document the patient demographics, types of DNAR orders, initiating physicians, reasons for DNAR, surrogate decision-makers, specific types of procedures withheld or withdrawn and outcomes. Thematic analysis was used for qualitative data, while inferential statistical analysis was applied to quantitative data.

Results: The mean age of patients was 71.32 years, with a male predominance (63.5%). The primary reasons for DNAR included "critical illness with poor prognosis" (33.9%), "advanced age with frailty and poor prognosis" (20.9%) and "massive haemorrhagic or ischemic stroke" (16.5%). Most DNAR decisions involved withholding resuscitation (90.4%) and were initiated mainly by internal medicine (52.2%) and emergency medicine teams (34.8%). Surrogate decision-makers were predominantly adult children (63.5%). Only one case had an advance directive. Majority of patients (80.9%) were admitted to wards, while 16.5% died in the emergency department. The median age of patients was significantly older when adult children (78 years) and spouses (76 years) were the surrogates, compared to when they were not involved (64.5 years and 62.5 years, respectively; $p < 0.001$ and $p = 0.003$, respectively). Conversely, the median age was significantly younger when parents (41.5 years) and siblings (64 years) were the surrogates, compared to when they were not involved (75 years and 74 years, respectively; $p < 0.001$ for both).

Conclusion: Advanced directives are rarely applied in Malaysia. DNAR decisions are typically made by surrogates when patients are critically ill, which is a common trend in many Asian cultures where discussing death is taboo. Cultural norms often lead families to withhold terminal diagnoses from patients, posing challenges for end-of-life care. The most frequent surrogates were adult children, who face dilemmas balancing aggressive treatment and their parents' wishes. The study underscores the need for better communication and decision-making support in emergency departments.

KEYWORDS:
Advanced directives, Do-Not-Attempt-Resuscitation, cardiopulmonary resuscitation, surrogate decision-maker, end-of-life

INTRODUCTION

First conceptualised in the 1970s,[1] the practice of Do-Not-Attempt-Resuscitation (DNAR) has garnered increasing global acceptance. DNAR is defined as a directive to refrain from initiating resuscitative measures including cardiopulmonary resuscitation (CPR) in the event of a cardiac arrest.[2] This practice is grounded in two fundamental principles of medical ethics: (1) respect for patient autonomy and (2) recognition of medical futility.[3]

Patient autonomy aims to safeguard human dignity by avoiding needless suffering due to unnecessary medical interventions.[4] On the other hand, medical futility asserts that a treatment is considered futile if it fails to meet its intended purpose. Specifically, medical futility is defined by the following criteria: (1) the establishment of a specific clinical goal (e.g., survival after cardiac arrest); (2) the identification of a specific course of action to achieve this goal (e.g., resuscitative measures); and (3) the determination that this course of action is ineffective in achieving the intended goal (e.g., survival after cardiac arrest).[5,6]

Among the key determinants in establishing medical futility are the duration the patient has been in cardiac arrest as well as the anticipated quality of life following resuscitation. Once medical futility is established, physicians are not ethically obligated to administer treatments that they judge to have no realistic likelihood of benefitting the patient.[7]

In this regard, a common misunderstanding about a DNAR order is the belief that DNAR will lead to the discontinuation of all forms of medical interventions.[2] In reality, implementing a DNAR order does not preclude the administration of palliative care measures such as oxygen,

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analgesics, sedatives and even antiarrhythmic agents and vasopressors. These measures are implemented to ensure that the dying passage of the patient is as comfortable as possible.[2,3]

Another important aspect of end-of-life care consideration is advanced directives. An advanced directive is defined as any form of expression that conveys an individual's thoughts, wishes or preferences for his or her end-of-life care.[3] These directives offer guidance on the restriction of medical care, including resuscitation in the event of cardiac arrest. Advance directives can be derived from discussions between healthcare staff with the patients and their family members, formal written directives, living wills or durable powers of attorney for healthcare decisions.[3]

Despite the nearly five-decade implementation of DNAR and advance directives globally,1 there remains a notable lack of studies on these practices in many Asian countries, including Malaysia. Many of the studies in the Asian context were conducted in countries such as Taiwan,[4,8] Japan,[9,10] South Korea[11,12] and Singapore.[13,14] To address this gap in the Malaysian context, this study was conducted to determine the key decision-making processes in recent DNAR cases in a tertiary hospital in Malaysia (including the physicians who initiated the decision discussion with the patients or their surrogate decision makers, the types of medical interventions withheld or withdrawn following the establishment of a DNAR as well as the reasons for initiating DNAR).

MATERIALS AND METHODS

This mixed method retrospective study was conducted from February 2023 to July 2023 in the emergency and trauma department (ETD) of Sarawak General Hospital (SGH), Malaysia. The DNAR cases were recruited sequentially during the study period. Permission to utilise the retrospective data was obtained from the head of ETD of SGH. Medical ethics approval from the Medical Research Ethics Committee (MREC) (NMRR ID-23-00019-NHE) in the Malaysian National Medical Research Register website (www.nmrr.gov.my) was obtained.

A surveillance form detailing the DNAR process such as the physician who initiated the DNAR discussion, the reasons for initiating the DNAR as well as the decision makers (i.e., the patient and/or surrogate decision makers) were recorded. DNAR decisions were broadly categorised into two types, i.e., "withholding of further resuscitative interventions" and "withdrawal of current resuscitative interventions".[2]

Additionally, the specific types of procedures withheld or withdrawn as part of the DNAR decision were also studied. The final dispositional decision made in the emergency department, i.e., (1) admission to a ward for end-of-life care, (2) patient's death occurring in the emergency department itself, (3) discharge to home with an appropriate palliative care plan, or (3) transfer to an alternative facility like a nursing home was determined (Table I).

After a DNAR decision was made by the managing team in the ETD SGH, the clinical progress of the patient was tracked until a final dispositional decision was made. Consent was sought and obtained from the patient's family members and relatives before the medical officer in-charge completed the study surveillance form. This form was designed to document key data of the DNAR decision-making process, as detailed in Table I. No personally identifiable or sensitive information, such as names or identification numbers, was recorded during this process.

For data analysis, the reasons prompting the initiation of DNAR discussions, as documented by the medical officers in charge, were first subjected to qualitative thematic analysis and coding with the purpose of identifying the overarching themes or reasons for the decision. Subsequently, an inferential statistical analysis of the quantitative data was carried out. The selection of the statistical test for categorical data (i.e., whether Chi-square test or Fisher's exact test), depended on whether the expected count in each cell of the compiled data table was five or greater. For continuous data, the selection to use either the independent student t-test or the Mann-Whitney U test was contingent upon the determination of data normality.

All DNAR cases aged 18 years and above, as decided in the ETD SGH from March 2023 to June 2023, were recruited in this study after obtaining informed consent from family members and relatives.

RESULTS

From March 2023 to June 2023, a total of 115 DNAR cases were recorded in ETD SGH. The mean age of these patients were 71.32 years (standard deviation +/- 16.23), with a gender distribution of 73 males (63.5%) and 42 females (36.5%).

Thematic analysis of the descriptions recorded in the surveillance forms revealed eight overarching reasons for initiating DNAR, with the most prevalent being "critical illness with poor prognosis" (39 cases, 33.9%) followed by "advanced age with frailty and poor prognosis" (24 cases, 20.9%), "massive haemorrhagic or ischemic stroke" (19 cases, 16.5%), and "long-term bedridden status with poor prognosis" (17 cases, 14.8%). Notably, only one case (0.9%) had an advance directive from a patient in an old folks' home.

Following the DNAR decision, most patients in fact did not pass away in the emergency department itself. Rather, a significant number, i.e., 93 cases (80.9%), were admitted to their respective wards. Deaths in the emergency department were recorded in only 19 cases (16.5%), while three cases (2.6%), were discharged home. The surrogate decision-makers were mainly the patients' adult children (73 cases, 63.5%), followed by their spouses (18 cases, 15.7%) and their siblings (15 cases, 13.0%). Healthcare providers only made decisions in the absence of other surrogates in one case (0.9%). The most avoided or withdrawn procedures in these DNAR cases were CPR in 114 cases (99.1%), endotracheal intubation in 95 cases (82.6%) and defibrillation in 14 cases (12.2%). The details of the descriptive statistics of these DNAR cases are described in Table II.

Table I: Types of data collected in the DNAR process

Demographic data
Age
Gender
Date and time of DNAR order
Details of the DNAR order
Type of DNAR order
▫ Withhold resuscitation
▫ Withdrawal of resuscitation
Physician who initiated DNAR
▫ Anaesthetist
▫ Emergency physician
▫ Internal medicine physician
▫ Surgeon
▫ Paediatrician
▫ Others. Please specify
Reason for DNAR order
Decision-making process
Decision maker:
▫ Patient himself/herself
▫ Surrogate decision-maker
o Spouse
o Adult child
o Parent
o Sibling
o Other relatives (if applicable)
Outcomes of discussion with patient or surrogate about DNR order
Types of interventions avoided/withdrawn
▫ Chest compression
▫ Endotracheal intubation
▫ Defibrillation
▫ IV-line insertion
▫ Further blood draw for investigation
▫ Feeding tube insertion
▫ All interventions avoided
Outcome of ED visit:
▫ Admission to ward
▫ Discharge home
▫ Death in department
▫ Transfer to other facility. Please specify:

The types of DNAR decisions were primarily categorised into two groups, i.e., withholding resuscitation, which accounted for 104 cases (90.4%), and withdrawal of resuscitation in 11 cases (9.6%). The internal medicine team initiated most of these cases (60 cases, 52.2%), followed by the emergency medicine team (40 cases, 34.8%). No statistical difference was noted in terms of outcomes in ETD stay according of the types of DNAR decisions (Table III).

Unsurprisingly, the median age of the patients was significantly older when adult children (i.e., patient's median age = 78 years) and spouses (i.e., patient's median age = 76 years) were involved in surrogate decision-making than when adult children and spouses were not involved in such decision-making (i.e., patient's median age of 64.5 and 62.5 years, respectively) ($p < 0.001$ and $p = 0.003$, respectively). On the contrary, the median age of the patients was significantly younger when their parents (i.e., patient's median age of 41.5 years) and siblings (i.e., patient's median age = 64 years) were involved in surrogate decision-making than when they were not (median age of 75.0 years and 74 years, respectively; $p < 0.001$ in both instances; (Table IV).

Regarding the analysis of the types of interventions avoided or withdrawn, only the number of endotracheal intubation procedures was found to be significantly different across the different categories of predominant reasons, as assessed using Fisher-exact test, $p < 0.001$. Post hoc analyses with pairwise comparisons using 28 z-tests of two proportions with a Bonferroni correction were subsequently performed with statistical significance accepted at $p < 0.01$. Statistically significant differences were noted in the proportion of patients with reason of "advanced age with frailty and poor prognosis" compared to patients with "post-CPR return of spontaneous circulation (ROSC) achievement but with poor prognosis" (n = 23, 95.8% vs n = 0, 0%), $p < 0.001$; as well as the proportion of patients who are "long term bedridden with poor prognosis" compared to patients with "post-CPR ROSC achievement but with poor prognosis" (n = 17, 100% vs n = 0, 0%), $p < 0.001$, were shown to be the two pairs with statistical significance. No significant difference was found in all other pairwise comparison analyses (Table V).

DISCUSSION

This study shows that advanced directives are rarely used in

Table II: Characteristics of the DNAR cases

Variables	Total, n (%)	Mean SD
Age		71.32 (16.23)
Gender of patients		
Male	73 (63.5)	
Female	42 (36.5)	
Types of DNAR		
Withhold resuscitation	104 (90.4)	
Withdrawal of resuscitation	11 (9.6)	
Teams that initiated DNAR in emergency department		
Anaesthesiology	2 (1.7)	
Emergency medicine	40 (34.8)	
General surgery	6 (5.2)	
Internal medicine	60 (52.2)	
Neurosurgery	6 (5.2)	
Oncology	1 (0.9)	
Reasons for DNAR		
Advanced age with frailty and poor prognosis	24 (20.9)	
Advanced cancer	7 (6.1)	
Critical illness with poor prognosis	39 (33.9)	
Long term bedridden with poor prognosis	17 (14.8)	
Massive haemorrhagic or ischemic stroke	19 (16.5)	
Polytrauma	2 (1.7)	
Post-CPR ROSC achievement but with poor prognosis	5 (4.3)	
Severe surgical conditions	2 (1.7)	
Availability of advanced directives		
Yes	1 (0.9)	
No	114 (99.1)	
Outcomes of ETD stay		
Admitted to respective wards	93 (80.9)	
Died in department	19 (16.5)	
Discharged home	3 (2.6)	
Involvement of the following surrogate decision makers*		
Spouse	18 (15.7)	
Adult child	73 (63.5)	
Siblings	15 (13.0)	
Parents	6 (5.2)	
Other relatives	16 (13.9)	
Healthcare providers	1 (0.9)	
Interventions/procedures avoided/withdrawn in the DNAR**		
CPR	114 (99.1)	
Endotracheal intubation	95 (82.6)	
Defibrillation	14 (12.2)	
Further blood tests	10 (8.7)	
Intravenous line insertion	5 (4.3)	

Note:
*In some cases, there were more than one surrogate decision maker involved in the discussion. The categories of surrogate decision makers listed are not mutually exclusive. It should be noted that although a number of categories of surrogate decision makers were listed in this study, ultimately however, DNAR decision is a clinician's decision, after discussion with these relatives and family members.
**In many cases, there were more than one intervention/procedure avoided/withdrawn. The categories of intervention/procedure listed are not mutually exclusive.
CPR = cardiopulmonary resuscitation, ROSC = return of spontaneous circulation, ETD = emergency and trauma department

Malaysia. Out of 115 cases studied, only one case had advanced directive. In the other 114 cases or 99.1%, prior DNAR decisions were made by the surrogates only when the patients were already very ill and near the end of their lives. In fact, in many other Asian cultures besides Malaysia, end-of-life decisions are also often shown to be delegated to their surrogates and not made by the terminally ill patients themselves.[4,7,15]

This is likely due to the fact that talking openly about death is often avoided in traditional Asian societies because it is largely perceived as a taboo topic.[15] In Chinese culture, for example, the impact of bad news on families is frequently believed to be deep, often leading to families withholding information on the terminal diagnoses from the patients themselves.[4] Inadvertently, families and healthcare teams often face awkward challenges in navigating through this complex emotional maze of end-of-life care.[15] In fact, according to Huang et al.[16], in many Asian cultures, people often avoid telling the truth directly about any serious illnesses, as this is often perceived to be rude or harmful. For example, in Japan, there is a preference for ambiguity over explicitness in end-of-life communications. The notion of a "good death" in the Japanese culture means not being

Table III: Categorical analysis of the outcomes in ETD stay according to the types of DNAR decisions

	Outcome in ETD stay			
	Admission to ward	Died in department	Discharged home	p-value*
Types of DNAR decisions				
Withhold resuscitation (% within types of DNAR)	84 (80.8%)	18 (17.3%)	2 (1.9%)	0.33
Withdrawal of resuscitation (% within types of DNAR)	9 (81.8%)	1 (9.1%)	1 (9.1%)	

Note: *As three cells (50%) have expected count less than 5, Fisher-exact test analysis was used.

Table IV: Comparison of median age of patients according to the presence of different surrogate decision makers

	Median age of patient (years old)		p-value
	Yes	No	
Spouse as surrogate decision maker	76.0	62.5	0.003
Adult child as surrogate decision maker	78.0	64.5	<0.001
Siblings as surrogate decision maker	64.0	74.0	<0.001
Parents as surrogate decision maker	41.5	75.0	<0.001
Other relatives	76.00	74.00	0.48

Note: as normality of data cannot be ascertained due to Shapiro-Wilk test <0.05 for one or both groups, Mann-Whitney U test was performed in all analyses.

Table V: Comparison of Reasons of DNAR according to different interventions/procedures avoided/withdrawn

Interventions or procedures	Categories of reasons of DNAR decisions								
	Advanced age with frailty and poor prognosis (n = 24)	Advanced cancer (n = 7)	Critical illness with poor prognosis (n = 39)	Long term bedridden with poor prognosis (n = 17)	Massive haemorrhagic or ischemic stroke (n = 19)	Polytrauma (n = 2)	Post-CPR ROSC achievement (n = 5)	Severe surgical conditions (n = 2)	p-value
CPR	24 (100%)	7 (100%)	38 (97.4%)	17 (100%)	19 (100%)	2 (100%)	5 (100%)	2 (100%)	1.00*
Endotracheal intubation	23 (95.8%)	6 (85.7%)	32 (82.1%)	17 (100%)	16 (84.2%)	0 (0)	0 (0)	1 (50%)	<0.001*
Defibrillation	5 (20.8%)	1 (14.3%)	5 (12.8%)	0	2 (10.5%)	0	1 (20%)	0	0.53*
No further blood tests	2 (8.3%)	0	5 (12.8%)	1 (5.9%)	2 (10.5%)	0	0	0	0.99*
Intravenous line insertion	1 (4.2%)	1 (14.3%)	3 (7.7%)	0	0	0	0	0	0.60*

Note: *analysed using Fisher-exact test

forthright or not knowing exactly about one's medical condition.[9] Consequently, most people in Japan consider "dying without awareness" of the exact illness or with the bliss of "not being informed of the bad news" as crucial during the final days of life of a person, which essentially, points to a significant cultural departure from the Western end-of-life care culture of open discussion with the patients.[9] Additionally, this study also showed that the most frequent surrogate decision-makers were the patients' adult children. This mirrors the findings from other past Asian studies.[4,15] For example, Cheng et al.[15] observed that in the Chinese culture, it is similarly common for the adult children to take on the role as the surrogate decision-makers. This responsibility, however, often places these adult children in a very tough spot. They often face the dilemma of choosing between aggressive medical treatments, driven by a sense of filial duty, and honouring the actual wishes of their dying parents. In this study, it is also observed that the proportion of endotracheal intubation withheld due to reasons of "advanced age with frailty and poor prognosis" and "long term bedridden with poor prognosis" were significantly greater compared to patients with reason of "post-CPR ROSC achievement but with poor prognosis" is hardly surprising given the fact that once ROSC was achieved, endotracheal intubation would follow suit.

This study has a number of pertinent limitations that deserve mentioning. First, the categorisation of reasons for DNAR decisions into distinct, exclusive categories for the purpose of statistical analyses is reductionistic and oversimplifies the complex clinical decision-making processes. In actual clinical practice, the reasons for initiating DNAR orders are frequently multifaceted and cannot be neatly compartmentalised. For example, a patient classified under "post-CPR ROSC achievement but with poor prognosis" might also have the reason of "advanced age with frailty and poor prognosis". Secondly, the study was conducted in a single hospital, which may limit the generalisability of the findings to other settings or populations. Furthermore, the small sample size in this study over a short period of five months might not have captured the full variability and trends in DNAR decision-making processes, especially in a diverse population. To enhance the generalisability of the findings, future studies should include multiple hospitals

across different regions of Malaysia. This would help capture a wider range of practices and influences on DNAR decisions. Third, this study was conducted as a retrospective study. Retrospective studies rely on existing records, which may be incomplete, inaccurate, or inconsistent. In this regard, the quality of the data obtained in this study depends on how well the DNAR decisions and associated details were captured at the time of care. There may be missing or incomplete records which can lead to biased results. Hence, a future prospective study is called for. Finally, this study also did not explore the different ethnic nuances and their socio-cultural and religious factors influencing DNAR decisions in a multicultural country like Malaysia. In this regard, incorporating in-depth qualitative interviews and focus groups with patients, families, and healthcare providers may be needed in future studies to explore these socio-cultural and religious beliefs that may influence DNAR decisions.

CONCLUSION

This study highlights the complexities and cultural nuances of Do Not Attempt Resuscitation (DNAR) decision-making in Malaysian emergency departments. It reveals the crucial role of surrogate decision-makers, predominantly adult children, highlighting the necessity for practical strategies to enhance communication and decision-making support within the high-stress and chaotic environment of an emergency department.

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The intersection of dermatology and immunology: Cutaneous manifestations, autoantibodies and quality of life in connective tissue diseases

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ABSTRACT

Introduction: Connective tissue diseases (CTDs) are autoimmune diseases with multiorgan involvement. CTDs present with a heterogeneous clinical manifestation, especially in the cutaneous system. This study aimed to describe the common cutaneous manifestations of CTDs, to determine the association with antinuclear antibody (ANA) and other associated antibodies, and to assess the impact of CTDs on patient's quality of life (QOL).

Material and Methods: This was a cross-sectional study conducted among patients 18 years and above, with a confirmed diagnosis of systemic lupus erythematosus (SLE), systemic sclerosis, dermatomyositis, mixed connective tissue disease (MCTD) or overlap syndrome, who attended the rheumatology clinic at Hospital Sultan Ismail Johor Bahru between March 2023 to June 2023. The assessment instrument used was the Dermatology Quality Life Index (DLQI).

Results: Among 79 patients recruited, the majority were females with a mean age of 39 ± 14.5 years. Malay was the predominant ethnic group. SLE was the most common CTD (64 patients, 81%), followed by systemic sclerosis (six patients, 7.6%), overlap syndrome (four patients, 5.1%), dermatomyositis (four patients, 5.1%) and MCTD (one patient, 1.3%). All patients had cutaneous involvement with photodermatitis being the commonest cutaneous manifestation (65 patients, 82.3%). ANA and anti-double stranded DNA (dsDNA) positivity were significantly associated with SLE while anti-scl70 and anti-centromere antibodies (ACA) were strongly associated with systemic sclerosis ($p < 0.05$). The presence of anti-dsDNA and anti-scl70 were significantly associated with renal involvement and interstitial lung disease (ILD) respectively ($p < 0.05$). CTD had a moderate effect on patient's QOL.

Conclusion: Photosensitivity was the commonest cutaneous manifestation among CTD patients. ANA was positive in the majority of SLE patients. The presence of anti-dsDNA was significantly associated with lupus nephritis, while anti-scl70 and ACA were strongly associated with systemic sclerosis and ILD. CTD had a moderate effect on patient's QOL.

KEYWORDS:
Clinical characteristics, connective tissue diseases, autoantibodies, quality of life, cutaneous manifestations, antinuclear antibodies

INTRODUCTION

Connective tissue diseases (CTDs) are defined as a group of complex chronic disorders with immune dysregulation that produces autoantibodies against their self-antigens.[1] CTDs include systemic lupus erythematosus (SLE), dermatomyositis or polymyositis, systemic sclerosis, Sjogren's syndrome, mixed connective tissue disease (MCTD) and overlap syndromes. The prevalence and incidence of each specific CTD varies geographically.[2]

CTDs can present with a heterogeneous clinical manifestation especially in the cutaneous system, ranging from non-specific cutaneous signs to disease-specific ones. The non-specific cutaneous signs include Raynaud's phenomenon, cutaneous vasculitis and livedo reticularis. The disease-specific cutaneous signs include discoid lupus erythematosus (DLE) and malar rash in SLE; Gottron's papule and heliotrope rash in dermatomyositis; as well as sclerodactyly, salt and pepper skin in systemic sclerosis.[3,4] Most CTDs have multiorgan involvement. The systemic manifestations of CTD like lupus nephritis in SLE and interstitial lung disease in systemic sclerosis can cause significant physical and functional impairment leading to poor quality of life (QOL).[5,6] Diagnosis of CTDs is usually based on a set of clinical and laboratory criteria. For instance, in SLE, diagnosis is based on the 2012 Systemic Lupus International Collaborating Clinics (SLICC) criteria, which needs fulfilment of at least four criteria, with inclusion of at least one clinical and one immunological criterion. If lupus nephritis is present, it can be a sole clinical criterion with either antinuclear antibodies (ANA) or anti-double stranded DNA antibody (anti-dsDNA) positive. Certain CTDs require measurements of laboratory tests such as creatine kinase (CK) which could be elevated in patients with dermatomyositis or low complement levels in SLE. Some CTDs are difficult to diagnose at the first encounter and require time and elaborate investigations to reach an accurate diagnosis.[3,4] ANA and enucleated antibodies (ENA) play important role in establishing diagnosis, monitoring and prognosis evaluation in patients with CTDs.[7,8]

To date, there is a lack of studies looking into the cutaneous manifestations of CTD, their associations with autoantibodies, and their impact on QOL in Malaysia and Southeast Asia. This study aimed to describe the common cutaneous manifestations of CTDs in the local population, to determine the association with ANA and other associated antibodies and to assess the impact of CTDs on patient's QOL.

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MATERIALS AND METHODS

Study Design

This was a cross-sectional study conducted from March 2023 to June 2023 at Hospital Sultan Ismail Johor Bahru, the main tertiary referral centre for rheumatology in Johor, Malaysia. All patients aged 18 and above, with a confirmed diagnosis of SLE, systemic sclerosis, dermatomyositis, MCTD or overlap syndrome who attended the rheumatology clinic during the study period were recruited. The diagnosis of CTD was confirmed by qualified rheumatologists based on internationally accepted criteria - the 2012 SLICC criteria for SLE, the 2013 ACR/EULAR criteria for systemic sclerosis, the 2017 ACR/EULAR criteria for adult dermatomyositis, the Alarcon-Segovia criteria for MCTD and the presence of at least two autoimmune rheumatological diseases for overlap syndrome. Patients who did not fulfil diagnostic criteria for CTD and patients who refused to participate in the study were excluded.

Sample Size Estimation

Sample size estimation was calculated using the population proportion formula by Lenneshow, Hosmer, Klar, Lwanga & Organization 1990.[9] A minimum sample size of 75 subjects was needed to reject the null hypothesis with a power of 0.8. The type I error probability associated with this test for this null hypothesis was 0.05.

Study Procedures

A written consent was obtained from all patients who fulfilled the inclusion and exclusion criteria. History taking and physical examination were performed and recorded in the clinical report form (CRF). Information from the electronic medical record (EMR), including relevant rheumatology history and findings, as well as investigation results were retrieved from the EMR and recorded in CRF.

Dermatology Quality Life Index

All subjects were required to fill up a validated and licensed Dermatology Quality Life Index (DLQI) form. The DLQI stratifies the QOL into five categories-: no effect at all on the patient's life (0–1), a small effect on the patient's life (2–5), moderate effect on the patient's life (6–10), very large effect on the patient's life (11–20) and extremely large effect on the patient's life (21–30).[10]

Statistical Analysis

Statistical analysis was performed using the Statistical Package of the Social Science version 25 (SPSS, IBM Corporation, Chicago, IL, USA). Baseline characteristics were expressed as numbers and percentages or mean and standard deviation. Comparison of categorical variables for association with autoantibodies was done using the Chi-square test/Fisher's exact test. A p-value of less than 0.05 was considered statistically significant.

Ethical Approval

This study was approved by the Medical Research and Ethical Committee, Ministry of Health, Malaysia (NMRR-23-00222-0A5).

RESULTS

A total of 79 patients were recruited. The majority of patients were females, with a female-to-male ratio of 10:1. The mean age was 39± 14.5 years with mean age at diagnosis 30± 14.6 years. The mean duration of disease was 9.4± 7.3 years. Malay was the predominant ethnic group with 45 patients (57%). Out of the 79 CTD patients, SLE was the most common, 64 patients (81.0%), while MCTD was the least common, one patient (1.3%). SLE was present in all patients with MCTD and overlap syndrome. The baseline characteristics are listed in Table I.

The clinical features of CTD and the associated antibodies are shown in Table II. All patients had cutaneous involvement, with photosensitivity being the commonest manifestation (65 patients, 82.3%). As for systemic symptoms, the majority of patients had musculoskeletal involvement (66 patients, 83.5%).

The majority of SLE patients had photosensitivity, while Raynaud's phenomenon, poikiloderma and skin tightness were the commonest cutaneous manifestations seen in systemic sclerosis. Table III summarises the commonest cutaneous manifestation seen in each CTD.

The frequency of positive autoantibodies is shown in Table II. The majority of patients (75 patients, 94.9%) had positive ANA, while anti-SSA/Ro and anti-dsDNA antibodies were present in 40.5% and 39.2% of patients respectively.

ANA and anti-dsDNA positivity were significantly higher among SLE patients compared to other CTDs while anti-scl70 and anti-centromere antibodies (ACA) were strongly associated with patients with systemic sclerosis ($p < 0.05$). Anti-dsDNA was also significantly associated with renal involvement mainly lupus nephritis, while anti-scl70 was significantly associated with respiratory symptoms, mainly interstitial lung disease (ILD) ($p < 0.05$). The association between CTDs and autoantibodies is summarised in Table IV.

CTDs generally had a moderate effect on patients' quality of life, with a mean DLQI score of 6.42± 5.53. There were 16 patients with a DLQI score of more than 10, with the majority of them having SLE (81.3%) and systemic symptoms (93.8%). The DLQI score for each CTD is summarised in Table V.

DISCUSSION

CTDs are autoimmune multisystem disorders that commonly involve the skin and mucous membranes. Cutaneous involvement may be the earliest manifestation of CTD and thus, important for early recognition of CTD. Our study showed that patients with CTD were mostly females and of childbearing age, similar to previous studies[11,12] SLE was the commonest CTD in our cohort, similar to the findings by Kadiru et al and Jethwa et al.[11,13] Although there are limited studies done looking at the prevalence and incidence of CTDs in different ethnic groups, we found that CTDs were highest in our Malay population. Our finding was also similar to a study done by Ng et al[14] which suggests that genetics may play a role.

Table I: Baseline characteristics in 79 patients with CTD

Clinical characteristics	Number of patients (%), n = 79
Mean age ± SD, years	39 ± 14.5
Mean age at diagnosis ± SD, years	30 ± 14.6
Gender	
Female	72 (91.0)
Male	7 (8.9)
Ethnic group	
Malay	45 (57.0)
Chinese	30 (38.0)
Indian	4 (5.1)
Mean duration of disease ± SD, years	9.4 ± 7.3
Connective tissue disease	
SLE	64 (81.0)
Systemic sclerosis	6 (7.6)
Dermatomyositis	4 (5.1)
MCTD	1 (1.3)
Overlap syndrome	4 (5.1)

Table II: Clinical features and associated autoantibodies

Clinical features	Number of patients, n = 79	Percentage (%)
Cutaneous manifestations	79	100
Photosensitivity*	65	82.3
Non-scarring alopecia	64	81.0
Malar rash	53	67.0
Oral ulcer	44	55.7
Discoid rash	32	40.5
Raynaud's phenomena	32	40.5
Purpura	28	35.4
Livedo reticularis	13	16.5
Chronic urticaria	10	12.7
Gottron's papule	8	10.1
Systemic manifestations		
Musculoskeletal	66	83.5
Haematology	35	44.3
Renal	20	25.3
Respiratory	16	20.3
Gastrointestinal	13	16.5
Cardiovascular	13	16.5
Neurological	8	10.1
Autoantibodies positivity at baseline		
ANA	75	94.9
Anti-SSA/Ro	32	40.5
Anti-dsDNA	31	39.2
Anti-RNP	27	34.2
Anti-Sm	25	31.6
Anti-SSB/La	9	11.4
Anti-riboprotein	4	5.1
Anti-scl70	3	3.8
Anti-centromere (ACA)	3	3.8
Anti-histone	1	1.3
Anti-jo 1	1	1.3

*Photosensitivity = eczematous or morbilliform rash at the extensor of the arms, hands, upper chest and back upon exposure to sunlight.

Table III: The commonest cutaneous manifestation in each connective tissue disease

CTD	Cutaneous manifestation, n (%)
SLE	Photosensitivity*, 59 (92.2)
Dermatomyositis	Heliotrope rash, 3 (75.0)
MCTD	Heliotrope rash, Gottron papule, chronic urticaria, 1 (100.0)
Overlap syndrome	Non- scarring alopecia, 4 (100.0)
Systemic sclerosis	Raynaud's phenomenon, poikiloderma, skin tightness, 5 (83.3)

*Photosensitivity = eczematous or morbilliform rash at the extensor of the arms, hands, upper chest and back upon exposure to sunlight

Table IV: Association between connective tissue diseases and autoantibodies

		Anti-dsDNA[b], n(%)		p value	ANA[a], n(%)		p value
		Present	Absent		Present	Absent	
SLE	Present	29(45.3)	35(54.7)	*0.02	63(98.4)	1(1.6)	*0.02
	Absent	2 (13.3)	13(86.7)		12(80)	3(20)	
Renal system involvement	Present	12(60)	8(40)	*0.03			
	Absent	19(32.2)	40(67.8)				
		Anti-scl70[a], n(%)		p value	ANA[a], n(%)		p value
		Present	Absent		Present	Absent	
Systemic sclerosis	Present	3(50)	3(50)	*0.00	2(33.3)	4(66.7)	*0.01
	Absent	0	73(100)		1(1.4)	72(98.6)	
Respiratory system involvement	Present	3(18.8)	13(81.3)	*0.007			
	Absent	0	63(81.3)				

[a]Fisher exact test
bPearson Chi-square
*p < 0.05

Table V: DLQI Scores for each CTD

Type of CTDs	DLQI<10 (63), n(%)	DLQI≥10 (16), n(%)
SLE	51 (80.9)	13 (81.3)
Systemic sclerosis	5 (7.9)	1 (6.3)
Dermatomyositis	3 (4.8)	1 (6.3)
Overlap syndrome	3 (4.8)	1 (6.3)
MCTD	1 (1.6)	0

DLQI: Dermatology life quality index
MCTD: Mixed connective tissue disease

Photosensitivity was the commonest cutaneous manifestation detected among our CTD patients and was present in almost all SLE patients. This finding was similarly reported by Jethwa et al.[13] Therefore the presence of photosensitivity should prompt the clinician to have a high index of suspicion for CTDs, especially SLE.

Autoantibodies are important in the diagnosis of CTD.[15–17] ANA can be detected with elevated titters usually ≥ 1:160 in CTDs, compared to the general population due to the method of detection of ANA by using indirect immunofluorescence assay.[18,19] ANA was the commonest autoantibody detected and was present in the majority of our SLE patients. This finding is consistent with its high sensitivity and specificity for SLE.[15,19,20] A negative ANA test may therefore suggest an alternative diagnosis for the patient.

Anti-dsDNA positivity in our SLE patients was significantly associated with the presence of lupus nephritis. Previous studies showed that anti-dsDNA was detected in 63–68% of patients with lupus nephritis, similarly to our current finding.[21,22] Therefore, a positive anti-dsDNA may prompt clinicians to be more vigilant in detecting renal involvement among SLE patients. Early detection of lupus nephritis is important for the initiation of treatment to prevent the progression of renal involvement in SLE.

In our study, the presence of anti-scl70 and ACA were significantly associated with systemic sclerosis and ILD. This association was also similarly seen in previous studies.[23–25] Therefore, screening for these antibodies is important to prognosticate patients with systemic sclerosis. Early referrals to rheumatology and pulmonology colleagues are vital so that early immunosuppressive therapy can be given to halt disease progression.

Many previous studies have shown that the QOL of patients with CTD was significantly affected in comparison to the general population.[26–28] The mean DLQI in our patients was 6.42 ± 5.53, indicating a moderate effect on their QOL. A study conducted by Trepanowski et al.[29] also showed that CTD patients were moderately affected by their disease. This similar DLQI was also seen in other chronic inflammatory skin conditions like psoriasis.[30] Therefore, appropriate support and counselling should be offered to CTD patients to help them in coping with their chronic condition.

Limitations

Limitations of this study include small sample size and short duration of study.

CONCLUSION

This study showed that photosensitivity was the commonest cutaneous manifestation seen among patients with connective tissue diseases (CTDs), especially systemic lupus erythematosus (SLE). Antinuclear antibody (ANA) was positive in almost all SLE patients. The presence of anti-dsDNA was significantly associated with lupus nephritis, while anti-scl70 and anti-centromere antibodies (ACA) positivity were significantly associated with systemic sclerosis. Anti-scl70 was also strongly associated with interstitial lung disease (ILD). Most patients with CTD were moderately affected by their disease. These findings highlight the important cutaneous features to recognise in aiding in the early diagnosis of CTDs. The presence of autoantibodies can guide physicians in the diagnosis of CTDs, detection of systemic involvement and initiation of effective treatment to reduce morbidity and improve patient's quality of life.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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DERMATOLOGY LIFE QUALITY INDEX (DLQI)

Hospital No: ..... **Date:** .....

Name: ..... **Score:** .....

Address: ..... **Diagnosis:** .....

.....

The aim of this questionnaire is to measure how much your skin problem has affected your life OVER THE LAST WEEK. Please tick (✓) one box for each question.

1.	Over the last week, how **itchy**, **sore**, **painful** or **stinging** has your skin been?	Very much A lot A little Not at all	☐ ☐ ☐ ☐		
2.	Over the last week, how **embarrassed** or **self conscious** have you been because of your skin?	Very much A lot A little Not at all	☐ ☐ ☐ ☐		
3.	Over the last week, how much has your skin interfered with you going **shopping** or looking after your **home** or **garden**?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant	☐
4.	Over the last week, how much has your skin influenced the **clothes** you wear?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant	☐
5.	Over the last week, how much has your skin affected any **social** or **leisure** activities?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant	☐
6.	Over the last week, how much has your skin made it difficultfor you to do any **sport**?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant	☐
7.	Over the last week, has your skin prevented you from **working** or **studying**?	Yes No	☐ ☐	Not relevant	☐
	If "No", over the last week how much has your skin been a problem at **work** or **studying**?	A lot A little Not at all	☐ ☐ ☐		
8.	Over the last week, how much has your skin created problems with your **partner** or any of your **close friends** or **relatives**?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant	☐
9.	Over the last week, how much has your skin caused any **sexual difficulties**?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant	☐
10.	Over the last week, how much of a problem has the **treatment** for your skin been, for example by making yourhome messy, or by taking up time?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant	☐

DERMATOLOGY LIFE QUALITY INDEX (DLQI) - INSTRUCTIONS FOR USE

The Dermatology Life Quality Index questionnaire is designed for use in adults, i.e. patients over the age of 16. It is self explanatory and can be simply handed to the patient who is asked to fill it in without the need for detailed explanation. It is usually completed in one or two minutes.

SCORING

The scoring of each question is as follows:

Very much	scored 3
A lot	scored 2
A little	scored 1
Not at all	scored 0
Not relevant	scored 0
Question 7, 'prevented work or studying'	scored 3

The DLQI is calculated by summing the score of each question resulting in a maximum of 30 and a minimum of 0. The higher the score, the more quality of life is impaired.

HOW TO INTERPRET MEANING OF DLQI SCORES

0 – 1	no effect at all on patient's life2
– 5	small effect on patient's life
6 – 10	moderate effect on patient's life
11 – 20	very large effect on patient's life
21 – 30	extremely large effect on patient's life

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ORIGINAL ARTICLE

Pulmonary tuberculosis diagnostic test using fluorescence immunoassay-based interferon gamma release assay with IchromaTM IGRA-TB

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ABSTRACT

Introduction: Tuberculosis (TB) is a serious global health problem in Indonesia, which is the country with the second-highest TB burden after India. Accuracy in TB diagnosis is the key to effective treatment and decreased transmission rate. One of the latest diagnostic methods is interferon gamma release assay (IGRA), which measures the interferon-γ release associated with Mycobacterium tuberculosis (MTB) infection. This study aims to determine the diagnostic value of IGRA-TB using IchromaTM IGRA-TB diagnostic kit (sensitivity, specificity, positive predictive value [PPV], and negative predictive value [NPV]), compared to Ziehl-Neelsen (AFB) staining, nucleic acid amplification-based test (Xpert-MTB) and chest-X Ray as the gold standard in TB diagnosis.

Materials and Methods: A cross-sectional observational study design was used. Patients were recruited through purposive sampling from pulmonology outpatient clinic and inpatient ward at Jemursari Islamic Hospital (RSI Jemursari), Surabaya from July 2023 to December 2023. All enrolled patients should have been previously tested positive or negative for pulmonary TB using AFB staining, Xpert MTB and chest x-ray. Blood samples of the patients were collected and processed using the IchromaTM IGRA-TB diagnostic kit. The results were then compared with gold standard methods for calculating the IGRA-TB diagnostic value.

Results: A total of 56 adult patients were enrolled in this study. The sensitivity, specificity, PPV, NPV and accuracy rate of IGRA-TB using IchromaTM IGRA-TB diagnostic kit were 80.56%, 85%, 90.62%, 70.83% and 82.14%, respectively.

Conclusion: IchromaTM IGRA-TB showed reasonably high diagnostic sensitivity and specificity, indicating that this method can be further utilised as a diagnostic and screening tool for pulmonary TB.

KEYWORDS:
Pulmonary tuberculosis, IGRA-TB, diagnostic value

INTRODUCTION

Tuberculosis (TB) remains a serious global health problem today. In 2019, it was estimated that there were over 10 million TB patients worldwide, with majority of cases were concentrated in Southeast Asia (44%), Africa (25%), and the Western Pacific (18%). Indonesia is ranked second as nation with the highest TB burden after India.[1] Rapid diagnosis of TB poses a challenge in clinical practice, especially in countries with a high TB burden, where delays in the diagnosis and initiation of TB treatment is a common occurrence.[2] Efforts to diagnose TB quickly and accurately are crucial for effective treatment and controlling the transmission of this disease in the community.[3,4]

There are various methods to confirm TB diagnosis, including chest X-ray, AFB staining, bacterial culture, nucleic acid amplification test and gene-based tests. The diagnosis of TB typically involves examinations such as Ziehl-Neelsen Acid-Fast Bacilli (AFB) stain and bacterial culture, which require 2 to 6 weeks for accurate results.[5] Although there is no perfect TB diagnostic test, diagnostic technology continues to evolve, becoming more accurate, simple and suitable for point-of-care treatment.[4] Advancements in testing including tests that are sensitive and specific, as well as affordable, rapid and usable by healthcare workers with minimal training at decentralised levels.[6]

A newer, modern solutions in TB diagnosis is a method called Interferon Gamma Release Assay (IGRA), which is specific to MTB antigens. IGRA-TB is an in vitro laboratory test that measures the release of interferon-γ (IFN-γ), an inflammatory cytokine released by T-cells and macrophage after Mycobacterium tuberculosis (MTB) exposure (Meldau et al). One of the methods of IGRA is by using IchromaTM IGRA-TB (Bioditech, Chuncheon, South Korea), which is an automated fluorescence lateral flow assay (LFA)-based IGRA.[7] This method is more practical and time-effective compared to the more widely available commercial IGRA method, which uses enzyme-linked immunosorbent assay (ELISA) or the enzyme-linked immunospot (ELISpot) assay technique.[7,8]

LFA-based IGRA has the potential to become a comparative method or a new gold standard for faster and more accurate

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TB diagnosis, especially in low-resource settings. This study aims to determine the diagnostic value of IGRA-TB using IchromaTM IGRA-TB diagnostic kit (sensitivity, specificity, positive predictive value [PPV] and negative predictive value [NPV]), compared to AFB staining, nucleic acid amplification-based test (Xpert-MTB) and chest-X ray as the gold standard in TB diagnosis in Indonesia.

MATERIALS AND METHODS

This study employed a cross-sectional observational method. Ethical approval for this research was granted by the Ethics Committee of RSI Jemursari Surabaya (Approval Number JS.A.SKR.2360.06.23).

Participants of the Study

Patients were recruited using purposive sampling from pulmonology outpatient clinic and inpatient ward at RSI Jemursari Surabaya from July 2023 to December 2023. Inclusion criteria were individuals aged ≥18 years diagnosed with TB based on clinical characteristics, radiology, TCM, and positive AFB for the TB group. Meanwhile, respondents aged ≥18 years with clinical symptoms such as cough, shortness of breath, weight loss resembling TB symptoms were included into the non-TB group. Individuals with HIV, cancer, uncontrolled diabetes and chronic TB were excluded. The research protocol was explained to participants at the respiratory outpatient clinic of RSI Jemursari Surabaya, and participants provided written informed consent for clinical examination and blood sample collection for IGRA-TB testing.

Blood Sample Preparation and IchromaTM IGRA-TB Testing

Procedures of IchromaTM IGRA-TB test was carried out following the manufacturer's (Bioditech, Chuncheon, South Korea) protocol. Blood sample collection is conducted at the RSI Jemursari Surabaya laboratory. Three millilitres of venous blood samples were collected from each participant (1 ml in the Nil tube, 1 ml in the Antigen tube, and 1 ml in the Mitogen tube. The three IGRA tubes (Nil, Antigen, and Mitogen) were then incubated at a temperature of 37^0C for 18–24 hours. After incubation, the samples in the IGRA tubes were centrifuged for 15 minutes at a speed of 2000-3000 RCF (G). The detection buffer in the detector tube was prepared by adding 100 µL diluent to the dried detection buffer containing anti IFN-γ and anti-chicken IgY, both of which were fluorescently labelled. After diluting the detection buffer in the detector tube with the diluent, 50 µL of the culture supernatant taken from the Nil tube was added, homogenised, and then 100 µL of the mixture was taken and dripped onto the nitrocellulose membrane on the cartridge. After incubating at room temperature for 15 minutes, the cartridge was moved and the fluorescence intensity was measured at 613 nm wavelength using the IchromaTM II instrument (Bioditech, Chuncheon, South Korea). The protocol was repeated for the culture supernatant in the antigen and mitogen tubes.

Analysis of IGRA-TB Diagnostic Value

The obtained data were used to calculate the diagnostic values of IGRA-TB, including sensitivity, specificity, PPV, NPV and the accuracy of the IGRA-TB test compared to the gold standard TB examinations, namely TCM, AFB and radiology.

RESULTS

A diagnostic test study of IGRA-TB was conducted on 56 participants which has been previously assessed as TB-positive or TB-negative by gold-standard tests. In this study, the median age of TB-positive participant was 47.5 years old (range: 19–79), meanwhile in the TB-negative participant, median age was 53 years old (range: 29–67). The majority of respondents belonged to the ≥ 60 years age group. The majority of participants were female in both TB-positive and TB-negative group (55.6% and 55%, respectively), Demographic characteristic of the respondents are displayed in Table I.

Out of the 56 samples obtained from patients at the respiratory outpatient clinic of RSI Jemursari Surabaya, 32 were determined as IGRA-TB positive, and 24 were IGRA-TB negative. From the analysis using diagnostic tests with the gold standard TB examination, the sensitivity, specificity, PPV, NPV and accuracy rate of IGRA-TB using IchromaTM IGRA-TB diagnostic kit were 80.56%, 85%, 90.62%, 70.83% and 82.14%, respectively.

DISCUSSION

In this study carried out in Indonesia, a TB-endemic country, LFA-based IGRA using IchromaTM IGRA-TB showed a reasonable sensitivity and specificity (80.56% and 85%, respectively). IGRA is a diagnostic method which indirectly assessed MTB infection by measuring IFN-γ release from T-cells, following the stimulation by antigens such as ESAT-6 and CFP-10.[9] These antigens were encoded in gene located in RD1 of the MTB complex gene, thus specific to the MTB complex infection.[9,10]

Currently, WHO recommends IGRA and tuberculin skin test (TST) as diagnostic methods in latent tuberculosis infection (LTBI). IGRA has shown remarkable sensitivity and specificity for diagnosing LTBI (91–94% sensitivity and 95–96% specificity).[11,12] TSTs have low specificity in populations vaccinated with BCG and low sensitivity in immunosuppressed individuals. Indonesia has a mandatory BCG vaccination program during childhood, thus IGRA is more suitable.[7,13,14]

Widely-available IGRA test kit is based on ELISA or ELISpot assay. An example of the ELISA-based kit is QuantiFERON®-TB Gold InTube (Cellestis Ltd., Carnegie, Australia) whereas the T-SPOT®.TBTM test (Oxford Immunotec Inc., Abingdon, UK) is based on the ELISpot assay. Meanwhile, the IchromaTM IGRA-TB is a fluorescence LFA, in which sandwich immunodetection method is used. Detector antibodies in buffer bind to antigens in the sample, forming antigen-antibody complexes and then migrate onto nitrocellulose matrix where it will be captured by the other immobilised-antibodies on a test strip. More antigens in the sample means more antigen-antibody complexes, and it leads to a stronger fluorescence signal by detector antibodies, which is captures by the instrument for Ichroma™ IGRA-TB tests to show latent TB-positive in the sample.[7,9]

Several studies comparing the diagnostic accuracy between LFA-based IGRA test using IchromaTM IGRA-TB test and ELISA-based test have shown that there is a high agreement

Table I: Demographic characteristic of participants

Parameter	TB-positive patients (n = 36)	TB-negative patients (n = 20)
Age (years)		
< 20	2 (5.6%)	0
20 – 29	7 (19.4%)	2 (10%)
30 – 39	5 (13.9%)	3 (15%)
40 – 49	7 (19.4%)	2 (10%)
50 – 59	8 (22.2%)	5 (25%)
≥ 60	7 (19.4%)	8 (40%)
Gender		
Male	16 (44.4%)	9 (45%)
Female	20 (55.6%)	11 (55%)

TB: tuberculosis

Table II: IGRA-TB diagnostic test results compared to the gold standard TB examinations

IGRA-TB	Gold-standard tests		Total
	Positive	Negative	
Positive	29	3	32
Negative	7	17	24
Total	36	20	56

IGRA: interferon-gamma release assay; TB: tuberculosis

between both test. Considering the simpler and less-time, cost and labour consuming process of IchromaTM IGRA-TB than ELISA-based test, the IchromaTM IGRA-TB has potential use as confirmatory test in low-resource settings.[8,15]

Some problems are related to IGRA accuracy in diagnosing TB, and this may explain the lower sensitivity and specificity found in this study. Some mycobacterial species in MTB complex such as M. kansasii, M. marinum and M. szugai possess CFP-10, ESAT-6 and TB 7.7 in their DNA sequence, therefore IGRA can show a false-positive owing to these species.[10] IGRA also show some false negative and indeterminate results of IGRAs in patients with active TB in some studies. The frequency of indeterminate results in IGRAs with active TB ranged from 1–20% and that of false-negative results ranged from 17–19%. All indeterminate results were due to low mitogen response in almost all studies. Factors such as Asian race, age > 65 years, sex, corticosteroid use, autoimmune disease, inpatient setting and number of comorbidities of anaemia, lymphocytopenia and hypoalbuminemia were significantly correlated with independent predictors of indeterminate results.[10] Another study also shows that indeterminate results could be attributed to the tube factor of IchromaTM IGRA-TB.[13] False-negative results were significantly correlated with elderly patients, female sex, acid-fast bacilli smear-negative, HIV co-infection and inflammatory diseases.[10]

It is also noted that IGRA cannot be used to discriminate LTBI and active TB, as IFN-γ release is an immune response caused by MTB infection, and the IFN-γ levels overlaps between LTBI dan active TB patients.[16,17] Another study shows that to discriminate between LTBI and active TB, interleukin (IL)-2 could be used as potential biomarker as it level was significantly higher in individuals with LTBI compared with patients with active TB.[18]

To the extent of our knowledge, this study presents a novelty as this is the first study assessing diagnostic value of LFA-based IGRA in diagnosing pulmonary TB. LFA-based IGRA using IchromaTM IGRA-TB has shown potential as sensitive and specific pulmonary TB diagnostic method, albeit it is more suitable in diagnosing LTBI. There are several limitations of this study. First, we use cut-off value for determining TB-positive or TB-negative as written in manufacturer's instruction, and this value may be lower or higher in places in different TB endemicity. This study is a single-centred study, and the number of samples are relatively low, therefore cautions are required to generalise the findings to the general population.

CONCLUSION

Our results showed that the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and accuracy rate of interferon gamma release assay (IGRA)-tuberculosis (TB) using IchromaTM IGRA-TB diagnostic kit for pulmonary TB were 80.56%, 85%, 90.62%, 70.83% and 82.14%, respectively. High sensitivity and specificity for this method suggests that it may be useful for pulmonary TB diagnosis, especially in lower-resource settings. Further studies are required to implement lateral flow assay (LFA)-based IGRA as point-of-care TB diagnostic method.

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SYSTEMATIC / NARRATIVE REVIEW ARTICLE

Global trends in the utilisation of NOMS framework for spinal metastasis management: A systematic review

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ABSTRACT

Introduction: Traditional risk stratification systems based on the clinicopathological criteria have limitations and may not accurately predict outcomes for all patients. The neurologic, oncologic, mechanical, and systemic (NOMS) framework aims to optimise treatment outcomes and improve patient care. Here, we aimed to provide a comprehensive overview of the NOMS framework within the context of spinal metastasis.

Materials and Methods: The study rigorously followed the guidelines set by PRISMA. We conducted an extensive search and be as transparent as possible across well-regarded databases such as PubMed and Euro PMC. The primary outcome measure focused on examining the feasibility of implementing the NOMS framework for patients with spinal metastasis in real-world clinical settings, and this measure was predefined and justified.

Results: This systematic review included three studies involving 300 participants with spinal metastases at the cervicothoracic junction. The studies examined surgical interventions like decompression, fusion and corpectomy within the NOMS framework. Across the studies, the NOMS approach is consistently associated with adverse outcomes, including complication rates, surgical revisions, hardware complications, deformities, tumour recurrence and variable survival rates. It is also linked to hospital stays, ICU durations and specific discharge statuses. Another study focused on spinal metastasis patients undergoing endoscopic surgery, highlighting the NOMS framework's connection to recurrence rates, performance metrics, neurological status, pain management, functional recovery and quality of life. In addition, other studies explored navigated instrumentation, with a primary focus on screw placement accuracy. All three studies demonstrated methodological rigor by reporting adequate allocation concealment.

Conclusion: NOMS framework consistently associates with adverse spinal metastasis surgery outcomes.

KEYWORDS:
NOMS framework, spinal metastasis, management, outcomes

INTRODUCTION

The neurologic, oncologic, mechanical, and systemic (NOMS) framework provides a systematic approach to the care of patients with spinal metastatic tumours, allowing for dynamic integration of novel systemic and radiation options.[1,2] It considers the unique challenges posed by spinal metastasis, such as the potential for neurologic compromise, the impact on oncologic management, the mechanical stability of the spine and the systemic effects of the disease. By considering these factors, the NOMS framework aims to optimise treatment outcomes and improve patient care.[1]

The adoption of the NOMS framework for managing spinal metastasis has gained global recognition and has been integrated into treatment protocols by various healthcare institutions.[3] Various decision-making algorithms, such as the NOMS framework, the spine instability neoplastic score (SINS) and the Tokuhashi score, assist in surgical decision-making.[4] Patient's tolerance to treatment procedures should be considered prior to the treatment.[5] Thus, NOMS framework serves as a comprehensive tool to steer treatment decisions, ensuring the inclusion of all pertinent factors in the decision-making process.[6,7]

The clinical burden of metastasis to the spine is substantial, with a reported 1-year prevalence of chronic spinal pain at 19%.[8] Additionally, spinal infections contribute to prolonged hospital stays, imposing significant financial strains on healthcare systems. Internationally, healthcare costs exceeding 10% of household income, termed high burden households, constitute approximately 30% of total household financial burdens.[8] Such financial strains can lead to material consequences like bankruptcy or psychological impacts. To effectively manage spinal metastasis, the NOMS decision framework integrates considerations of neurologic, oncologic, mechanical and systemic factors to guide treatment strategies. Rehabilitation interventions are pivotal within the NOMS framework, emphasising treatment tolerance and facilitating recovery.

We aimed to provide a comprehensive overview of the NOMS framework within the context of spinal metastasis. We examined the existing literature to evaluate the effectiveness of the NOMS framework in guiding treatment decisions and improving patient outcomes.[1,9] Additionally, we will explore the incorporation of other risk stratification tools, such as the

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SINS, in conjunction with the NOMS framework to further refine risk assessment.[10] The findings of this review will provide valuable insights for clinicians and researchers in the field, ultimately leading to improved patient care and outcomes.

MATERIALS AND METHODS

The study rigorously followed the guidelines set by Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA), ensuring a systematic and comprehensive approach.[11] It is worth mentioning that this research was not funded by any external sources, maintaining its impartiality. We conducted an extensive search and be as transparent as possible across well-regarded databases such as PubMed and Euro PMC. Detailed search queries are shown in Table I.

The study focused on patients with spinal metastasis (P) and utilised the NOMS framework (I) as an intervention for reasons that will be explained later. Since evaluating the feasibility of implementing the NOMS framework in clinical settings was the primary objective (O), there was no specific comparator (C). Noteworthy is that during database searches, date restrictions, limits based on language or type of studies were not applied, instead, a thorough approach using controlled vocabulary, keywords and synonyms were undertaken.

After conducting the initial search, duplicate records were eliminated using the deduplication feature in rayyan.ai. The remaining eligible studies then underwent a two-step screening process. In the first step, titles and abstracts were assessed for relevance, and articles meeting predetermined inclusion and exclusion criteria were selected for full-text review. It is important to highlight that all authors participated in both stages of screening, with any conflicts or discrepancies resolved through discussion to reach a consensus.

The inclusion criteria of the study comprised of publications available in English or translated into English, with both full-text and abstracts accessible. These publications specifically focused on evaluating the feasibility of implementing the NOMS framework for patients with spinal metastasis in clinical settings. Exclusion criteria consisted of abstracts without corresponding full-text articles, secondary literature, studies that did not assess the feasibility of the NOMS framework for this patient population in clinical settings, and studies that did not report on the specified outcomes.

For the final analysis, selected articles were assessed. This assessment covered various aspects such as bibliographic data, study design, participant characteristics and intervention details (if applicable), as well as outcome data. The primary outcome measure focused on examining the feasibility of implementing the NOMS framework for patients with spinal metastasis in real-world clinical settings, and this measure was predefined and justified.[1]

We evaluated the quality and potential bias of each included study using Newcastle–Ottawa scale (NOS) for non-randomised intervention studies. The overall risk of bias in this systematic review was assessed by considering the cumulative risk identified across all included studies.

The analysis of the data was conducted descriptively. Weighted means were calculated and reported along with range values when applicable. Due to variations in study designs and implementation, a meta-analysis was not performed, and the data were not combined.

RESULTS

In the context of search queries, a comprehensive search was conducted across scholarly databases, resulting in the identification of a cumulative total of 70 publications. This dataset encompassed records procured from two primary sources, namely PubMed and Euro PMC, comprising 14 and 56 records, respectively. Prior to the formal screening phase, diligent efforts were made to identify and eliminate any duplicate records, amounting to a total of three such records, in order to maintain the integrity of the dataset. Following this initial curation process, a refined dataset of 67 records remained, all of which were subjected to rigorous scrutiny for adherence to predetermined eligibility criteria. A substantial portion of these records, totalling 58, were excluded from the analysis due to non-conformity with the inclusion criteria. Subsequently, among the records that successfully cleared this preliminary screening, active efforts were exerted to retrieve nine reports deemed relevant to the research objectives. Nonetheless, it is noteworthy that one report proved unobtainable. Consequently, a total of eight reports were meticulously assessed for their eligibility, resulting in the exclusion of five reports. Of these, four were excluded for their failure to engage with the NOMS framework, while one was dismissed for its identification as a meeting abstract. This systematic review incorporated a select group of three studies (n = 300), which were found to align closely with the predefined inclusion criteria.[12–14] Detailed study flow is presented in Figure 1.

The research endeavours took place in a range of geographical settings. Hubertus et al.[13] involved collaboration among seven academic institutions across Europe, fostering a multinational research effort.[13] In contrast, Suvithayasiri et al.[14] spanned multiple countries, including South Korea, Thailand, Taiwan, Mexico, Brazil, Argentina, Chile and India, reflecting a global scope.[14] On the other hand, Hubertus et al.[12] was specifically conducted in Berlin, Germany, focusing on a more localised context.[12] The total number of participants in each study varied, with Hubertus et al.[13] encompassing a substantial cohort of 238 individuals, Suvithayasiri et al.[14] involving 29 participants, and Hubertus et al.[12] comprising a cohort of 33 subjects.[12–14] The temporal aspect also varied, with Hubertus et al.[13] extending over a comprehensive 14-year period, Suvithayasiri et al.[14] spanning a decade, and Hubertus et al.[12] being conducted within a relatively shorter 3-year timeframe.[12–14]

The assessment of outcomes within the NOMS framework revealed noteworthy distinctions across the studies. Hubertus et al.[13] harnessed the NOMS framework to prognosticate the overall complication rate during hospitalisation (n = 82; 34%; p = 0.026), alongside secondary outcomes

Table I: Detailed search queries

Database	Search permuatations	Total study retrieved
PubMed	"NOMS"[All Fields] AND ("framework"[All Fields] OR "framework s"[All Fields] OR "frameworks"[All Fields]) AND ((("spinal"[All Fields] OR "spinalization"[All Fields] OR "spinalized"[All Fields] OR "spinally"[All Fields] OR "spinals"[All Fields]) AND ("metastasi"[All Fields] OR "neoplasm metastasis"[MeSH Terms] OR ("neoplasm"[All Fields] AND "metastasis"[All Fields]) OR "neoplasm metastasis"[All Fields] OR "metastasis"[All Fields])) OR (("spinal"[All Fields] OR "spinalization"[All Fields] OR "spinalized"[All Fields] OR "spinally"[All Fields] OR "spinals"[All Fields]) AND ("metastasation"[All Fields] OR "metastasic"[All Fields] OR "metastasing"[All Fields] OR "metastasise"[All Fields] OR "metastasised"[All Fields] OR "metastasises"[All Fields] OR "metastasising"[All Fields] OR "metastasization"[All Fields] OR "metastasizes"[All Fields] OR "metastasizing"[All Fields] OR "neoplasm metastasis"[MeSH Terms] OR ("neoplasm"[All Fields] AND "metastasis"[All Fields]) OR "neoplasm metastasis"[All Fields] OR "metastase"[All Fields] OR "metastases"[All Fields] OR "metastasize"[All Fields] OR "metastasized"[All Fields])))	14
Euro PMC	"NOMS framework" AND "spinal metastasis" OR "spinal metastases"	56

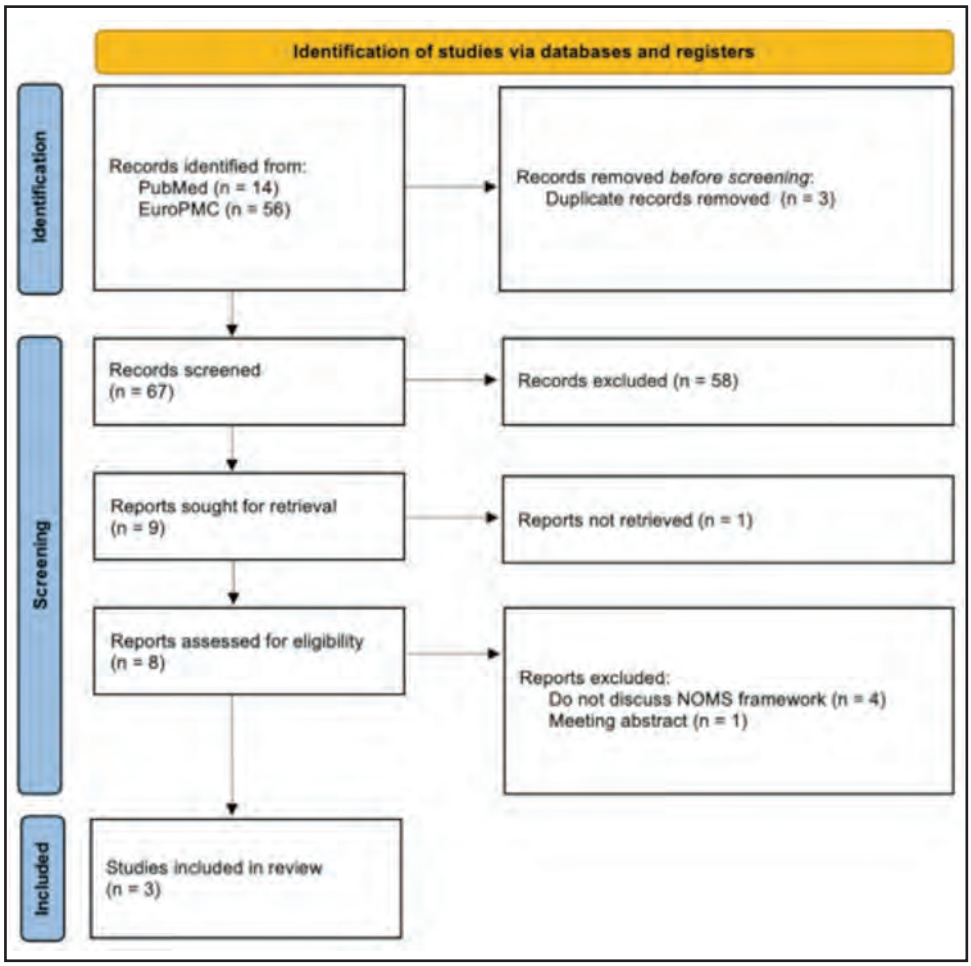

Fig. 1: PRISMA flow diagram of current systematic review.

encompassing surgical revision rate (n = 1; 3.4%), hardware failure (n = 8; 18%; p < 0.0001), postoperative mortality (n = 12; 5%; p = 0.7792), length of hospital stay (15 ± 9 days; p < 0.0001), and ICU duration (1 ± 4 days; p < 0.0001).[13] Conversely, Suvithayasiri et al.[14] primarily explored the symptomatic tumour recurrence rate using the NOMS framework, demonstrating correlations with performance status – Eastern Cooperative Oncology Group (ECOG) (p < 0.05), neurological status – Oswestry Disability Index (ODI) and Neck Disability Index (NDI) (p < 0.05), pain levels – Numeric Rating Scale (NRS) and Visual Analogue Scale (VAS) (p < 0.05) and quality of life determined by EuroQoL 5-Dimension 5-Levels (EQ5D5L) with p value less than 0.05.[14] Lastly, Hubertus et al.12 primary outcome of interest was the evaluation of CFRP pedicle screw placement accuracy (n = 69 vs 68 vs 25; 74% vs 69% vs 49% for intraoperative CT vs

Table II. Characteristics of included study that assess the NOMS framework in spinal metastasis patients (n = 300)

Study ID, NOS	Location of study was conducted	Total cohort	Study duration	Patients	Interventions	Outcomes	Allocation concealment
Hubertus 202113 7 (good)	Seven academic institutions across Europe	238	2005 - 2019	Metastases at the CTJ (C7–T2)	Posterior decompression only, posterior decompression and fusion, anterior corpectomy and fusion, and anterior corpectomy and 360° fusion	**Primary:** The overall complication rate during the hospital stay. Secondary: Surgical revision rate, hardware failure, secondary deformity, local tumour recurrence, postoperative survival, length of hospital stay, length of stay on an intensive care unit (ICU), and discharge status	A – Adequate
Suvithayasiri 202314 6 (good)	South Korea, Thailand, Taiwan, Mexico, Brazil, Argentina, Chile, and India	29	2012 - 2022	Patients with spinal metastases who underwent endoscopic spine surgery	Uniportal and biportal endoscopy	**Primary:** Symptomatic tumour recurrence rate Secondary: Performance status, neurological status, pain levels, functional disability, and quality of life.	A – Adequate
Hubertus 202212 6 (good)	Berlin	33	2018 - 2021	Navigated instrumentation using carbon fibre reinforced (CFRP) polyether ether ketone (PEEK) pedicle screw implants with or without combined corpectomy	Radiolucent carbon-fibre reinforced PEEK implants	**Primary:** The accuracy of CFRP pedicle screw placement Secondary: The assessability of the screws, duration of surgery, number of intraoperative scans per patient, number of navigated screws per patient, number of instrumented segments per patient, and the inter-observer reliability between resident and expert observers	A – Adequate

robotic CT vs cone beam CT group, respectively, with a p value of < 0.001), with the NOMS framework aiding in the stratification of secondary outcomes including screw assessability (n = 92 vs 90 vs 48, p = 0.047), surgery duration (n = 248 min vs 202 min vs 193 min, p = 0.731), intraoperative scans (n = 2 vs 2 vs 2, p = 0.698), navigated screws (n = 8 vs 8 vs 8, p = 0.836), instrumented segments (n = 5 vs 5 vs 5, p = 0.835), and inter-observer reliability by Landis & Koch > 0.6.[12] This framework facilitated a comprehensive understanding of the multifaceted dimensions of each study's research questions and outcomes, enriching their respective findings. It is worth noting that allocation concealment was reported as adequate in all three studies, emphasizing the commitment to methodological rigour.

DISCUSSION

These studies highlight the importance of considering the NOMS framework in the treatment decision-making process for spinal metastases. While surgical management plays a significant role, the use of minimally invasive treatment modalities such as stereotactic body radiotherapy (SBRT) is also gaining prominence.[6] The NOMS framework provides a comprehensive approach that takes into account the neurologic, oncologic, mechanical and systemic factors to guide treatment decisions and optimise patient outcomes.[15]

Support for the feasibility of implementing the NOMS framework in clinical settings for spinal metastasis patients lies in its standardisation capabilities. NOMS offers a uniform approach to documenting interventions and outcomes, which proves particularly beneficial for conditions as intricate as spinal metastasis, necessitating consistent and well-documented care.[1,15,16] Moreover, NOMS promotes evidence-based practice by facilitating systematic recording and tracking of intervention outcomes by clinicians. This, in turn, fosters a more informed approach to patient care, aligning with the goal of delivering tailored care to meet the unique requirements of spinal metastasis patients.[1,7,9] The framework further emphasises patient-centred care by honing in on outcomes and interventions that directly address individual patient needs, further enhancing the patient's experience. Additionally, NOMS empowers data-driven decision-making by allowing healthcare providers to collect and analyse data. This, in turn, aids in making informed decisions about spinal metastasis patient care, potentially leading to more effective care plans and improved patient outcomes.[15,17] Lastly, it serves as a catalyst for interdisciplinary collaboration, facilitating communication and fostering a holistic care approach among healthcare professionals when dealing with the multifaceted needs of spinal metastasis patients.

However, there are opposing views regarding the feasibility of implementing the NOMS framework in clinical settings for spinal metastasis patients. Critics contend that its comprehensive nature can be intricate and time-consuming, potentially adding to clinician's workloads in fast-paced clinical environments, potentially diminishing consistent utilisation.[7,18] Furthermore, the framework's implementation may necessitate significant resources in the form of training, technology and data collection and analysis infrastructure, which may not be readily available in all healthcare facilities. Concerns also arise regarding potential data overload, as NOMS generates substantial data.[15] Without efficient data management systems, healthcare providers may encounter difficulties in extracting meaningful insights from the vast amount of information, which could impede practical application. Integration challenges may also emerge when attempting to align the NOMS framework with existing electronic health record systems or other documentation tools, potentially resulting in redundant efforts and documentation inconsistencies.[15,19] Furthermore, the framework's applicability in the context of spinal metastasis patients may be questioned due to limited research directly addressing this patient population. The absence of specific evidence regarding its effectiveness for these patients raises concerns about its appropriateness. Lastly, the complexity of spinal metastasis patient needs may not be fully encompassed by the NOMS framework, necessitating potential customisations to adequately address the unique challenges posed by this patient group.[15,17]

Both Hubertus et al.[12] and Suvithayasiri et al.[14] investigated the application of the NOMS framework to analyse spine metastasis encounter several limitations. Hubertus et al.[12] acknowledge the retrospective design and small sample size of their study, along with the absence of systematic outcome assessments such as pain and quality of life scores, as well as follow-up on implant durability. They also face challenges in comparing individual radiation exposure due to different dosage units recorded by various modalities. Similarly, Suvithayasiri et al.[14], in their retrospective study, encounter inherent biases and suggest the necessity for a control group to better demonstrate the efficacy of the endoscopic spine surgery (ESS) technique. They also note variations in practice, equipment settings, and learning curves among surgeons, alongside potential selective bias in patient inclusion, posing significant challenges. Additionally, the poor prognosis of spinal metastasis patients impacts dropout rates, although mean survival time remains consistent with previous literature.

Clinical Implications

Clinicians can employ the NOMS framework to assess the comprehensive needs of spinal metastasis patients, encompassing physical, psychological and social aspects, and monitor their progress throughout hospitalisation. Additionally, NOMS can facilitate the development of standardised care plans tailored to the specific nursing interventions and outcomes relevant to spinal metastasis patients, ensuring consistent and evidence-based care.2[0] Additionally, clinician can use NOMS to evaluate patients' educational requirements regarding their condition, treatment choices and self-management strategies, enabling the creation of customised education plans.[3] The framework also aids in symptom tracking and gauging the effectiveness of interventions, allowing for timely adjustments to treatment plans.

At rehabilitation facilities, NOMS can measure and document the functional outcomes of spinal metastasis patients, guiding physical therapy and rehabilitation efforts.[19] Furthermore, it plays a crucial role in tracking pain-

related outcomes, facilitating the assessment of pain management intervention effectiveness. In palliative care settings, NOMS assists in assessing and documenting changes in patients' quality of life over time, guiding interventions to enhance comfort and well-being.[3,21] Additionally, it aids in documenting communication and collaboration among the healthcare team, ensuring that palliative care goals align with the patient's preferences.

The NOMS framework can standardise data collection on nursing outcomes and interventions, enhancing research reliability.[17,19] Researchers can leverage NOMS to generate the evidence on the efficacy of various nursing interventions and their impact on patient outcomes.20 NOMS can support care continuity for chronic spinal metastasis patients by documenting long-term outcomes and interventions.

Future Directions

The NOMS framework can potentially lead to improved patient-centred care by emphasising nursing outcomes and interventions.[7] This might pave the way for more personalised and effective care tailored to the unique needs and preferences of spinal metastasis patients. Second, as healthcare technology and data analytics continue to advance, there is potential for enhanced data collection and analysis using digital solutions. This could offer deeper insights into which nursing interventions yield the best outcomes for these patients, ultimately improving the quality of care. Third, interdisciplinary collaboration is vital for the complex care of spinal metastasis patients, involving nurses, physicians, physical therapists, social workers and others. NOMS could serve as a shared language, facilitating communication and collaboration among healthcare professionals.[19] Fourth, the framework may contribute to evidence-based practice by standardising the measurement and reporting of nursing outcomes, supporting the generation of evidence that informs best practices and guidelines for spinal metastasis patient care. Fifth, the rise of telehealth and remote monitoring highlights the potential for adapting the NOMS framework to enable remote assessment and monitoring. This could lead to more timely interventions and reduced reliance on in-person visits. Sixth, healthcare organisations might incorporate NOMS into their quality improvement initiatives, using it to track nursing outcomes and interventions over time. This data-driven approach can help identify areas for enhancement, ultimately elevating the quality of care delivered to spinal metastasis patients. Finally, NOMS can also be used to assess patient education needs and track patient self-management outcomes, potentially empowering spinal metastasis patients to actively engage in their care and make informed decisions.[3,15,20]

CONCLUSION

The neurologic, oncologic, mechanical, and systemic (NOMS) framework serves as a steadfast and invaluable tool in the realm of spinal metastasis surgery research, consistently demonstrating its capacity to elucidate associations with adverse surgical outcomes.[12,13] Within the context of investigations into spinal metastasis surgery, the NOMS framework has emerged as a comprehensive and structured approach that facilitates the categorisation and evaluation of critical parameters and endpoints.[15] Its unwavering utility lies in its ability to provide a standardised platform for defining nomenclature, thereby ensuring a common language for researchers and clinicians to communicate effectively. Furthermore, the framework extends its utility into the realm of outcomes assessment, systematically encompassing various dimensions of surgical efficacy and patient well-being. By meticulously considering a spectrum of parameters and management strategies, the NOMS framework not only establishes a robust foundation for research endeavours but also consistently unveils vital insights into the relationships between these multifaceted variables and the occurrence of adverse surgical outcomes.[15] Its enduring relevance underscores its significance as an indispensable tool in advancing our understanding of spinal metastasis surgery and enhancing the management of this complex clinical scenario.

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Exploring nasopharyngeal carcinoma genetics: Bioinformatics insights into pathways and gene associations

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ABSTRACT

Introduction: The pathogenesis of nasopharyngeal carcinoma (NPC) is intricate, influenced by a combination of factors including host genetics, viral infection and environmental elements, resulting in genetic and epigenetic modifications. Despite a positive prognosis for early-stage patients, most NPC cases are diagnosed at an advanced stage, highlighting the pressing need for enhanced accessibility to early diagnosis and treatment. The underlying molecular pathways driving NPC progression remain elusive. This study focuses on the use of bioinformatics techniques and databases in carrying out research to gain insights into gene relevance and potential applications in NPC.

Materials and Methods: Searches encompassed articles published in English from January 2017 to June 2024, utilising keywords such as 'nasopharyngeal carcinoma,' 'bioinformatics,' 'gene expression' and 'gene microarrays' across PubMed, MEDLINE and Scopus databases. The Gene Expression Omnibus (GEO) database was utilised to access NPC messenger RNA (mRNA) expression profiling studies.

Results: Most studies utilised the GEO database to identify differentially expressed genes (DEGs) between normal and NPC tissues, followed by functional analysis using gene ontology (GO) and Kyoto Encyclopaedia of Genes and Genomes (KEGG) pathways. Protein protein interaction (PPI) networks of DEGs were commonly constructed using STRING and visualised with Cytoscape software. The integration of GO and KEGG pathway analysis alongside PPI network construction provides valuable insights into the dysregulated pathways and molecular mechanisms underlying NPC pathogenesis. Microarray analysis, particularly datasets such as GSE12452, GSE64634 and GSE34573, has enabled the identification of DEGs associated with NPC. PPI network analysis identifies hub genes, such as DNALI1, DNAI2 and RSPH9, implicated in NPC pathogenesis. Validation of gene expression patterns through platforms like GEPIA and Oncomine validates the clinical relevance of identified biomarkers. Furthermore, studies employing RNA sequencing and bioinformatics approaches uncover novel genes involved in NPC radio resistance and prognosis, paving the way for personalised therapeutic strategies.

Conclusion: Integration of bioinformatics analysis provides insights into the complexity of tumour biology and potential molecular pathways, enabling the development of enhanced strategies for early detection, outcome prediction, recurrence detection and therapeutic approaches for NPC.

KEYWORDS:
Nasopharyngeal carcinoma, bioinformatics, differentially expressed genes, clinical application

INTRODUCTION

Nasopharyngeal carcinoma (NPC) is among the most ubiquitous head and neck malignancies in China, Southeast Asia, the Middle East and North Africa.[1] Due to the interaction of host genetics, viral infection and environmental factors, NPC pathogenesis is multifactorial and strongly correlated with genetic and epigenetic alterations.[2] Despite the promising outlook for early-stage NPC patients, the majority of newly diagnosed cases manifest with locally advanced disease. Presently, there is limited access to early NPC diagnosis and treatment, and the precise molecular pathways driving the evolution of NPC remain unclear. Therefore, it is crucial to investigate potential biomarkers to facilitate early identification and enhance the prognosis of NPC patients. Analysing biological signals, understanding them and managing data are all components of bioinformatics. This has been made easier and more feasible by developments in artificial intelligence and machine learning algorithms, which have increased the usefulness of bioinformatics in the biology of cancer.[3] There is currently a wide range of bioinformatics tools being developed to help address complicated issues ranging from predicting clinical outcomes to identifying factors responsible for altering the tumour-immune milieu. With the rapid development of gene chip and RNA sequencing technologies, bioinformatics analysis is being used in screening for potential biomarkers for various diseases, particularly cancers, in addition to its emerging role in precise screening, prompt diagnosis and molecular-targeted treatment for various types of cancers.[4] The clinical application of bioinformatics uses bioinformatics information and techniques to aid in disease diagnosis, treatment, prevention and control, as well as the development of chemical, structural and biochemical methodologies for clinical

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research.[5] Bioinformatics techniques, for example, are employed in cancer research to detect biomarkers in many types of malignancies at various phases - start, progression and late. Thus, the use of bioinformatics enables personalised clinical treatment for each type of cancer. Bioinformatics techniques are frequently used in research that offer the data required to establish a link between a genetic mutation or variation and a given clinical result.

Bioinformatics gives new insights and core data for discovering reliable and functional differentially expressed genes (DEGs), microRNAs (miRNAs), circular RNAs (circRNAs) and long non-coding RNAs (lncRNAs). Various computational techniques are utilised for investigating biological databases in an effort to develop novel methods and protocols for processing genomic and proteomic data to use in a range of sectors such as the development of pharmaceuticals, medicine and other related industries.[6] The Gene Expression Omnibus (GEO) managed by National Centre for Biotechnology Information is a public archive for high-throughput experimental data from a variety of sources.[7] It is the largest and most complete public gene expression database available for free download, with the option for users to contribute their own data for sharing and validation. These data comprise proteomic research from mass spectrometry and serial analysis of gene expression (SAGE), as well as data from single and dual channel microarray-based investigations measuring messenger RNA (mRNA), genomic DNA and protein abundance.[8] The functional study of DEGs included pathway enrichment using Gene Ontology (GO) and the Kyoto Encyclopaedia of Genes and Genomes (KEGG).[9,10] The KEGG database was used to investigate the metabolic and functional pathways. With the aid of the Search Tool for the Retrieval of Interacting Genes (STRING) and Cytoscape software, a protein protein interaction (PPI) network of DEGs can be found and visualised.[1,11]

Furthermore, web-based technologies for cancer research and diagnostics are made easier by Gene Expression Profiling Interactive Analysis (GEPIA).[12] Advances in microarray technology allow for the collection of large volumes of data on DEGs from specific cancer cells. This enormous amount of data needs the use of computational tools and databases to store, decipher and extract valuable information from the obtained data, such as the identification of new biomarkers for cancer diagnosis. The present work focuses on the application of bioinformatics techniques and databases in NPC through an extensive literature search. In this review, we explored bioinformatics approaches to get additional insight into the relevance and possible uses of genes in NPC.

MATERIALS AND METHODS

Electronic literature searches were conducted in PubMed, MEDLINE and Scopus for articles published in English from January 2017 to June 2024. Search words used were 'nasopharyngeal carcinoma', 'bioinformatics', 'gene expression' and 'gene microarrays', in combination with 'AND' and 'OR'. Additional relevant articles pertinent to this review were identified by reviewing the references of articles that had been retrieved. The inclusion criteria were bioinformatics tools including genomics, transcriptomics or proteomics for the analysis of data in NPC. Studies without available data were excluded. The PRISMA guideline was followed wherever possible.[13] In addition, the GEO database (http://www.ncbi.nlm.nih.gov/gds/)[7] was accessed to retrieve related NPC mRNA expression profiling studies.

RESULTS

Selections of Studies

A total of 308 articles were extracted from electronic databases. Following the removal of duplicates, there were 298 studies left. After the titles and abstracts were screened, 249 papers were eliminated. Of the remaining 49 articles assessed for eligibility, 11 were excluded following full-text review. Finally, 38 articles were included for the review (Figure 1).[7,9-12,14-46]

Tools of Bioinformatics in NPC

The findings from the bioinformatics tools play a crucial role in the management of NPC by facilitating the analysis and interpretation of biological data, which is essential for understanding the disease, developing personalised treatment strategies, and predicting outcomes. Furthermore, bioinformatics is essential for the identification of biomarkers and clinical decision assistance for NPC. By leveraging advanced computational techniques to analyse complex molecular data, bioinformatics tools enable personalised medicine approaches and facilitate more precise and effective management of NPC patients.

Among the bioinformatics tools used were GO and KEGG, PPI, GEPIA, Weighted Gene Co-expression Network Analysis (WGCNA), Database for Annotation, Visualisation and Integrated Discovery (DAVID), STRING and Cytoscape software.[7,9-12,14,15] The majority of the investigations used the associated GEO database for selecting the DEGs between normal nasopharyngeal tissues and NPC tissues from the microarray expression profiles. Targeted DEG functional analysis was reviewed using GO and KEGG pathway enrichment analysis.[9,10] In most of the studies, a PPI network of DEGs was built by STRING and visualised using Cytoscape software.[11]

MyCancerGenome is a resource for understanding the genetic underpinnings and clinical implications of various cancers, including NPC.[16] This platform provides detailed insights into genetic mutations associated with NPC, helps in identifying targeted therapies, and connects clinicians and patients with relevant clinical trials. Understanding the mutation status of MSH6 and CDKN2A can help oncologists decide whether certain targeted treatments or immunotherapies might be effective. This is particularly important for NPC, which has a distinct genetic and aetiological profile often associated with EBV infection. MSH6 is a DNA mismatch repair gene.[17] Alterations in this gene can lead to microsatellite instability, which has implications for cancer progression and treatment response. MSH6 status is used as an inclusion criterion in several clinical trials for NPC, indicating its significance in the development of targeted therapies. CDKN2A is involved in cell cycle regulation.[18] Its mutations can disrupt normal cell cycle control, contributing to cancer development and progression.

The Cancer Genome Atlas (TCGA) plays a pivotal role in advancing our understanding of NPC by providing comprehensive genomic data and facilitating research into its molecular underpinnings. Although NPC was not one of the primary cancers studied in the original TCGA project, the data and methodologies developed by TCGA have significantly influenced NPC research.[19] TCGA's approach to characterising cancer genomes has been applied to NPC, leading to the identification of key genetic alterations and pathways involved in this cancer. Alterations in genes such as *TP53* and *PIK3CA* in NPC, which are critical for understanding the disease's course and possible treatment targets have been found.[20] TCGA's integration of genomic, transcriptomic and epigenomic data has been mirrored in NPC studies, providing a holistic view of the disease. This integrated approach helps in identifying potential biomarkers for early detection and targets for therapy. To fully analyse and interpret NPC-related genomic data, researchers frequently use a combination of tools and databases. The different bioinformatics tools used in many facets of NPC research are shown in Table I.[7,9-12,14,15]

Microarray Analysis for NPC

Hundreds of DEGs implicated in different signalling networks, molecular functions and biological processes can be identified using gene microarrays, which are high-throughput platforms for the investigation of gene expression. The efficiency and accuracy of analysis are improved when microarray technologies and bioinformatics tools are combined.[21] GSE12452 dataset was the most used by researchers (n = 13), followed by GSE64634 (n = 7) and GSE34573 (n = 7), respectively (Table II). Other datasets were GSE53819 and GSE13597 (n = 4), GSE52068, GSE62336, GSE32960 and GSE36682 (n = 2). Sengupta et al used GSE12452 dataset to measure mRNA expression levels for essentially all human genes and all latent Epstein-Barr virus (EBV) genes in nasopharyngeal carcinoma tissue samples and normal nasopharyngeal tissues.[22] Nine of the ten core genes *(FN1, MMP1, MMP3, PLAU, PLAUR, SERPINE1, SPP1, COL8A1, COL10A1)* were shown to be potentially valuable as NPC diagnostic biomarkers by Guo et al.[23] using GSE12452.

The two most used platforms in microarray technology were Affymetrix platform (GPL570 [HG-U133_Plus_2] Affymetrix Human Genome U133 Plus 2.0 Array) and IIlumina platform (Human Methylation450 BeadChip).[24] Affymetrix arrays, which are often referred to as high-density oligonucleotide arrays or oligonucleotide arrays, use a collection of 11–20 Perfect Match and Mismatch oligonucleotides to represent each gene. One of the most sophisticated methods for microarray-based gene expression analysis is Illumina technology. It has a minuscule feature size, dense features and the capacity to analyse several samples simultaneously. With the use of microarray technology, it has become possible to analyse over 10,000 genes at once and uncover genetic anomalies in tumours on a genome-wide scale by analysing the genetic profiles of biological samples. DNA-to-RNA and DNA-to-DNA strands are examples of complementary nucleotide chains that hybridise to create the foundation of microarray technology.[25] Because of this technology, it is now feasible to analyse tumour growth, disease progression, cellular response to stimuli and therapeutic target identification by connecting physiological cell states to gene expression patterns. Table III shows the common microarray datasets and platform used for GEO database analysis.

Identification of DEGs

The online programme GEO2R (http://www.ncbi.nlm.nih.gov/geo/geo2r) was used in most investigations to process the raw microarray data of the datasets acquired from the GEO database and identify genes that are expressed differently in NPC tissues compared to normal nasopharyngeal mucosa.[26] GEO2R is an online tool allowing users to compare different data sets in a GEO series in the identification of DEGs across experimental conditions. GEO2R presents a simple interface that allows users to perform sophisticated analysis of GEO data to help identify and visualise DEGs.[7] Unlike GEOs and other dataset analysis tools, GEO2R does not rely on curated records and cross-examines original submitter-supplied data directly. This expands the utility of the database to a much wider audience, allowing a greater proportion of GEO data to be analysed in a timely manner and with more flexibility in determining comparison of groups of samples and type of analysis to perform.

The GEO database includes microarray datasets, such as GSE12452 and GSE53819. These datasets are used to find and analyse DEGs between diseased and healthy individuals. These datasets highlight the efficacy and scale of microarray technology for bioinformation collection.

CircRNA_0000285 has been suggested by Shuai et al.[27] as a potential new biomarker for NPC radiosensitivity. The integrated analysis of three transcriptome profiling datasets allowed the study to identify DE of lncRNAs, circRNAs and mRNAs between NPC and chronic nasopharyngitis (CNP) tissues simultaneously. A total of 50 mRNAs were found to be the last functioning genes in the circRNA miRNA mRNA network. Environmental stress, cell motility and migration, cytoskeleton, antiproliferative activity, regulation of voltage-gated calcium channels, cell proliferation and apoptosis, desmosome formation, annexin, B lymphocyte antigen receptor, bimodal regulator of epidermal growth factor receptor and mitogen activated protein kinase signalling, extracellular matrix protein, and chromosome segregation are among the physiological and pathological mechanisms linked to the functions of these target genes.

Chen et al.[28] identified aberrantly methylated DEGs or DEGs regulated by differentially methylated miRNA in a study that integrated methylation and miRNA expression patterns. They also created a pipeline for aggregating consensus DEGs from diverse datasets on several platforms, including microarray and RNA sequencing. Six mRNA expression datasets and two methylation datasets were specified for further study. They established robust consensus DEGs by merging several types of datasets and analysing them using bioinformatics. The study found that most DCGs were downregulated and likely to lose connection in cancer. 98% of differentially co-expressed partners (DCPs) that lost positive correlations with PAX5 were upregulated, while 85% of DCPs that lost negative correlations were downregulated.

Actively expressed EBV genes, including *EBNA1*, were co-expressed with upregulated DNA methyltransferase and PolyComb Group proteins. This suggests that EBV interacts with the host genome and modifies host genome methylation, leading to NPC.

1,218 (555 upregulated and 663 downregulated), 1,232 (348 upregulated and 884 downregulated) and 1,301 (553 upregulated and 748 downregulated) genes were found after analysis of the GSE12452, GSE34573, and GSE64634 datasets by Zhu et al.29 The cluster analysis of DEGs indicated significant changes between the normal nasopharyngeal mucosa and NPC specimens.

GO Terms Enrichment and KEGG Pathway Analysis

A variety of GO tools were available for extracting statistically meaningful findings from the investigation of the GO database. The GO resource (http://www.geneontology.org) is a contemporary biological database that created a set of organised, controlled vocabularies to explain gene function analysis.[9] The GO analysis was used to classify genes into molecular function, cellular component and biological process types. The pathway analysis of KEGG (www.genome.jp/kegg/pathway.html) was utilised to determine DEGs at the level of biological function.[10] KEGG is a knowledge repository that connects genomic data to higher level functional information for a methodical examination of gene function. It is frequently used to locate groups of co-expressed genes that have a common route. It stores graphical representations of biological processes, including metabolism, membrane transport, signal transduction and the cell cycle. The 'clusterProfiler' package (http://bioconductor.org/packages/release/bioc/html/clusterProfiler.html) in R software was used in most of the studies to investigate the biological function of DEGs using GO and KEGG pathway enrichment analysis.[30]

Gene Functional and Pathway Enrichment Analysis of DEGs

The DAVID database (http://david.abcc.ncifcrf.gov) is a web-based bioinformatics enrichment tool that allows for thorough high-throughput gene functional annotation analyses.[15] It incorporates a variety of public gene and protein annotation sources, providing information on over 1.5 million genes from over 65,000 species. DEGs were primarily engaged in cilium movement and the drug metabolism-cytochrome P450 pathway, which has been shown to be essential for the treatment of cancer according to a functional and pathway enrichment analysis conducted by Ye et al.31 using the dataset GSE64634. *DNALI1, RSPH4A, RSPH9, DNAI2* and *ALDH3A1* were also found to be hub DEGs in the study, whereas PPI module analysis showed that these hub genes interacted closely and may have a role in the pathway and biological processes linked to NPC.

PPI Network Construction and Hub Genes Identification

The connection between protein molecules is known as the PPI, and it is used to explore correlations related to genetic networks, biochemistry and signal transduction. Cytoscape software (version 3.4.0; http://www.cytoscape.org/) was used to design and visualise a PPI network, and the online search tool STRING (http://string-db.org) to investigate the relative interaction of the DEGs.[11] The ten most important hub genes were found in the study by Zhu et al.[29] using PPI network design. These were *DNALI1, DNAI2, RSPH9, RSPH4A, NDC80, TYMS, CCDC39, DNAH5, CALM*1 and *CCDC114*. The hub gene with the greatest level of linkage was DNALI1. Using the PPI network, Lu et al.32 discovered additional molecules associated with vimentin, revealing the linked genes to be *AURKB, AKT1, TPM4, DMD, TTN, TPM1, CASP7, CASP3, CASP6,* and *CASP8*. The findings further showed that vimentin engages in the p53 and tumour necrosis factor (TNF) signalling pathways and plays a critical role in the epithelial-mesenchymal transition process.

Validation of Expression and Clinical Analysis of Hub Genes

The GEPIA (http://gepia.cancer-pku.cn) and Oncomine databases (https://www.oncomine.org) were tools for comparing the expression levels of important genes in normal nasopharyngeal tissues and NPC.[12,33] The expression of 25 core genes was confirmed in NPC tissues by Guo et al.[23] by uploading the 25 core genes to the GEPIA database. Ten of the core genes—*FN1, MMP1, MMP3, PLAU, PLAUR, SERPINE1, SPP1, COL8A1, COL10A1,* and *COL17A1*—were found to be significantly overexpressed in NPC tissues when compared to normal nasopharyngeal tissues. The results aligned with the GSE40290 and GSE53819 datasets. Table IV shows some of the most highly expressed genes in NPC.[34-41]

Application of Bioinformatics in the Diagnosis and Management of NPC

By employing RNA sequencing and bioinformatics analysis to analyse and integrate the DEGs between radioresistant and radiosensitive NPC tissue samples, Sun et al.[42] discovered three key genes, *DOCK4, MCM9* and *POPDC3*, that may be implicated in the radioresistance of NPC. The results of this investigation offer fresh insights into the process underlying NPC radioresistance, and more experimental research focusing on these key genes is necessary. A work by Xue et al.[43] offered a theoretical foundation for the clinical application of *LRRC46, PCDP1* and *c9orf24* in the therapy of NPC in the future. The results of this study demonstrate that *c9orf24, PCDP1* and *LRRC46* are identified as putative gene markers for NPC using a variety of methodologies, such as microarray-based analysis, WGCNA analysis, GO and KEGG functional enrichment studies, and PPI network analysis. The identification of *LRRC46, c9orf24* and *PCDP1* may be useful in identifying NPC and offer novel therapeutic approaches.

In a work by Guo et al.[23], bioinformatic techniques utilising GSE40290 and GSE53819 were used to determine DEGs and possible pathways for NPC. There were 314 DEGs in all, and it was found that nasopharyngeal carcinogenesis could be linked to a number of biological processes and signalling pathways, such as those related to the extracellular matrix, the NF-κB signalling pathway, cancer pathways, the B cell receptor signalling pathway and the interaction between the extracellular matrix and receptors. Further investigation identified the main genes with significant diagnostic value for NPC as *FN1, MMP1, MMP3, PLAU, PLAUR, SERPINE1, SPP1, COL8A1 and COL10A1.*

Using three data sets (GSE68799, GSE12452, and GSE53819), Huang et al.[44] used WGCNA to identify and validate hub

Table I: Common bioinformatics instruments applied to different elements of the analysis of nasopharyngeal cancer

Bioinformatic tool	Description/usage
Genome analysis toolkit (GATK)	Variant discovery and genotyping in NPC genomes
Spliced Transcripts Alignment to a Reference (STAR)	RNA-seq alignment and transcript quantification
DESeq2	Differential gene expresson analysis in NPC RNA-seq data
Cufflinks	Transcript assembly and differential expression analysis
STRING	Protein-protein interaction networks in NPC
DAVID	Functional enrichment analysis of NPC-related genes
Integrative Genomics Viewer (IGV)	Visualisation of genomic data including NPC mutations and CNVs
MutSigCV	Identification of significantly mutated genes in NPC
UCSC Genome Browser	Genome annotation and visualisation tool
GenePattern, Broad Institute	Access to various tools for gene expression analysis, clustering, etc.
OncoPrint	Visualisation of oncogenic alterations in NPC
TCGA Data Portal	Access to NPC genomic data from the Cancer Genome Atlas
COSMIC	Catalogue of somatic mutations in NPC and other cancers
ENCODE	Exploration of regulatory elements and gene expression in NPC

NPC: Nasopharyngeal carcinoma

Table II: The common GSE dataset used[7]

Differentially expressed Genes	Numbers	Title/status
GSE40290	1	Molecular classification of non-keratinizing nasopharyngeal carcinoma using mRNA expression profiling
GSE53819	4	Genome-wide expressing profiling of nasopharyngeal carcinoma primary tumours versus non-cancerous nasopharyngeal tissues
GSE64634	7	mRNA expression profiling of nasopharyngeal carcinoma
GSE12452	13	mRNA expression profiling of nasopharyngeal carcinoma
GSE34573	7	A global view of the oncogenic landscape in nasopharyngeal carcinoma: an integrated analysis at the genetic and expression levels
GSE48501	1	Gene expression data from human radioresistant and radiosensitive nasopharyngeal carcinoma cells
GSE13597	4	Expression data from biopsies of nasopharyngeal carcinoma and non-malignant controls
GSE52068	2	Genome-wide analysis of DNA methylation between nasopharyngeal carcinoma tissues and normal nasopharyngeal epithelial tissues
GSE62336	2	Methylome study in nasopharyngeal carcinoma
GSE32960	2	microRNA profile of human nasopharyngeal tissues: nasopharyngeal carcinoma tissues vs. normal nasopharyngeal tissues
GSE36682	2	MicroRNA signatures correlate with diagnosis, distant metastasis and prognosis in nasopharyngeal carcinoma
GSE68799	1	RNASeq identified human transcriptome alterations in Chinese nasopharyngeal carcinoma
GSE43039	1	microRNA expression profiling of human nasopharyngeal carcinoma tissues and chronic nasopharyngitis specimens
GSE70970	1	Comprehensive microRNA profiling of nasopharyngeal carcinoma specimens
GSE95166	1	Designated experiment to screen for lncRNAs whose expressions are dysregulated in nasopharyngeal carcinoma tissue
GSE126683	1	Highlight its biologic importance, and suggest a therapeutic role for inhibitors of NF-KB pathway activation in the treatment of Waldenström's macroglobulinemia

genes. Hub genes with predictive values were screened using a different data set, GSE102349. Functional tests verified that *IGSF9* expression boosted NPC cell invasion, migration and proliferation in vitro. Patients with NPC had high expression levels of *IGSF9*, which was a suitable prognostic gene. As a member of the immunoglobulin superfamily, *IGSF9* is essential in suppressing the formation of synapses by controlling calmodulin-like activity. In addition to IGSF9 potentially causing NPC cell metastasis via the phosphatidylinositol 3-kinase/protein kinase B (Akt) signalling pathway, calmodulin is implicated in cancer metastasis.

An assortment of newly discovered methylation genes and miRNA were found by Wang et al.[45] and may be useful as possible biomarkers for NPC prognosis. The unfavourable prognosis of NPC may be associated with hypomethylation of *SRC, SMAD3, YWHAZ* and *HSPA4,* as well as hypermethylation of *miR129-2*. The capacity of miRNA biology to target numerous genes is its biggest advantage when applied to the clinical care of patients with NPC. However, before this four-miRNA signature can be successfully implemented clinically, more research is needed to understand the regulatory roles of the four miRNAs connected to p53 signalling or other important signalling pathways in the genesis and development mechanism of NPC and the specific regulatory mechanisms.

Zheng et al.[46] looked for changes in the regulators of the NF-κB pathway in NPC using whole-exome sequencing. Numerous genes involved in the regulation of the NF-κB pathway, such as *TNFAIP3, CYLD* and *NFKBIA,* were discovered to have many loss-of-function mutations. The investigation also revealed a noteworthy occurrence of

Table III: Microarray datasets and platform used for GEO databases[7]

Differentially expressed Genes	Platform	Nasopharyngeal	Normal carcinoma	Key findings
GSE40290 GSE53819	GPL8380 GPL6480	8 18	25 18	Core genes, including FN1, MMP1, MMP3, PLAU, PLAUR, SERPINE1, SPP1, COL8A1, COL10A1, had high diagnostic value for NPC
GES64634 GSE12452 GSE34573	GPL570 GPL570 GPL570	12 31 16	4 10 4	ARMC4, SERPINB3, MUC4 etc. have a close relationship with NPC
GSE48501	GPL570	14	Not stated	Identified three core genes, DOCK4, MCM9, and POPDC3 among 12 common downregulated genes
GSE34573 GSE12452 GSE64634 GSE13597 GSE53819 SRP058243 GSE52068 GSE62336 GSE32960 GSE36682 GSE36682	GPL570 GPL570 GPL570 GPL96 GPL6480 Illumina Hiseq 2000 Illumina Illumina GPL14722 GPL15311 GPL20699	15 31 12 25 18 41 24 25 312 62 246	4 10 4 3 18 4 24 25 18 6 17	Promoter hypermethylation, expression up-regulation, and association with overall survival, genes such as SCUBE2, PRKCB, IKZF1, MAP4K1, and GATA6 could be promising novel diagnostic biomarkers
GSE12452 GSE53819	GPL570 GPL6480	49	28	The expression levels of CDK1, CDC45, RSPH4A, and ZMYND10 probably affected survival of NPC patients according to GEPIA database, and identification of small-molecule compounds which may be efficacious in the treatment of NPC
GSE53819	Agilent-014850	18	18	c9orf24, PCDP1, and LRRC46 are identified as potential gene for NPC
GSE68799 GSE12452 GSE53819 GSE102349	Not stated	46	Not stated	Three hypoxia signatures (99-gene, 26-gene and 15-gene) have prognostic value in NPC patients
GSE12452 GSE13597 GSE43039 GSE70970 GSE95166 GSE126683	GPL570 [HG-U133A] Affymetrix nCounter® Arraystar V4 Agilent-045997 Arraystar V3	10 3 20 17 4 3	31 25 20 246 4 3	lncRNA-miRNA-mRNA networks play significant roles in the development and progression of tumors
circRNA_0000285	Arraystar, Inc	42	42	KIAA0101 ranked top overexpressed gene lists in GSE6631 dataset. highly expressed in NPC tissues and cell lines
GSE64634 GSE53819 GSE12452	GPL6480 GPL570 GPL570	14 18 31	4 18 10	A total of 306 DEGs and 13 hub genes were identified and may be regarded as diagnostic biomarkers for NPC
GSE12452 GSE34573 GSE64634	GPL570 GPL570 GPL570	31 16 12	10 3 4	Upregulated DEGs were significantly enriched in biological processes, including 'cell adhesion', 'cell division', 'mitosis' and 'mitotic cell cycle'
GSE12452 GSE34573	GPL570	31 13	10 3	DEGs were mostly enriched in ciliummovement, antimicrobial humoral response, O-glycan processing, mucosal immune response, hormone and neurotransmitter biosynthetic process, and drugmetabolism-cytochrome P450 pathway
GSE64634 GSE12452	GPL570	12 31	4 10	Critical node proteins were identified in the network, including CDK1, SMC4, KNTC1, KIF23, AURKA and ATAD2 involved in NPC
GSE12452 GSE13597 GSE34573 GSE53819 GSE64634	GPL570 GPL96 GPL570 GPL6480 GPL570	50	22	Vimentin promotes the negative biological behaviours of NPC, including its occurrence, malignancy, and poor prognosis
GSE32960	GPL570	312	18	Identification of NPC patients with a four-miRNA signature may increase the prognostic value and provide reference information for precision medicine

Table III: Microarray datasets and platform used for GEO databases[7]

Differentially expressed Genes	Platform	Nasopharyngeal	Normal carcinoma	Key findings
GSE12452 GSE34573	GPL570	44	13	Module's analysis revealed that cyclin-dependent kinase 1 and exportin 1 were involved in the pathway of Epstein Barr virus infection
GSE52068 GSE62336	Illumina	24 25	12 25	Identified crucial genes that were indicted to be hypomethylated, instead of hypermethylated, in the NPC samples, including SRC, SMAD3, YWHAZ and HSPA4
GSE12452 GSE13597	GPL96	56	13	Up-regulated genes were significantly involved in cell cycle, oocyte meiosis, DNA replication and p53 signalling pathway

GEO: Gene Expression Omnibus, NPC: Nasopharyngeal carcinoma, DEG: Differentially expressed genes

Table IV: The genes and mRNAs that are significantly expressed in nasopharyngeal carcinoma, together with their corresponding pathways, target genes and role in the pathogenesis

Gene/mRNA	Target Genes/proteins	Pathways	Role in NPC pathogenesis
EBER34	EBV proteins (LMP1, LMP2A)	NF-κB, JAK/STAT	Immune evasion, cell growth and survival, oncogenic potential
LMP134	TRAF proteins, IKK complex	NF-κB, JNK, PI3K/AKT	Cell proliferation, inhibition of apoptosis, metastasis
BART34	Various cellular genes	miRNA regulatory pathways	Regulation of apoptosis, immune response, epithelial-mesenchymal transition (EMT)
BCL235	Pro-apoptotic proteins (BAX, BAK)	Intrinsic apoptotic pathway	Anti-apoptotic, tumour survival and growth
STAT336	Cyclin D1, BCL2, VEGF	JAK/STAT	Cell proliferation, survival, angiogenesis
EGFR37	RAS, PI3K, PLCγ	EGFR, MAPK, PI3K/AKT	Cell proliferation, survival, migration, angiogenesis
PD-L138	PD-1 receptor on T cells	Immune checkpoint	Inhibition of T cell function, immune evasion, tumour progression
VEGF39	VEGFRs	VEGF signalling pathway	Angiogenesis, tumour blood supply, growth, and metastasis
MMP940	Extracellular matrix components	ECM remodelling	Breakdown of the extracellular matrix, tumour invasion, and metastasis
CXCL1241	CXCR4 receptor	Chemokine signalling pathway	Tumour cell migration, invasion, metastasis

NPC: Nasopharyngeal carcinoma

mutations in other genes associated with DNA repair, apoptosis and cell division. The researchers found that increased NF-κB pathway activity in NPC was associated with mutations in the regulators of the NF-κB pathway. IκBα inhibitors are among the possible therapeutic targets in the NF-κB pathway that the researchers identified. They also discovered a connection between worse clinical outcomes for NPC patients and mutations in the regulator of the NF-κB pathway.

DISCUSSION

In this review, we summarised integrated bioinformatics techniques that allow for the discovery of important gene functions and related biological mechanisms linked with NPC pathogenesis. We examined and compared their essential information and features of OMIC databases, array technology platforms, and main outcomes (Table III). These tools enable researchers to quickly examine a large number of datasets from complex data platforms, discover genes, proteins, gene alterations or mutations associated with patient survival, ask specific questions and test hypotheses. Each bioinformatics tool has distinct advantages. The most comprehensive source of knowledge on the roles played by genes is the GO knowledge base. Genes were classified into several different categories for the GO analysis, and functional and metabolic pathways were discovered using the KEGG database. Some databases offer additional features, such as the top differential gene display function in GEPIA, which enables clinicians and researchers to choose potential target genes for diagnosis or treatment.

Over the years, novel approaches based on scientific knowledge from cancer bioinformatics, such as gene therapy and molecular-targeted therapies, have contributed to remarkable achievements and clinical benefits.[47] Based on these technologies, a few possible RNA and protein biomarkers have been discovered. Precision therapy and prognosis relied on verified biomarkers with improved screening, diagnosis, and monitoring capabilities. Based on this, gene chip, RNA sequencing, and bioinformatics analysis have emerged, providing a thorough screening of tumour biomarkers as well as a means for understanding the significance of detailed biomarkers in cancer pathology. The pathogenesis of cancer, including gene mutation, transcriptional regulation, protein synthesis, and metabolic alterations, is a systematic mechanism.[48] Based on these relationships, integrating two or more types of omics research and using machine learning methods to perform association analysis on molecules at multiple levels could compensate for

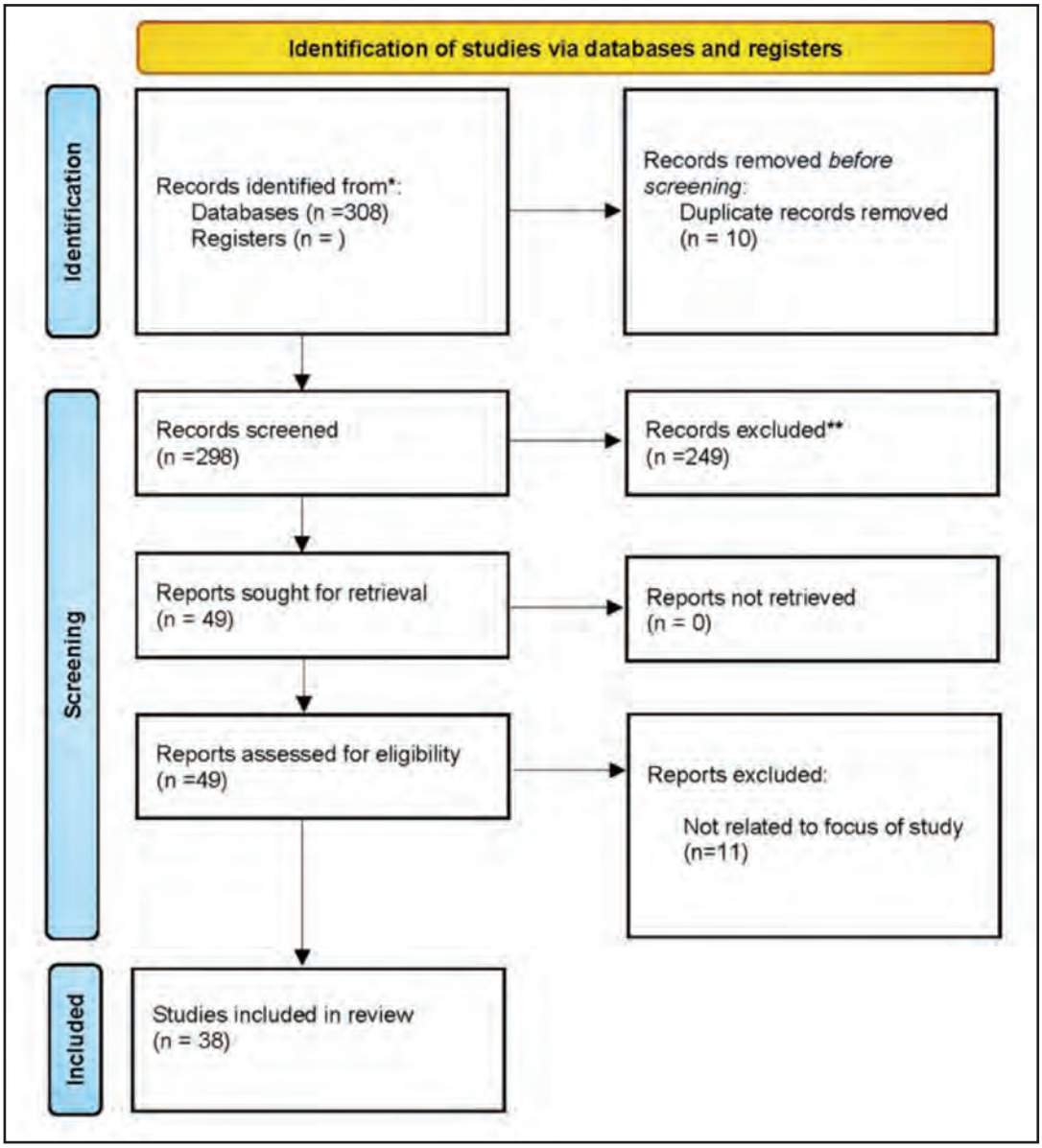

Fig. 1: PRISMA flow diagram of study selection.

the lack of data caused by single omics analysis and reduce the likelihood of false positive results. To advance the study and development of tumour biomarkers, multi-omics integration has emerged as a new trend.

Understanding the genetic profile of nasopharyngeal cancer by the related cancer gene atlas has been instrumental in identifying potential biomarkers and therapeutic targets, which can ultimately improve diagnosis and treatment outcomes for patients. In addition to TCGA, there are several other initiatives and resources that focus on cancer genomics and may provide insights specifically related to NPC. International Cancer Genome Consortium (ICGC) is an international collaboration that aims to catalogue genomic abnormalities in various types of cancers, including NPC.[49] It facilitates data sharing and collaborative research among scientists worldwide. Catalogue of Somatic Mutations in Cancer (COSMIC) is a database that catalogues somatic mutations and other genetic alterations in human cancers, including NPC.[50] It provides detailed information on mutations, copy number variations and gene fusions found in cancer samples. GEO is a public repository that archives and freely distributes high-throughput gene expression and molecular abundance data, including data related to NPC.[7] Researchers can access datasets to explore gene expression patterns, biomarkers, and potential therapeutic targets in NPC. Although not specific to cancer, Encyclopaedia of DNA Elements (ENCODE) provides valuable genomic data on regulatory elements and gene expression across different tissues, which can be informative for understanding gene regulation in NPC.[51]

A majority of the research did, however, point out some limits of the bioinformatics tool in addition to its clear benefits in the identification of particular biomarkers. First, the small sample size decreased statistical power, particularly due to

the tiny patient populations in some subgroups, which led to variable results for various subgroups.[47] Second, there were no body fluid-related data included in the study to reflect vimentin's diagnostic significance as a non-invasive marker for NPC and no animal tests to confirm and investigate the biological activities of vimentin in NPC.[32] Third, a thorough and systematic investigation of gene expression and epigenetic modifications was still absent.[28] This might be beneficial i0n offering insight on the progression of cancer and identifying possible biomarkers, particularly for NPC. Because of the substantial infiltration of immune and stromal cells into the tumour, analysis without sufficient control of tumour composition may result in bias or false negative. Because most studies lack this information, future studies should specify the tumour analysis based on the section of tissue used in order to standardise the percentage of cancer cells being analysed.

While many bioinformatics tools are versatile and can be applied to multiple cancer types, some tools are more specialised or more frequently used in certain cancers due to the specific needs of those cancers. Tools like Genome Analysis Toolkit (GATK) and MuTect2 are fundamental for variant analysis in NPC as well as other cancers.[52] GATK facilitates the identification of mutations, insertions and deletions in the genome, whereas MuTect2, a GATK tool, aids in the identification of somatic point mutations and indels in tumour-normal pairs that are utilised in NPC genomic investigations. The choice of tools for transcriptomic and proteomic analysis might vary depending on the specific cancer type and the focus of the study. Comprehensive databases like TCGA provide a wealth of data for multiple cancers, facilitating cross-cancer comparisons and integrative analyses. TCGA provides comprehensive genomic data for various cancers such as breast, lung, and colorectal cancers. Tools like cBioPortal and OncoLnc make it easier to access and analyse this data.[53,54] In contrast, clinical trial databases and survival analysis tools are universally important across all cancer types for evaluating treatment outcomes and patient prognosis. The application of bioinformatic tools in NPC allows for the detection of gene fusions (which are important in NPC because they may influence tumour development), the identification of recurrent copy number variations, the provision of access to NPC genomic data from large-scale studies such as TCGA for thorough analysis, and the analysis of survival data based on clinical factors and molecular profiles in NPC patients. In other cancer types, bioinformatic tools identify somatic mutations (which are important for comprehending the burden of mutations and possible driver mutations), analyse protein-protein interaction networks (which are vital for comprehending intricate interactions in signalling pathways), and provide regulatory element data across a range of tissues, which helps comprehend gene regulation and epigenetic modifications.

Although these integrative bioinformatics tools may provide better knowledge and understanding, several key aspects of these tools need further verification. While multidimensional analysis and data comparison can be achieved through the selection of datasets and their sources, variations in the split points and datasets collected may lead to substantially distinct conclusions. There may be limitations stemming from the limited utilisation of chosen databases from GEO, in addition to the variability in sample sizes among researchers. Since the genetics of NPC is poorly known, improved treatment strategies like targeted therapy and immunotherapy are desperately needed.[28,55] Diverse NPC subtypes exhibited distinct genomic modifications, with undifferentiated NPC exhibiting a high incidence of mutations. Confirming the expression and function of the identified hub DEGs in NPC requires additional research. Computational cancer research may benefit greatly from the traditional methods of statistics and bioinformatics for the analysis of biological sequences, large-scale OMIC data sets, the genome and protein three-dimensional structure.[56] It is envisioned that advances in systems biology and cancer bioinformatics will enhance therapeutic design, prevention and diagnostics.

Although bioinformatics has revolutionised our understanding of many aspects of NPC, there are several limitations and challenges in using bioinformatics to fully elucidate its pathogenesis. NPC pathogenesis involves intricate interactions between genetic, epigenetic and environmental factors. Integrating data from multiple omics platforms (genomics, transcriptomics, proteomics) to capture this complexity is challenging. Bioinformatics tools often struggle with integrating diverse datasets to provide a comprehensive understanding of NPC biology. Access to large, well-annotated datasets of NPC samples is limited. Small sample sizes and heterogeneity among patient populations (e.g., ethnic diversity, Epstein-Barr virus status) can complicate bioinformatics analyses and limit the generalisability of findings. Bioinformatics often identifies associations or correlations between molecular features and NPC pathogenesis. However, validating these findings experimentally (in vitro or in vivo) to understand functional relevance and causality is resource-intensive and time-consuming. NPC pathogenesis is dynamic, involving evolving interactions between tumour cells and the microenvironment over time. Bioinformatics analyses capture snapshots of molecular profiles, but understanding temporal changes and dynamic interactions requires sophisticated computational models and longitudinal data. NPC pathogenesis involves not only genomic alterations but also epigenetic modifications, protein interactions, metabolic changes and immune responses. Bioinformatics tools primarily focus on genomics and transcriptomics, potentially overlooking other crucial aspects of NPC biology. NPC incidence varies significantly across populations, with distinct genetic and environmental risk factors. Bioinformatics analyses may not fully account for ethnic or geographic variability, limiting the applicability of findings to diverse populations. NPC pathogenesis involves complex networks of molecular interactions. Bioinformatics approaches, while powerful, often simplify these networks into linear pathways or regulatory modules, potentially oversimplifying the true complexity of NPC biology.

CONCLUSION

Bioinformatics methods have been extensively employed in the research of NPC to characterise genomic changes, signalling networks, differentially expressed genes (DEGs)

and cellular heterogeneity. These findings have improved our understanding of the molecular mechanisms behind NPC and have the potential to stimulate the development of novel therapeutic strategies. The application of bioinformatics tools has significantly improved patient outcomes, made it simpler to assess complex data, find potential biomarkers and therapy targets. The development of bioinformatics technology has facilitated the search for potential prognostic biomarkers for NPC. With a greater understanding of the complexity of tumour biology and potential molecular pathways provided by the bioinformatics integration analysis, improved strategies for early detection, outcome prediction, disease recurrence detection and therapeutic approaches for NPC will be possible.

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SYSTEMATIC / NARRATIVE REVIEW ARTICLE

Efficacy of dexmedetomidine in postoperative nausea and vomiting in laparoscopic bariatric surgery: A systematic review and meta-analysis of randomised clinical trials

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ABSTRACT

Introduction: Postoperative nausea and vomiting (PONV) is a common side effect of all types of surgeries, especially so in bariatric surgery. Dexmedetomidine (DX) is an α2-agonist that may be useful as an adjunct prophylactic medication for PONV. This meta-analysis aims to evaluate the efficacy of DX in reducing the incidence and severity of PONV in laparoscopic bariatric surgeries.

Materials and Methods: Databases were searched for articles with the determined MESH terms and keywords before February 2022. Identified articles were screened and 13 randomised clinical trials (RCTs) were included in this meta-analysis based on the inclusion criteria. Data were extracted from the articles and statistical analysis was performed using Review Manager.

Results: Administration of DX significantly reduced the incidence of PONV and Numerical Rating Scale (NRS) scores for PONV. The outcome was probably due to the intrinsic sympatholytic effect of the medication, reduction of postoperative pain and total postoperative opioid usage. DX showed better efficacy as PONV prophylaxis if the duration of surgery was < 120 minutes. Delivery of DX as a continuous infusion without a loading dose before infusion was found to be effective in reducing PONV compared to infusion after a loading dose.

Conclusion: Administration of DX can reduce the incidence of PONV in patients undergoing laparoscopic bariatric surgery. However, further studies are required to investigate the optimal dose of DX as an antiemetic, considering its side effects to increase the applicability of our results in future guidelines for laparoscopic bariatric surgery.

KEYWORDS:
PONV, Laparoscopic bariatric surgery, Dexmedetomidine, Meta-analyses

INTRODUCTION

Postoperative nausea and vomiting (PONV) is a common side effect of anaesthesia in all types of surgeries and is often rated as worse than pain related to surgery itself.[1] It is one of the most common causes of patient dissatisfaction after anaesthesia, with reported incidences of 30% in all post-surgical patients and up to 80% in high-risk patients.[2] Various risk factors for PONV have been identified, including the female gender, history of PONV, motion sickness, duration of anaesthesia with volatile anaesthetics, postoperative opioids and laparoscopic surgeries.[3]

Obesity in the global population is growing at an alarming rate and Malaysia is not an exception. According to the latest National Health and Morbidity Survey 2019, obesity in the Malaysian population was 19.7%.[4] A high prevalence of obesity increases the need for bariatric surgery, as it is the most effective treatment for morbid obesity with a BMI of >35 kg/m^2, resulting in sustained weight loss and reduced obesity-related comorbidities.[5]

However, there are no currently established clear guidelines that can effectively reduce PONV in patients going for bariatric surgery. Conventional guidelines currently recommend the use of multimodal prophylaxis in patients with risk factors, one such being a combination of ondansetron and dexamethasone.[6] Even with the current supra-optimal prophylaxis, Halliday et. al found that PONV could go up to 59% in bariatric surgery patients.[7] This could partly be due to inadequate prophylaxis or inadequate published evidence to guide clinicians on the choice of the optimal combination for individual patients.

The efficacy of new drugs should be explored in view of the ineffective prophylaxis in the current state. Dexmedetomidine (DX) is an α2-adrenoreceptor agonist with sedative, analgesic, and sympatholytic properties. It has been used for bariatric as well as non- bariatric surgeries to suppress PONV, and as a sedative in critically ill patients ventilated in intensive care. Currently, multiple promising trials show the efficacy of DX in preventing PONV. To our knowledge, there is no conclusive review to ascertain the effectiveness of the results. Hence, this meta-analysis aims to evaluate the current studies on the role of DX compared with other antiemetics prophylaxis for reducing the incidence of PONV in individuals undergoing laparoscopic bariatric surgery.

MATERIALS AND METHODS

This meta-analysis of randomised clinical trials (RCTs) was performed following the Preferred Reporting Items for

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Systematic Reviews and Meta-Analyses (PRISMA) statement and the review protocol can be found in the International Prospective Register of Systematic Reviews (PROSPERO), registration number: CRD42022309684.

Search Strategy and Study Selection

A systematic search was conducted using the following online databases: PubMed, SpringerLink, EBSCOhost, Scopus, Science Direct and Ovid MEDLINE to identify relevant studies available from inception to February 2022. We searched for randomised controlled trials on the use of DX for PONV prophylaxis for laparoscopic bariatric surgeries.

The search strategy consisted of Medical Subject Headings (MeSH) terms ("dexmedetomidine AND laparoscopic bariatric surgery AND postoperative nausea and vomiting", "dexmedetomidine AND postoperative nausea and vomiting") and free text words ("dexmedetomidine AND laparoscopic bariatric surgery AND postoperative nausea and vomiting", "dexmedetomidine AND laparoscopic bariatric surgery AND postop nausea and vomiting", "dexmedetomidine AND laparoscopic bariatric surgery"). A search for grey literature was conducted in the OpenGrey database and manual search was also performed in the reference lists of the relevant studies. A reference list of searched data was created, and the abstracts were reviewed by two independent authors (THY, TJH). Controversy over the eligibility of an abstract was resolved by another author (THS).

Inclusion and Exclusion Criteria

All RCTs comparing the safety and efficacy of DX to any other drugs (placebo, opioids, dexamethasone, clonidine, xylocaine) in laparoscopic bariatric surgery under general anaesthesia were included. All studies that reported PONV or made a distinction between nausea or vomiting (considered as PONV) were included. Duplicated articles, editorial articles, case reports, reviews, comments, guidelines, wrong population, wrong drug, wrong study type, non-English, non-laparoscopic bariatric surgery and conference abstracts were excluded from this review.

Data Extraction and Quality Assessment

Available data from chosen RCTs were maximally extracted and tabulated on Excel sheets by several authors (THY, TJH). The data extracted were authors, country, publication year and participant's characteristics, study design, type of surgery, gender, body mass index (BMI), ASA physical status classification, treatment regimen, duration of surgery, duration of anaesthesia, incidence of postoperative nausea and vomiting, numerical nausea score, time to discharge from PACU, total postoperative opioid dose, total volatile agent usage, pain score, total intraoperative opioid usage and postoperative analgesia. The authors were contacted via electronic mail in an attempt to retrieve the missing information.

Critical appraisal of all selected studies was done using the Cochrane Risk of Bias Tool as shown in Figure 1 and 2.

Data Analysis

All statistical analyses were performed using the Review Manager (RevMan version 5.4.1, The Cochrane Collaboration, 2020) software. The primary goal of this meta-analysis was to compare the incidence of PONV after the use of DX and other anti-emetics. The NRS used to measure the severity of PONV in the identified studies was used for data analysis. Secondary outcomes were duration of anaesthesia, duration of surgery, time to safe extubation, time to discharge from post-anaesthesia care unit (PACU), total intraoperative opioid use and total postoperative analgesia. Subgroup analyses of intraoperative comparator i.e., DX versus placebo were done to improve the homogeneity between the groups. Data were only pooled if an outcome was identified in at least three RCTs. Relative risk or risk ratio (RR) with a 95% confidence level was measured for dichotomous outcomes while mean difference (MD) or standard mean difference (SMD) with standard deviation (SD) was measured for continuous outcomes.

A funnel plot was created to detect publication bias. Statistical heterogeneity was assessed using the χ^2 test and the I^2 statistic. A two-tailed p-value of < 0.05 was accepted as statistically significant. An I^2 of less than 25% is viewed as low heterogeneity, between 25% and 50% as moderate, and over 50% as high heterogeneity. Random-effect model was used if significant heterogeneity was detected with the assumption that a single true effect size did not occur across the included studies. Otherwise, a fixed-effect model was used. Data analysis was carried out by two investigators (NHT, THY). Resolution of any discrepancies was conducted by discussion with the third investigator (THS).

This research was presented, and approval was obtained from the International Medical University Joint-Committee on Research and Ethics. (IMUJC); Project ID No.: IMU 551-2022.

RESULTS

Study Selection

A total of 295 relevant publications were identified through a systematic literature search and five were manually extracted from relevant literature review articles.[8-12] From these 13 RCTs were selected for review.The characteristics of each study were extracted and documented (Tables I and II) and a summary of the outcomes extracted are shown in Table III. The risk of bias for each trial was assessed as shown in Figures 1 and 2. The risk of bias in most domains was graded as low. However, all trials were graded as 'unclear risk' under the 'Other bias' domain. Overall, the quality of the included trials was graded as moderate because of the high risk of selective reporting bias in some and the unclear risk of other bias in all studies. A summary of the outcomes of the analysis is shown in Figures 1 and 2. The detail of data extraction is added as a supplementary file and in Tables I and II.

The incidence of PONV post-laparoscopic bariatric surgery comparing DX with other antiemetics was reported in 12 articles. Overall, there was a significant risk reduction in the incidence of PONV with the use of DX (RR = 0.48 [0.41, 0.57]; $p < 0.00001$] as shown in Figure 4. All compared medications

showed risk reduction except clonidine which suggested no difference in risk of incidence of PONV. The lowest risk of PONV was observed when compared to dexamethasone (RR = 0.26 [0.11 – 0.63]; p = 0.003, followed by desflurane (RR = 0.28 [0.14. 0.54]; p = 0.0002, opioid (RR = 0.47 [0.36,0.62]; p < 0.00001), and lastly placebo (RR = 0.48 [0.37, 0.62]; p < 0.00001).

An average of 120 minutes were taken as the expected duration of laparoscopic bariatric surgery averaged from the duration of surgery documented in the included studies (Figure 5). There was a significant reduction in the incidence of PONV with the use of DX if the duration of surgery was < 120 minutes (RR = 0.38 [0.26, 0.57]; p < 0.00001). On the other hand, there was no difference in the incidence of PONV if the surgery was > 120 minutes (RR = 0.62 [0.28, 1.34]; p = 0.22).

Some selected trials prescribed an IV bolus DX before starting an infusion (Figure 6).[10,11,13,16,19] There was a significant risk reduction in the incidence of PONV in both groups. However, risk reduction without IV bolus DX before an infusion (RR = 0.42 [0.25, 0.71]; p = 0.001) was more compared to those with IV bolus followed by infusion (RR = 0.51 [0.40, 0.65]; p = < 0.0001).

RCTs were further analysed by subgrouping the articles based on the percentage of male gender in the study participants. This was because most of the studies did not state the exact number of males and females who participated in the trials. Attempts were made to contact the respective authors with no response. As illustrated in Figure 7, the risk of PONV was reduced in both male-predominant (RR = 0.42 [0.30, 0.59]; p < 0.00001) and female-predominant (RR = 0.45 [0.35, 0.58]; p < 0.00001) groups with the use of DX.

The heterogeneity across the 11 studies was low to moderate.

Numerical Rating Scale of PONV

Five RCTs measured the severity of PONV using NRS. Similar subgroup analyses on PONV were performed. However, one of the studies interpreted the data using the median and interquartile range, hence the result from that study was excluded in the sub-group analyses.[21]

Analysis showed a significant difference in the standard mean difference (SMD) of NRS for PONV (SMD = -1.21 [-1.89, - 0.54]; p = 0.0004). SMD was also found to be significantly lower when DX was compared to dexamethasone (SMD = -2.33 [-2.94, -1.73]; p = 0.0001). There was high total heterogeneity (I^2 = 84%) and subgroup heterogeneity (I^2 = 94.3%) (Figure 8).

Considering the duration of surgery, the SMD of NRS for PONV was significantly reduced in the > 120-minute subgroup (SMD = -1.53 [-3.0, 0.04]; p = 0.06). No difference in NRS subgroup analysis was found with a duration of surgery < 120 minutes (SMD = -1.52 [-3.09, -0.04]; p = 0.06. High total heterogeneity (I^2 = 89%) was detected but subgroup heterogeneity was not significant (Figure 9).

Groups with a higher number of female participants scored lower on the NRS for PONV with the use of DX (SMD = -0.97 [-1.32, -0.62], p < 0.00001) compared to the groups in which there were a higher number of males (SMD = -01.53 [-3.09, 0.04], p = 0.06). It appears that females responded better to the DX than the males. A low subgroup difference was detected although there was a high total heterogeneity (I^2 = 84%) (Figure 10).

Total Dose of Postoperative Analgesia Used

Six studies documented the total dose of analgesia used by the participants postoperatively. In general, DX was shown to reduce the total postoperative analgesia requirement (SMD = -1.87 [-3.31, -0.42], p = 0.01). However, subgroup analyses revealed that the total postoperative analgesia used was significantly lowered when comparing DX to placebo (SMD = -4.04 [-6.99, -1.09]). No difference in SMD was noted when DX was compared to dexamethasone and opioids. High total and subgroup heterogeneity were detected (Figure 11).

There was no difference in the SMD of total postoperative analgesia used even when participants were given an IV bolus DX before DX infusion. The subgroup heterogeneity was low despite a high total difference (Figure 12).

Time to Discharge from Post-Anaesthesia Care Unit (PACU)

Time to discharge from PACU was recorded in seven studies, one study was not included for pooled analysis as the result was reported in the median and interquartile range. DX significantly reduced the time to discharge from the PACU (SMD = -0.36 [CI -0.57, -0.15], p = 0.001) (Figure 13). Subgroup analysis of DX versus placebo and opioid respectively, DX only showed a significant reduction in the time to discharge from PACU when compared to placebo (SMD = -0.83 [CI-1.17, -0.48], p < 0.00001). There were high subgroup differences and moderate total heterogeneity. No significant difference in the time to discharge from PACU was seen when DX was compared to opioids.

The use of IV bolus and no bolus before initiating infusion of DX during induction did not influence the time to discharge from PACU. Moderate total heterogeneity and low subgroup heterogeneity were noted (Figure 14).

Total Intraoperative Opioid Used

Seven studies reported data on the total dose of intraoperative opioids used. Pooled analysis showed that the use of DX intra-operatively did not affect the amount of intraoperative opioid consumption (SMD = -1.14 [-2.47, 0.19]; p = 0.09). Subgroup analysis showed that only when compared to dexamethasone, DX had a significant reduction in total intraoperative opioid use (SMD = -1.83 [-2.39, -1.28], p < 0.00001). High total and subgroup heterogeneity were detected (Figure 15).

When the outcome of IV bolus DX followed by infusion was compared with infusion of DX without bolus the subgroup analysis revealed a significant reduction in the total amount of opioid consumption in the group without IV bolus DX (SMD = -1.70 [-3.02, -0.38], p =0.01). In contrast, no significant difference was seen in those treated with pre-infusion IV bolus DX (SMD = -0.70 [-3.04, 1.64], p = 0.56).

Table I: Characteristics of selected RCTs comparing dexmedetomidine and other antiemetics in laparoscopic bariatric surgery[8-20]

Study author and year	Country	Study design	Type of surgery	No of participants		ASA		BMI		Treatment regimens		Age		Male%		Duration of surgery (mins)		Duration of anaesthesia (mins)	
				Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control
Tufanogullari et al.	Dallas, Texas	db rct	Laparoscopic bariatric	20	20	II 14(70) III 6(30)	II 14(70) III 6 (30)	W 127± 20 H 169 ± 10	127± 25 165± 12	0.2 mcg/kg/h	NS	47±10	43±16	15%	15%	110 ± 62	116 ± 52	145 ± 63	153 ± 54
				20		II 2 (10) III 18 (90)		138± 41 169± 8		0.4 mcg/kg/h		48 ± 9		20%		107 ± 35		143 ± 51	
				20		II 4 (20) III 16 (80)		151± 36 172± 13		0.8 mcg/kg/h		40±10		45%		111±56		145±55	
Halaweh et al.	New York	db rct	Laparaoscopic bariatric	30	30	I 24(80) II 6(20)	I 28(93.3) II 2(6.7)	43.4 ± 4.4	42.5 ± 4.7	IVI 0.3 mcg/kg/h dex	IVI 3 mg/h morphine	35.2 ± 10.2	31.8 ± 8.5	23%	23%	N/A		N/A	
Ibrahim et al.	Saudi Arabia	sb rct	Laparoscopic bariatric	52	51	II 29 (56.8) III 22 (43.1)	II 35(67.3) III 17(32.9)	45.0 [43.0–46.0]	44.0 [42.0–45.0]	IV dex 0.1 ug/kg + IVI 0.5ug/kg/h + IV ketamine 0.5mg/kg	IV fentanyl1ug/kg	30 [22-36]	32 [23-39]	40.38%	37.25%	40.5 ± 9.04	43.0 ± 9.86	63.7 ± 8.61	64.8 ± 9.19
Sherif & Elsersy	Egypt	db rct	Laparoscopic bariatric	49	49	NA		44 ± 3 (43.2-45)	45±4 (42.9-45.1)	IV dex 1ug/kg + IVI 0.4ug/kg/h	NS	39±9	39±8	16.33%	22.45%	N/A		N/A	
				46				44±4 (43.3-46)		IV xylocaine 2 mg/kg + 1.5 mg/kg/h		38±9		28.26%					
Bakhamees et al.	Middle East	db rct	Laparoscopic bariatric	40	40	II 26	II 24	43± 6	42± 5	0.8 mcg/kg bolus, 0.4 mcg/kg/h	normal saline of same volume	30±6	29±8	53.33%	60%	157±29	155±27	N/A	
						III 14	III 16												
Sabra et al.	Saudi Arabia	db rct	Laparoscopic bariatric	36	36	I 13	I 11	W 137.9 ±8.4	W 143.2 ± 8.5	1 mcg/kg dex, odansetron 4mg, dexamethasone 8 mg	odansetron 4mg, dexamethasone 8mg	32.2± 8.3	24.1±6.7	47.22%	41.66%	121.58±33.7	138.2±22.23	174.47±36.2	153.92±33.3
						II 19	II 21	H 1.76± 0.33	H 1.7 ± 0.05										
Ziemann et al .	United states of America	sb rct	Laparoscopic bariatric	60	59	N/A		44.15 ± 7.46	45.32 ± 6.97	IV Dex 0.5 mcg/kg IVI Dex 0.1-0.3 mcg/kg/h	0.5-1 mcg fentanyl and inhalation anaesthetics	50.5± 13.7	50.4±12.4	35%	27.12%	131±69	118±50	195±73	175±57
										IVI Propofol 75-150 mcg/kg/min IV Ketamine 0.5 mg/kg									
Elbakry et al.	Egypt	DB rct	Laparoscopic sleeve gastrectomy	50	50	N/A	N/A	42.55+/-4.36	41.60+/-4.38	IVI Propofol 100-200mcg/kg/hr and Dex 0.5-1mcg/kg/hr	Inhalation desflurane and oxygen mixture	34.35+/-11.15	35.31+/-10.43	34%	30%				
Mostafa et al.	Egypt	db rct	laparoscopic bariatric	30	30	N/A	N/A	41.37 ± 6.96	39.93 ± 5.83	IV Dex 1mcg/kg IVI Dex 0.5mcg/kg.h	Normal saline	30.77±6.9	29.9±6.78	36.67%	43.33%	91.33±57.64	85.07±12.4	108.67±14.1	101.9±15.69
Naja et al.	Lebanon	db rct	Laparoscopic bariatric	30	30					IVI Dex0.5-0.8ug/kg/h	IVI Clonidine 0.8-1.2ug/kg/30min	31.21±6.9	32.13 +-9.6	43.33%	23.33%	126.03±24.6	138.01±38.1	171.5±27.6	182.3 ± 39.9
Narejo et al.	Saudi Arabia	db rct	Laparoscopic bariatric	20	20	II 16	II 16	45.05 ± 6.21	45.33 ± 6.06	IVI Dex 0.2-0.7 mcg/kg/h	IV Remifentanil 5mg	38.05± 11.33	31.45± 10.23	30%	35%	74.6±23.19	63.25±16.18	3.9±1.8 (awaken)	3.65±2.16

Table I: Characteristics of selected RCTs comparing dexmedetomidine and other antiemetics in laparoscopic bariatric surgery[8-20]

Study author and year	Country	Study design	Type of surgery	No of participants		ASA		BMI		Treatment regimens		Age		Male%		Duration of surgery (mins)		Duration of anaesthesia (mins)	
				Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control
-						III 4	III 4												
-	Egypt	db rct	Laparoscopic bariatric			II 19	II 21	H 1.76± 0.33	H 1.7 ± 0.05	IV Dexamethasone 8mg	IV Dexamethasone 8 mg								
Salama & Abdallah				30	30	II 30	II 30	49.33+/-8.84	48.77+/-3.41	IVI Dex 0.4mcg/kg/h PO 75mg Pregabalin	Placebo capsule + normal saline infusion	33.80 ± 8.84	33.93±9.14	43.33%	36.67%	117.77±5.98	117.87±6.54	N/A	
-				46				44±4 (43.3-46)		IV Xylocaine 2 mg/kg IVI Xylocaine 1.5 mg/kg/h		38±9		28.26%					
Zeeni et al.	Lebanon	db rct	Laparoscopic bariatric	27	29	N/A		42.14+/-6.13	41.78+/-5.86	IVI Dex1mcg/kg IVI Dex 0.5 mcg/kg/h	IVI Morphine 0.08 mg/kg/10 min	38.04 ± 12.43	38.03± 10.44	Not stated	Not stated =	100.15±25.23	103.72±24.36	108.52±24.83	110.28±22.66

Table II: Outcomes of interest extracted from respective selected trials[8-20]

Author	Drugs	Outcome													
		Incidence of PONV[n(%)]	NRS nausea	Rescue phenylephrine [n(%)]	Time to discharge from PACU	Safe extubation	Rescue antiemetic	Duration of surgery (mins)	Duration of anaesthesia (mins)	Dose	Postop opiod use	Volatile anaes use	Intraoperative fentanyl (mcg)	Pain score	Total intraop opiod
Abu Halaweh et.al.	dex (nausea) morphine dex (vomiting) morphine	8(26) 19(63.3) 3(10) 7(23.3)					5.7+-3.1			0.3mcg/kg/h	6.1±3.1 (morphine) 4.7±2.9	N/A	2mcg/kg (induction) 2mcg/kg		
Bakhamees et.al.	Dex Control	2(5%) 3(7.5%)				5.1+-0.7 7.5 +- 1.3		157 ± 29 155 ± 27		0.8ug/kg bolus 0.4mcg/kg/h	5±1.4 (morphine) 10.2±1.3	N/A propofol infusion	199.4±44.6 362.2±57.2	1H 3(2-4) 2H 2(1-3) 1H 6(5-8) 2H 5(2-5)	362.2+-57.2 199.4+-44.6
Elbakry et al.	DEX Control DEX Control	5(10%) nausea 15(30%) 3(6%) vomiting 14(28%)			43.43+-10.36 52.12+-9.66	19.56+-5.31 20.36+-4.34	8.31+-2.34 ondan 11.34+-1.36	104.14±31.36 102.45 ± 30.33		0.5 - 1ug/kg/h	5.36±3.14 (morphine) 10.35±2.41	N/A desflurane vs tiva	N/A		5.36+-3.14 (morphine) 10.35+-2.41

Table II: Outcomes of interest extracted from respective selected trials[8-20]

Author	Drugs	Outcome													
		Incidence of PONV[n(%)]	NRS nausea	Rescue phenylephrine [n(%)]	Time to discharge from PACU	Safe extubation	Rescue antiemetic	Duration of surgery (mins)	Duration of anaesthesia (mins)	Dose	Postop opiod use	Volatile anaes use	Intraoperative fentanyl (mcg)	Pain score	Total intraop opiod
Ibrahim et al.	OFA	18(35.3)			30.0 [25.0-35.0]	9.0[9.0-11.0]		40.5 ± 9.04	63.7±8.61	0.1ug/kg	10 (0-10) median IQR morphine	sevoflurane 1.5-2.0 minimum alveolar concentration			
	MMA	24(46.2)			20[20.0-25.0]	5.5[4.0-9.5]		43.0±9.86	64.8±9.19	0.5ug/k/h	10 (10-20)	sevoflurane 1.5-2.0 minimum alveolar concentration	1mcg/kg (induction)		
Mostafa et al.	Dex	4(13%) nausea				5.8+-1.39		91.33±57.64	108.67±14.1	1ug/kg	43±15.12 (ketorolac)	sevoflurane 2-3%	178.33±25.2		178.33+-25.2
	Control	7(23%)				5+-1.73		85.07±12.4	101.9±15.69	0.5ug/kg/h	75.5±15.26	sevoflurane 2-3%	217.24±27.6		217.24+-27.6
	Dex	0 vomiting													
	Control	1(3.33%)													
	Dex	0 nausea and vomiting													
	Control	2(6.66%%)													
Naja et al.	dex	13(52)						126.03±24.6	171.5±27.6		337.50+-85.3(perop)	sevoflurane 1-1.5%	337.5±85.3	2.09+-1.9	337.5+-85.3
	clonidine	9(37.5)						138.01 ± 38.1	182.3 ± 39.9	0.5-0.8 ug/kg/h	371.71 +-73.9 (perop)	sevoflurane 1-1.5%	371.71 ± 73.9%	3.38+-2.8	371.71+-73.9
Narejo et.al.	dex	1 (5%) PACU			47.35 + -8.56	2.75 + -1.48	0.5+-2.24 meto	74.6 ± 23.19			3.7 ± 2.68 (morphine)	desflurane MAC 0.7-1%	2 mcg/kg (induction)	4.26 ± 1.97	
	remifentanil	6 (30%)			51.8 + -8.33	5.55 + -2.52	2.0 +-4.10	63.25 ± 16.18		0.2-0.7ug/k/h	3.0±3.58	desflurane MAC 0.7-1%	2 mcg/kg (induction)	4.15 ± 1.93	
	ex remifentanil	3 (15%) Ward 13 (65%)													
Sabra. et al.	Dex	2 (5.6%) nausea	34.22 ± 10.48				2.33 +-2.93 ondan	121.5 8± 33.7	174.47 ± 36.2	1 ug/kg	74.44 ± 12.29 (tramadol)	sevoflurane 1.0-2.5%	50.42±13.96	4.26 ± 1.97	50.42 ± 13.96
	Control	8 (22.2%)	62.5 ± 13.34				3.58+-2.68	138.2 ± 22.23	153.92 ± 33.3		89.89 ± 15.08	sevoflurane 1.0 2.5%	88.89 ± 25.83	4.15 ± 1.93	88.89 ± 25.83
	Dex	2 (5.6%) retching													
	Control	5 (13.9%)													
	Dex	1 (2.8%) vomiting													
	Control	6 (16.7%)													
	Dex	5 (13.9%) overall													
	Control	19 (53.8%)													
	Dex	34.22 ± 10.48													
	Control	62.5 ± 13.34													
Salama et al.	Dex	1	2.3+/-0.5 1(0-10points)					117.77±5.98			15.07 ± 2.65 (morphine)	sevoflurane 2%	134.17 ± 36.84		134.17 ± 36.84
	Control	10	2.0+/-0.5					117.87 ± 6.54		0.4 ug/kg/h	45.93 ± 4.56	sevoflurane 2%	254.17 ± 42.59		254.17 ± 42.59
Sherif & Elsersy	dex	20(40)	0.5±0.7 (4point) 0-none 1-nausea no vomiting 2-vomiting 3-severe persistent vomiting							1 ug/kg	14 ± 4 (morphine)	sevoflurane 2%	14 ± 15	186 ± 2 QoR	14 ± 15* (10-19)
	xlocaine	30 (61)	0.9±0.8							0.4 ug/k/h	18 ± 4	sevoflurane 2%	26 ± 16	173 ± 6	26 ± 16* (21-30)
	control	39 (79)	1.3±0.8								29±5	sevoflurane 2%	56 ± 17	140 ± 6	56 ± 17 (51 61)

Table II: Outcomes of interest extracted from respective selected trials[8-20]

Author	Drugs	Outcome													
		Incidence of PONV[n(%)]	NRS nausea	Rescue phenylephrine [n(%)]	Time to discharge from PACU	Safe extubation	Rescue antiemetic	Duration of surgery (mins)	Duration of anaesthesia (mins)	Dose	Postop opiod use	Volatile anaes use	Intraoperative fentanyl (mcg)	Pain score	Total intraop opiod
Tufanogullari et al	0.2	6 (31)	arrival in PACU 1±1* 30 min 1±2* 60 min 2±3	2(10)	81+-33	5+-3		110±62	145±63		113 ± 85 (fentanyl)	N/A (end tidal concentration only)	N/A	5 2	
	0.4	6 (31)	arrival in PACU 2±3 30 min 1±2* 60 min 1±2*	4(20)	82 +-24	6+-4		107 ± 35	143±51	0.2-0.4 ug/kg/h	108 ± 67			5 3	
	0.8 control	11 (57)	arrival in PACU 1±2 30 min 1±2* 60 min 1±3	10(50)*	87 +-24	9 +-6		111 ± 56	145 ± 55		120 ± 78			4 3	
		16 (84)	arrival in PACU 3±3 30 min 3±3 60 min 3±3	4(20)	104+-33	7+-3		116±52	153 ± 54		187 ± 99			6 3	
Zeeni et al.	DEX		PACU 2.5 [0-7] 60 min 2.5 [0-5] 24 hours 2 [0-6.75]		78.37 ± 27.10	108.52 +-24.83		100.15 ± 25.23	108.52±24.83	1ug/kg	12.22±5.54 (morphine)	sevoflurane 2%	2 mcg/kg (induction)	6[4-8.25]	1.63 ± 0.77 (remifen)
	Morphine		PACU 3 [0-7] 60 min 0.5 [0-4.75] 24 hours 3 [3-7]		76.62 ± 19.92	110.28+-22.66		103.72 ± 24.36	110.28±22.66	0.5ug/kg/h	23.48 ± 6.22	sevoflurane 2%	2 mcg/kg	7[3.5-9.5]	1.92 ± 0.77
Ziemann et al.	TIVA	12 (20%)		13 (21.7%)	44+-19			131 ± 69	195±73	0.5 ug/kg	2.29 ± 1.52 hydromorphe	infusion propofol seveoflurane MAC 0.7-1.3	0.5-1 mcg/kg (induction)		
	Classic	22 (30.5%)		18 (30.5%)	44+-23			118 ± 50	175±57	0.1-0.3 ug/kg/h	2.08 ± 1.17				

Table III: Summary of outcomes

Outcomes and subgroup analysis	Included studies	Result
3Incidence of PONV		
Incidence of PONV based on drug classes	12	Reduction in the incidence of PONV with use of DX (RR = 0.48 [0.41, 0.57]; p < 0.00001)
DX and duration of surgery	10	Significant reduction in the incidence of PONV with the use of DX if the duration of surgery was less than 120 minutes. (RR = 0.38 [0.26, 0.57]; p < 0.00001)
IV bolus DX prior to IV DX infusion.	11	Risk reduction without IV bolus DX prior to an infusion (RR = 0.42 [0.25, 0.71]; p = 0.001) was more compared to those with IV bolus DX (RR = 0.51 [0.40, 0.65]; p = < 0.0001).
Gender preponderance	11	Risk of PONV was reduced in DX group, without significant difference for the subgroup analysis between male >30% and <30%.
Numerical Rating Scale (NRS) of PONV		
NRS of PONV with DX versus other antiemetics	5	DX significantly lowered the risk of PONV compared to other groups. (SMD = -2.33 [-2.94, -1.73]; p = 0.0001)
Duration of surgery	4	DX significantly lower the risk of PONV in duration of surgery <120 minutes compared to >120 minutes of surgery. (SMD -1.28 (-2.30, -0.25)
IV bolus DX prior to IV DX infusion	2	
Gender preponderance	4	NRS of PONV is significantly lower in groups of < 30% male participants compared to >30% male participants. (SMD = -0.97 [-1.32, -0.62], p <0.00001) vs (SMD = -01.53 [-3.09, 0.04], p = 0.06)
Total dose of postoperative analgesia used		
DX versus other antiemetics	6	DX was shown to reduce the total postoperative analgesia requirement (SMD = -1.87 [-3.31, -0.42], p = 0.01) only significantly lowered when comparing DX to placebo (SMD = -4.04 [-6.99, -1.09]). No difference in SMD was noted when DX was compared to dexamethasone and opioid
IV bolus DX prior to IV DX infusion.	6	
Time to discharge from post-anaesthesia care unit (PACU)		
DX versus other antiemetics	5	DX significantly reduced the time to discharge from the PACU (SMD = -0.36 [CI -0.57, -0.15], p = 0.001). On subgroup analysis, DX only showed a significant reduction in the time to discharge from PACU when compared to placebo.
Total intraoperative opioid used		
DX versus other antiemetics	8	The use of DX intra-operatively did not affect the total amount of intraoperative opioid consumption (SMD = -1.14 [-2.47, 0.19]; p = 0.06).
IV bolus vs no bolus DX prior to infusion	8	An IV bolus dose of DX did not affect the total intraoperative opioid consumption
Time to safe extubation		
DX versus other antiemetics	6	No difference in the time to safe extubation with DX compared to other drugs.
IV bolus vs no bolus DX prior to infusion	6	Significant reduction in the time to extubation in the subgroup without a bolus dose (SMD = -1.73 [-1.31, - 0.33], p = 0.02).

Even though high subgroup heterogeneity was detected, the total heterogeneity was low (Figure 16).

Time to Safe Extubation

Seven trials reported data on time taken for safe extubation. One study was excluded from analysis as the result was reported in the median and interquartile range. Pooled analysis revealed no difference in the time to safe extubation with DX compared to other drugs. Nevertheless, subgroup analysis demonstrated a significant reduction in the time to safe extubation when DX was compared to opioids (SMD = -2.79 [-4.06, -1.52], p < 0.0001). High total heterogeneity and moderate subgroup heterogeneity were recognised (Figure 17).

When comparing the effect of bolus and no bolus before infusion of DX, the result revealed a significant reduction in

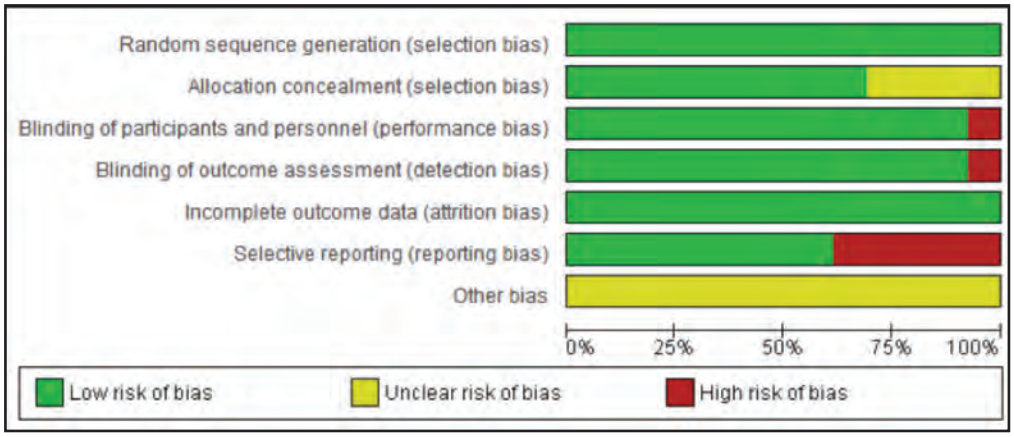

Fig. 1: Risk of bias graph.

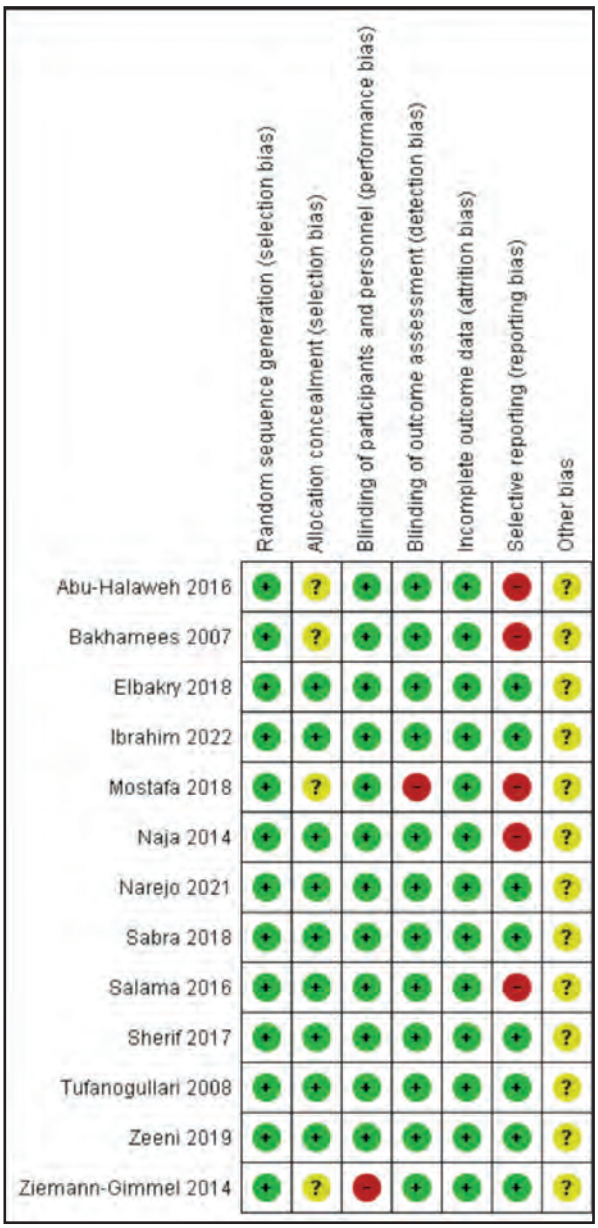

Fig. 2: Risk of bias summary

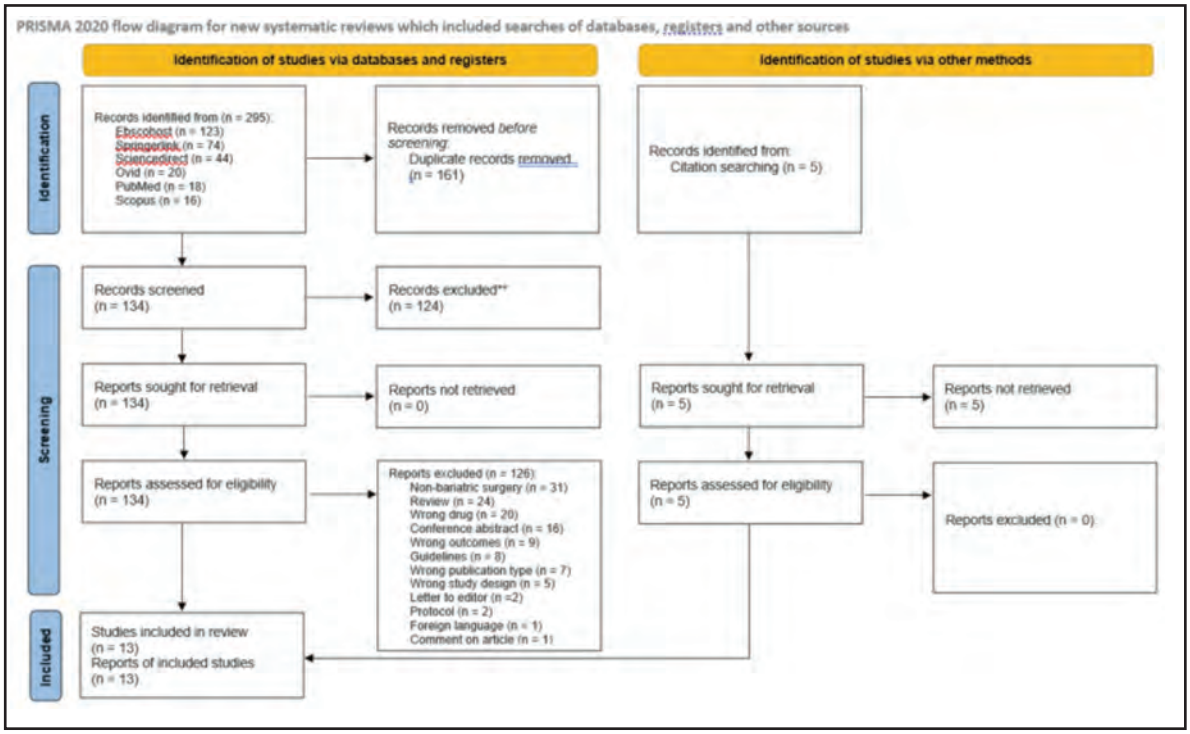

Fig. 3: Flow diagram using PRISMA flowchart

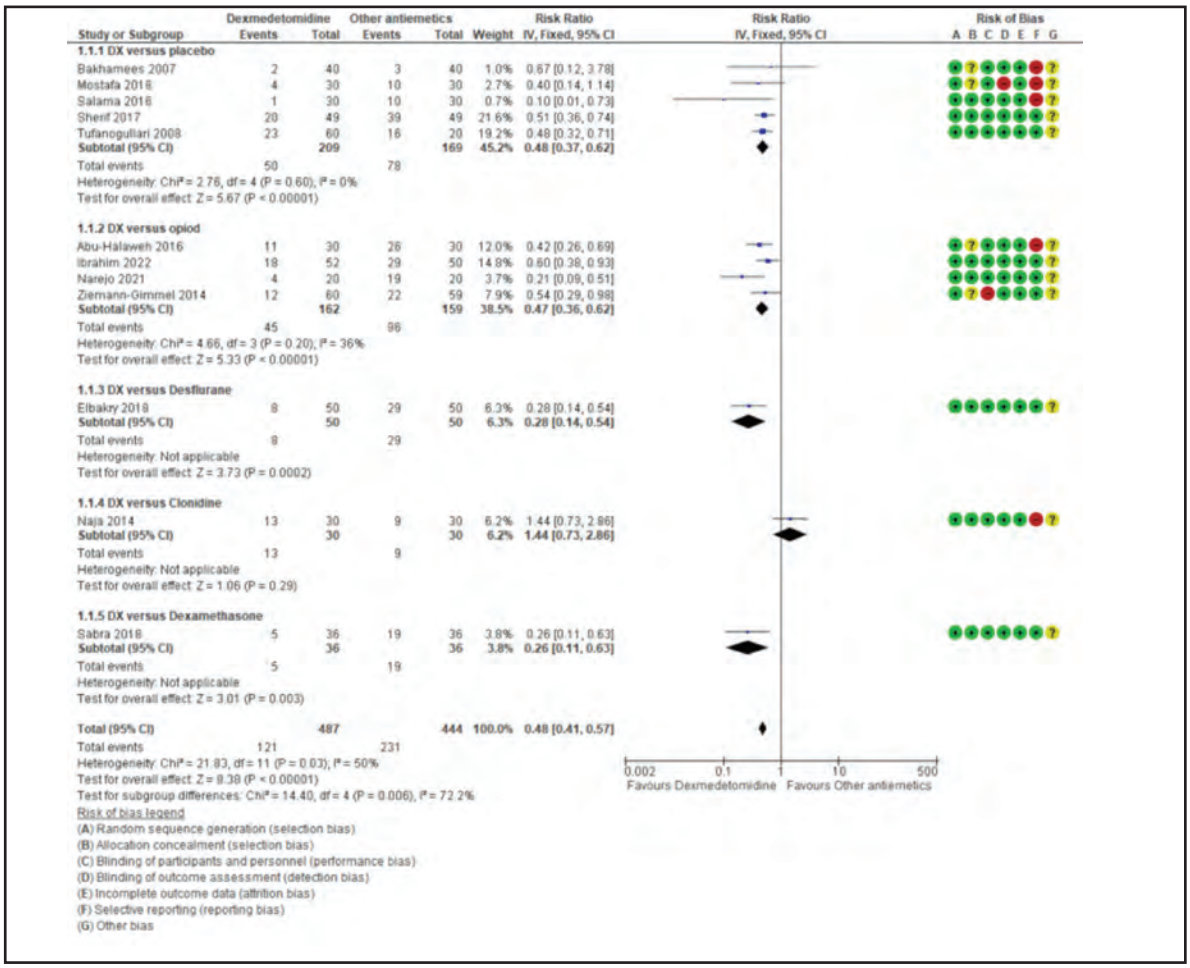

Fig. 4: Forest plot comparing the incidence of PONV of DX versus other antiemetics and subgroup analyses across various groups of antiemetics.

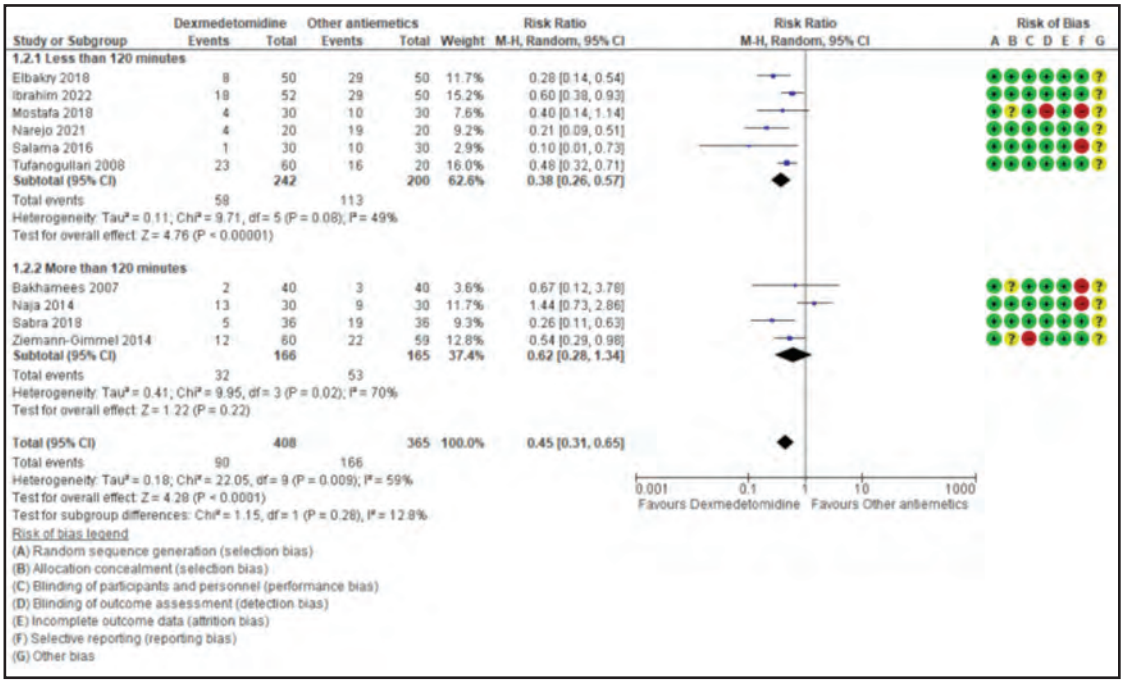

Fig. 5: Forest plot comparing the incidence of PONV with DX versus other antiemetics and subgroup analyses of duration of surgery.

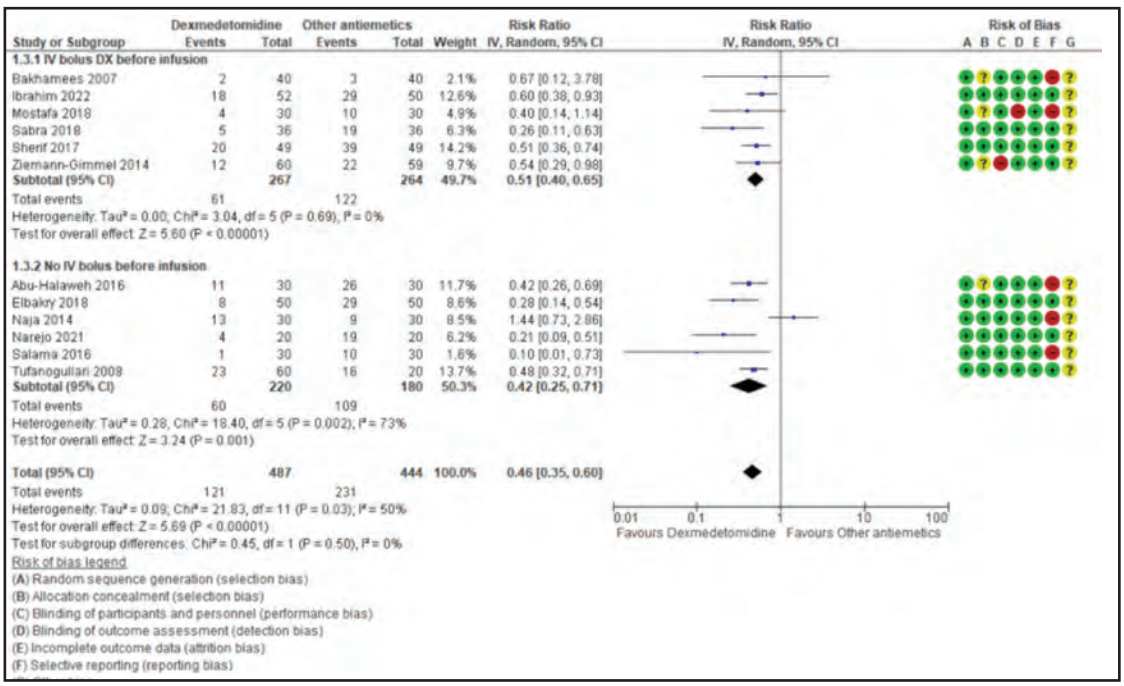

Fig. 6: Forest plot comparing the incidence of PONV with DX versus other antiemetics and subgroup analyses of administration of IV bolus and no IV bolus of DX before DX infusion.

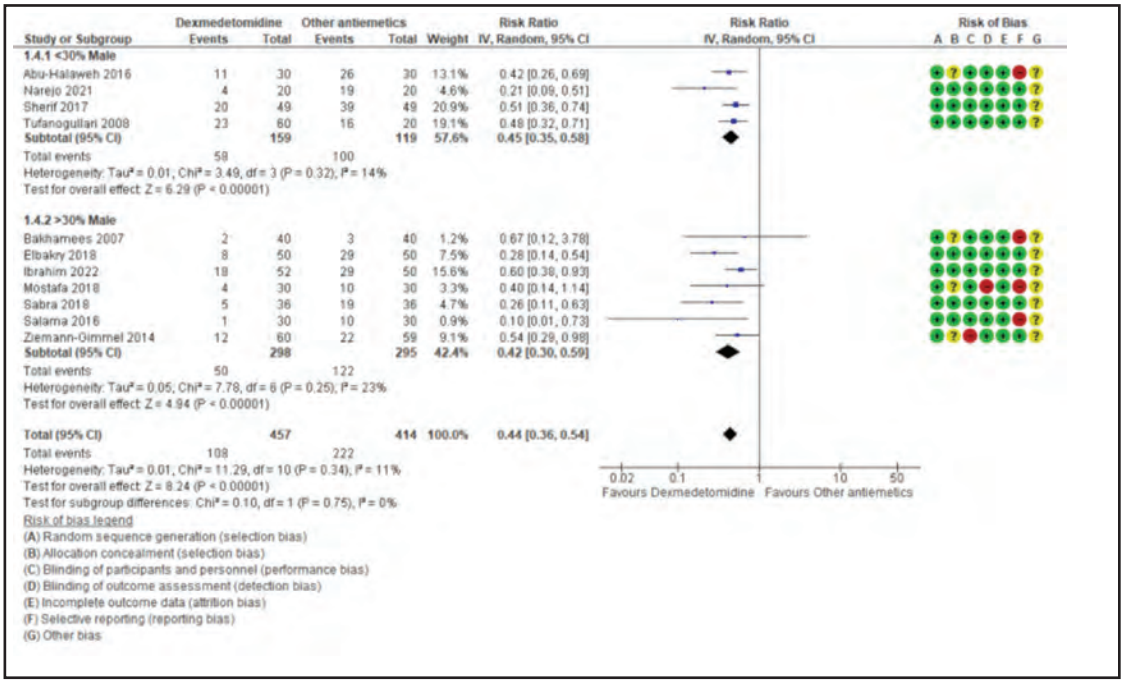

Fig. 7: Forest plot of incidence of PONV using DX versus other antiemetics and subgroup analyses of gender preponderance among participants.

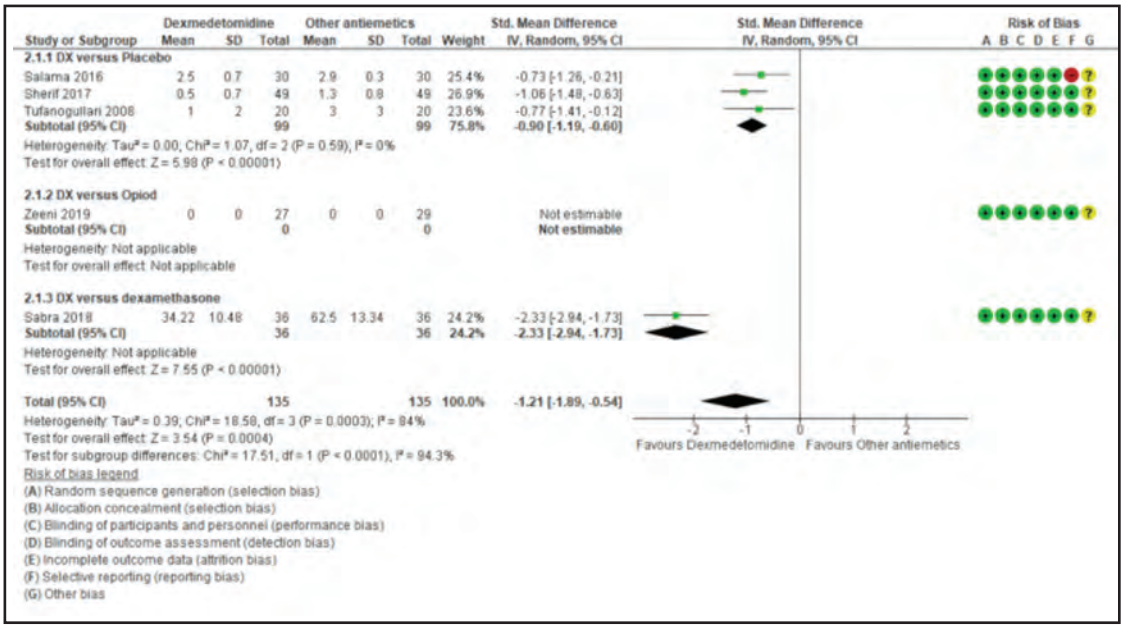

Fig. 8: Forest plot comparing the NRS scores of PONV using DX versus other antiemetics and subgroup analyses across various groups of antiemetics and opioids.

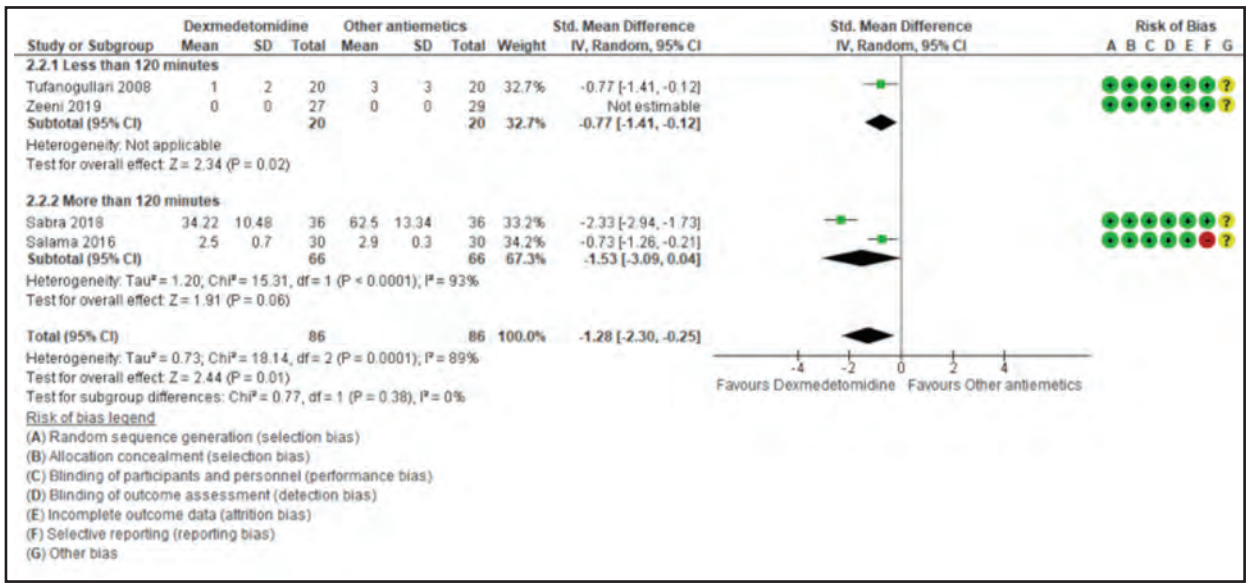

Fig. 9: Forest plot of comparison: NRS of PONV of DX versus other antiemetics and subgroup analyses of duration of surgery.

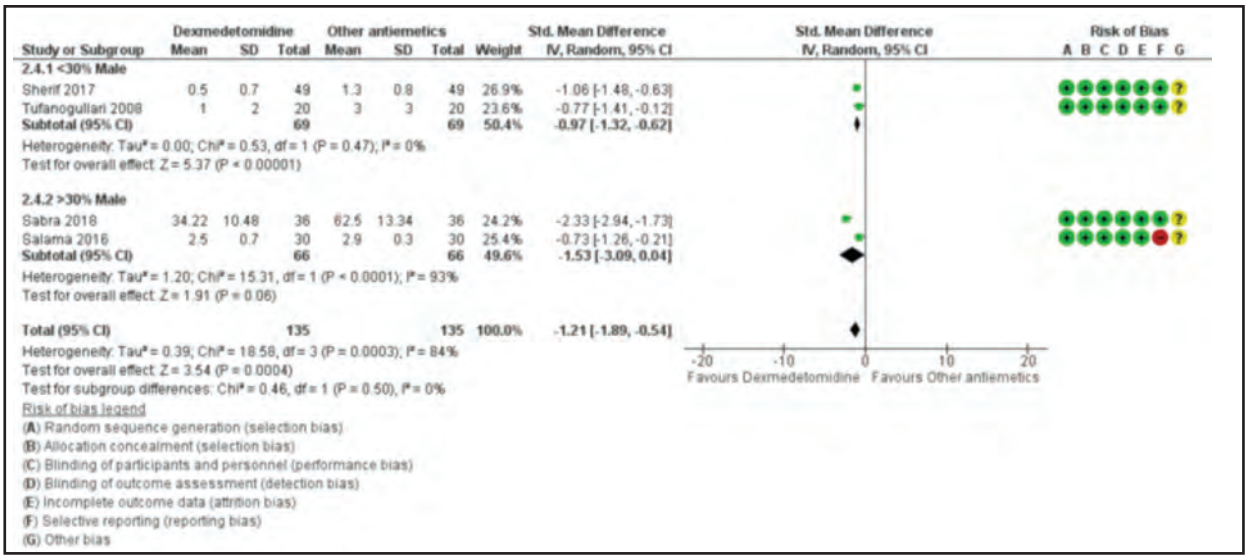

Fig. 10: Forest plot of comparison: NRS of PONV of DX versus other antiemetics and subgroup analyses of duration of surgery.

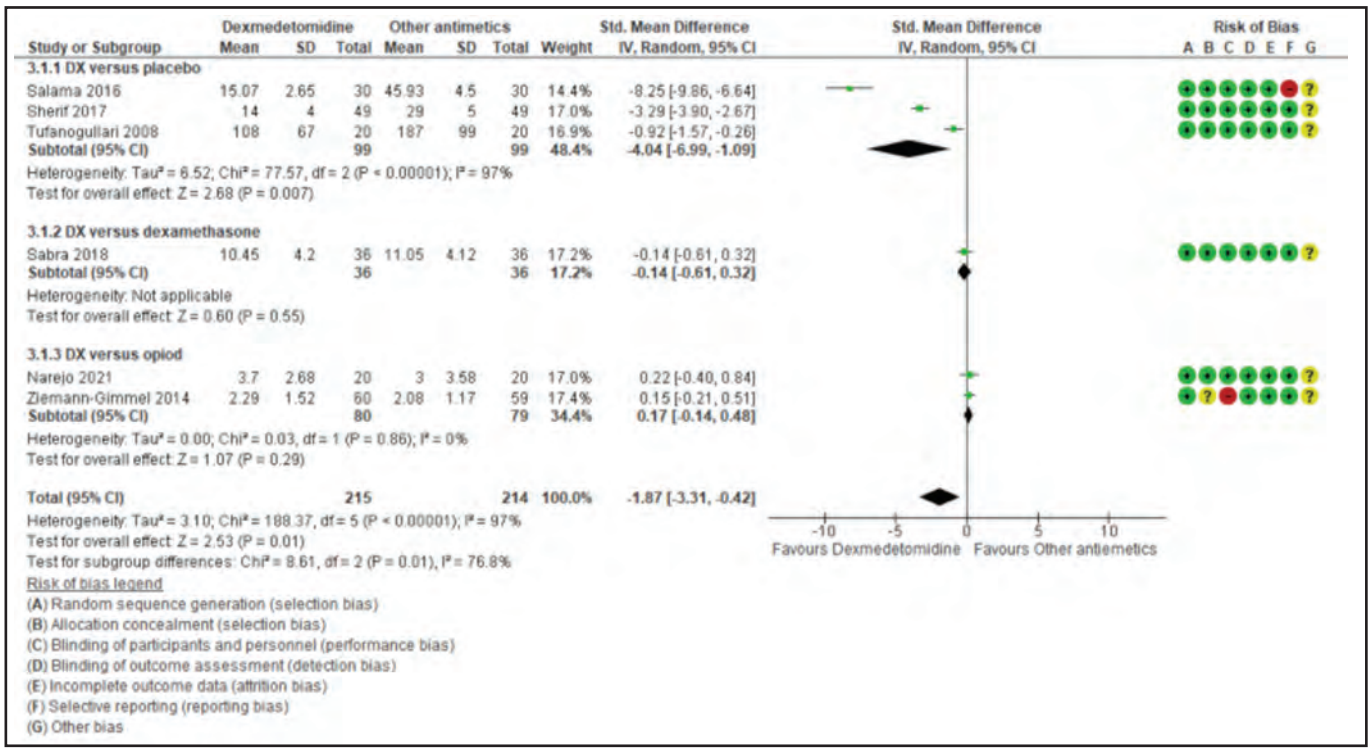

Fig. 11: Forest plot comparing total dose of postoperative analgesia used with DX versus other antiemetics and subgroup analyses across various groups of antiemetics.

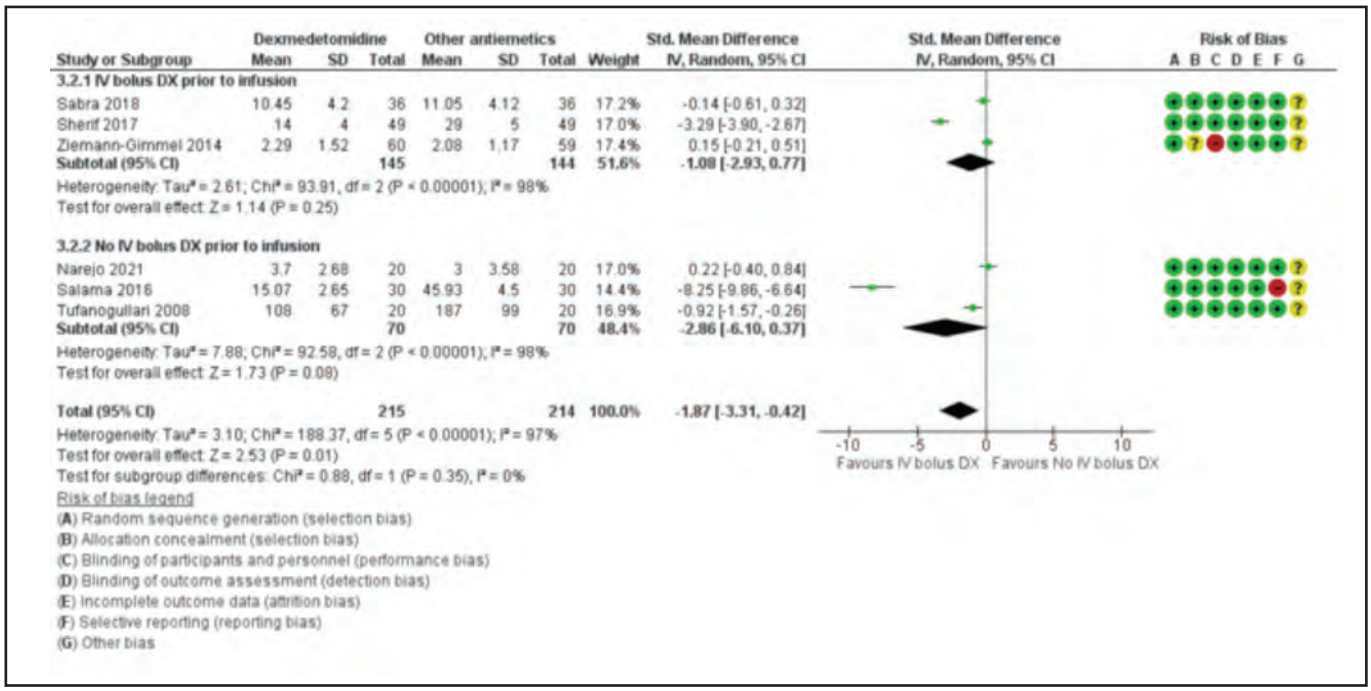

Fig. 12: Forest plot comparing total dose of postoperative analgesic used with DX versus other antiemetics and subgroup analyses of administration of IV bolus DX before IV DX infusion.

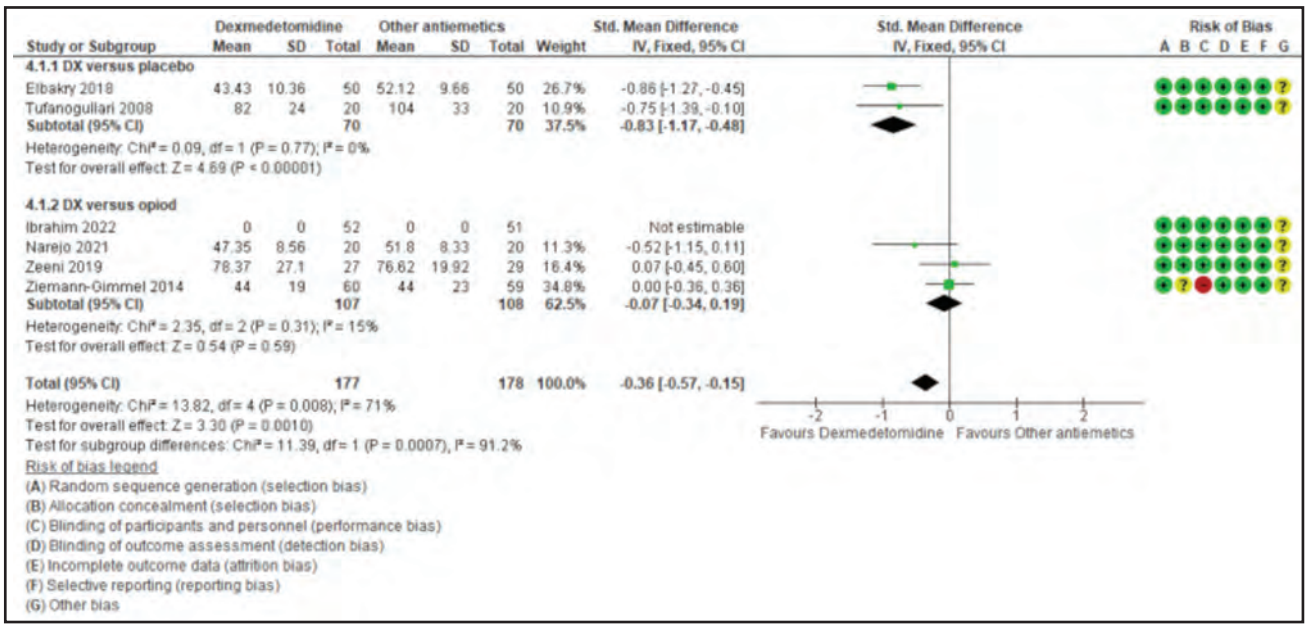

Fig. 13: Forest plot comparing time to time to discharge from PACU with DX versus other antiemetics and subgroup analyses across various groups of antiemetics.

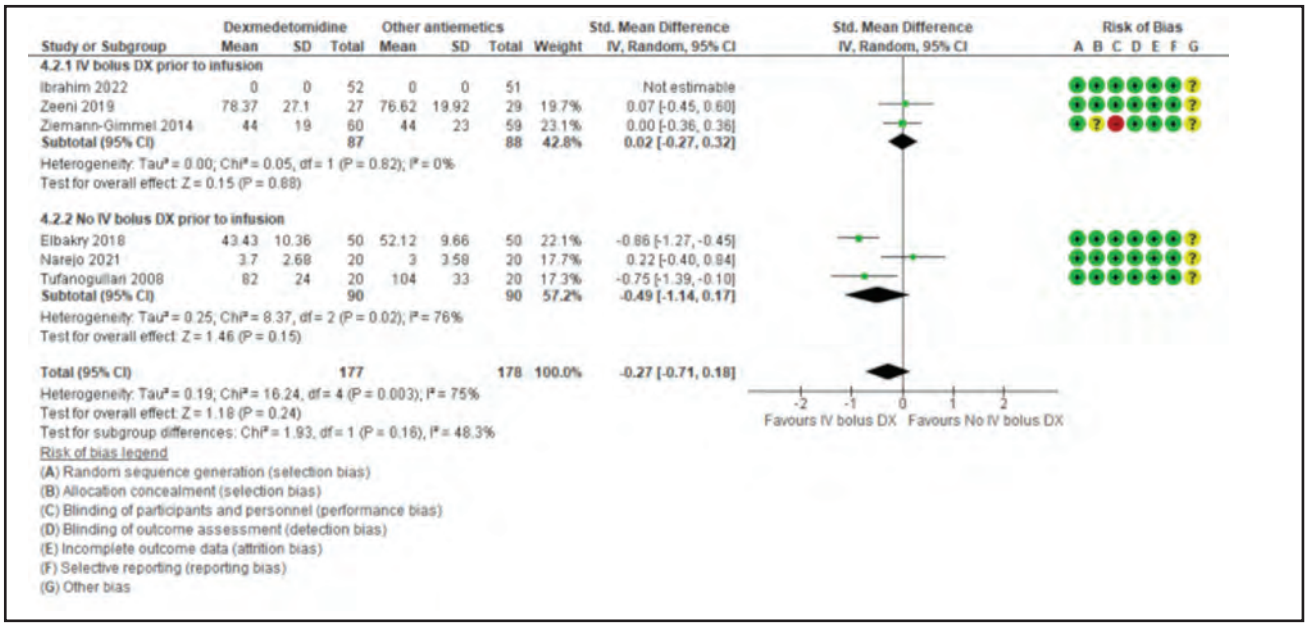

Fig. 14: Forest plot comparing time to discharge from PACU with use of DX versus other antiemetics and subgroup analyses of administration of no IV bolus and IV bolus of DX before initiating IV DX infusion.

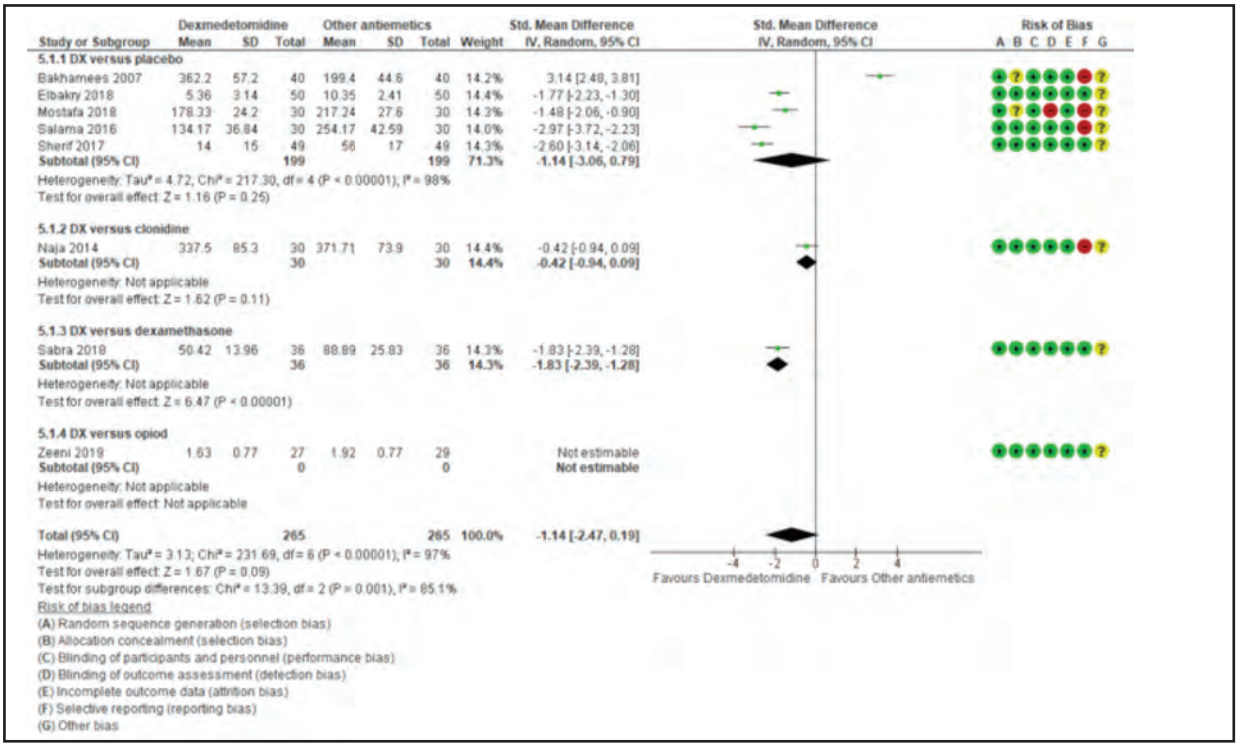

Fig. 15: Forest plot comparing DX versus other antiemetics and subgroup analyses across various groups of drugs in terms of total intraoperative opioid utilisation.

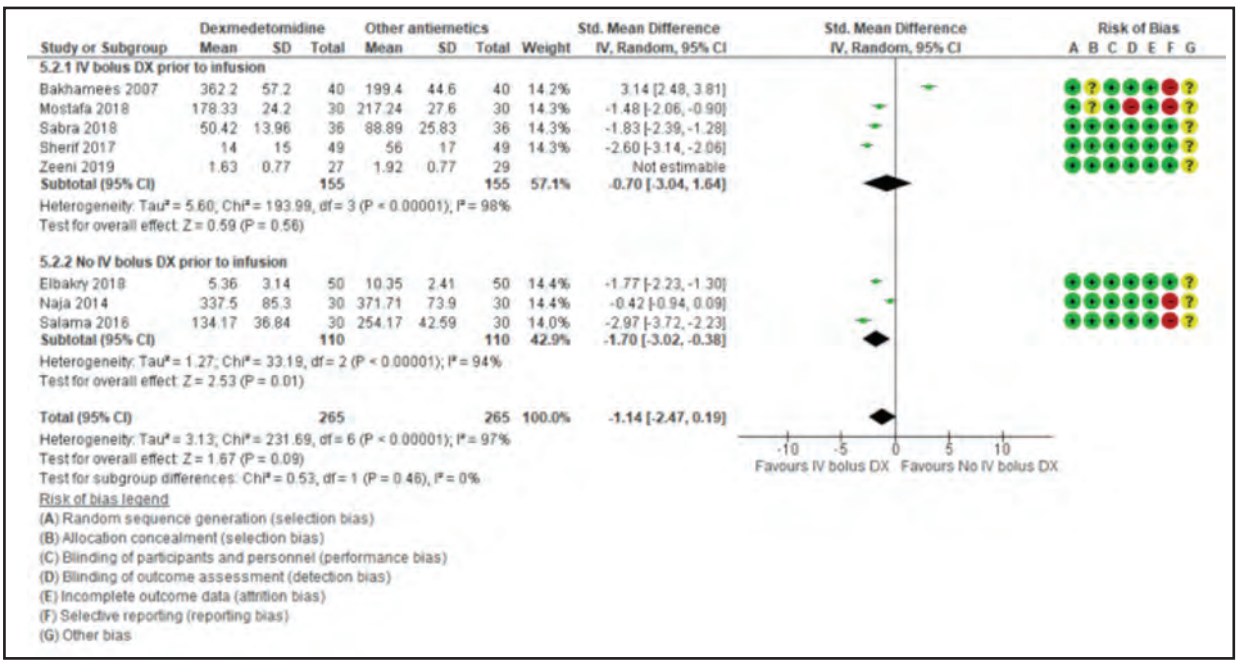

Fig. 16: Forest comparing total intraoperative opioid use with DX versus other antiemetics and subgroup analyses of administration of IV bolus DX before IV DX infusion.

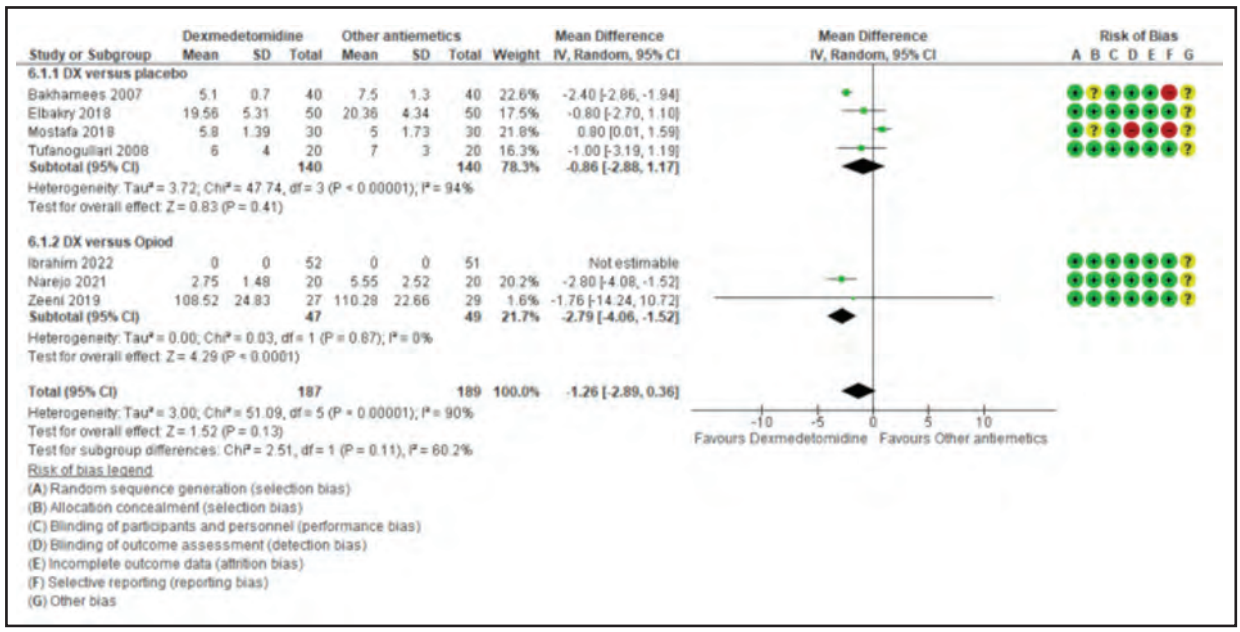

Fig. 17: Forest plot comparing time to safe extubation using DX versus other antiemetics and subgroup analyses across various groups of antiemetics.

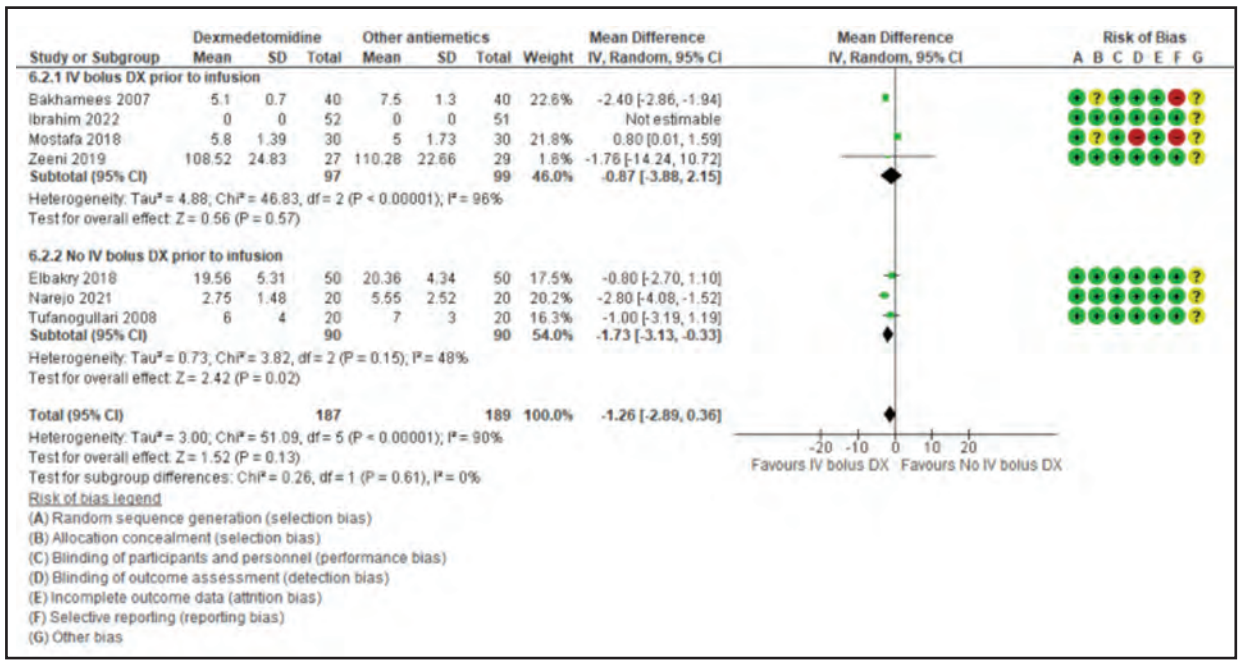

Fig. 18: Forest plot comparing time to safe extubation with DX versus other antiemetics and subgroup analyses of application of IV bolus to no bolus DX before DX infusion.

the time to extubation in the subgroup without a bolus dose (SMD = -1.73 [-1.31, - 0.33], p = 0.02). No subgroup difference was identified despite a high total heterogeneity.

DISCUSSION

Some of the risk factors that have been established to demonstrate a positive association with PONV are female gender, past history of PONV, use of volatile anaesthetics, nitrous oxide, and amount of postoperative opioids.[6] Even though the association of BMI as a risk factor for PONV remained debatable, laparoscopic bariatric surgery has been conclusively proven to have a high rate of PONV.[6,21-23] This is an important issue to be addressed as vomiting may lead to complications such as aspiration pneumonia, wound dehiscence as a result of increased intraabdominal pressure, oesophageal rupture, electrolyte, and fluid imbalance, which may lead to increased incidence of hospital readmission, longer hospital stay, and higher healthcare expenditures.[24] Current guidelines on PONV are not specific for bariatric surgery, but a multimodal pharmacologic approach is encouraged as prophylaxis for patients at high risk of PONV. This meta-analysis demonstrated that the incidence of PONV was significantly reduced after administration of DX. This result was similar to other studies on the use of DX in gynaecological, abdominal, breast, paediatric strabismus, nasal surgeries, and post-craniotomy.[25-28] This was found to be more pronounced in surgeries that lasted < 120 minutes, as a shorter time for surgery also meant reduced exposure to volatile anaesthetics and lower doses of opioids which are major risk factors for PONV.

Furthermore, the analgesic effect of DX as suggested by many studies (Figure 12) reduced the total amount of postoperative opioid requirement, thus reducing the incidence of opioid-related adverse effects, particularly nausea and vomiting.[26,29,30] One would expect the analgesic effect of DX to reduce the total intraoperative opioid use, and this was seen in the studies by Le Bot et al. and Jin et al. in various types of surgeries including neurosurgery, gynaecology, ophthalmology, and others. In contrast, in our study, subgroup analysis did not show a significant difference in the total dose of intraoperative opioids administered (Figure 16).[30,31] It is worth noting that there was high heterogeneity in the results due to several reasons. Firstly, the anaesthetic regimen widely differed from one another, for instance, Salama et al.[19] prescribed PO 75 mg pregabalin before surgery, while Ziemann et al[11] administered a single dose of IV ketamine 0.5 mg/kg. These medications may have influenced the total dose of opioids used by the anaesthetist during the surgery. Secondly, the duration of surgery as mentioned before, ranged from 40 minutes up to 150 minutes, which would also significantly alter the requirement of intraoperative opioids. Most of the included studies aimed to investigate the analgesic effect of DX and some studies compared the analgesic effect of DX to a variety of opioids resulting in greater expectation of significant differences in results related to opioids.

We found that NRS demonstrated a significant difference in scores for PONV with reduced incidence of PONV. This indicates that DX was able to reduce severity and the incidence of PONV. This was probably due to the intrinsic effect of DX whereby the sympatholytic effect of α2-adrenergic receptor agonist reduces plasma concentration of catecholamine, a known attributing factor of PONV, as well as the analgesic-related effect discussed in the earlier section.[30,32] Similarly, the severity was only markedly reduced if the surgery lasted < 120 minutes. The result was subjected to high total and subgroup heterogeneity which may be due to a few factors. Firstly, the lack of a standardised scoring system caused by use of different scale systems in various studies for example, the 11-point VRS scale by Tufanogullari et al,[8] 4-point scale by Sherif and Elsersy[9] and the visual analog score (VAS)of 100 points used by Sabra et al.[18] Secondly, Wilkstrom et al.[33] found that although NRS correlates to patients' verbal scale, there was only moderate correlation to their retrospective reported experience. This meant that NRS might suffer from subjectivity and patients' perspectives and be sensitive to changes in other factors such as small fluctuations in symptoms and complexity in translating the exact severity into scores. Besides that, premedication i.e., with ondansetron, which was given in some trials may have affected the overall NRS. Lastly, the documentation interval of NRS varied across different trials, which may have affected the overall analysis of the results.

The significant reduction in the mean NRS for PONV was most obvious when DX was compared with dexamethasone. Multiple studies identified dexamethasone as an efficacious prophylactic agent for PONV.[26,34-36] The combination of single dose IV DX 1ug/kg, dexamethasone 8 mg, and ondansetron 4 mg in the intervention group in one of the studies, suggested promising antiemetic results when combining DX and dexamethasone. Our findings were in discordance with the affirmation.[37] (Figure 8) Up to date, there are insufficient trials available that focus on the synergistic effect of DX and dexamethasone, hence more studies are needed to affirm the efficacy of this combination.

It appears that administering a loading dose of DX before starting infusion will not make a difference in terms of PONV as a continuous infusion was sufficient to significantly, lower the incidence and NRS of PONV. This result was similar to a study by Jin et al.[30] In addition, with these two ways of administering the DX, there was no effect on the total intraoperative and postoperative opioid consumption. In contrast, a loading dose of DX may raise the concern of a higher incidence of adverse effects of DX such as hypotension and bradycardia.[8,30,38] Therefore, DX as a continuous infusion without a loading dose appears safer and more effective.

All the included trials did not report the incidence or NRS of PONV based on gender. As mentioned earlier, female gender is one of the strongest predictors of PONV.[6] Since the exact numbers of participants based on gender were unavailable, subgroup analysis was done based on the proportion of male to female participants in the study. The benchmark was set to be 30%. A group with < 30% male was considered female-predominant, therefore, a higher incidence and NRS of PONV were expected. Overall, both groups responded to DX and there was a significant reduction in NRS in the female-predominant group, suggesting that females responded better to DX than males.(Figure 10)

The use of IV bolus and no bolus before initiating infusion of DX during induction did not influence the time to discharge from PACU and no significant difference was noted when DX was compared to opioids. Subgroup analysis of DX versus placebo and opioid respectively, DX only showed a significant reduction in the time to discharge from PACU when compared to placebo. There were high subgroup differences and moderate total heterogeneity. This could be secondary to other factors like pain scores, sedation, and vital signs that may influence the time to discharge from PACU. Future research specifically targeting DX, other anti-emetics, and factors affecting the stay in PACU before discharge may address this limitation.

A review of the data obtained from the included articles revealed a lower mean arterial pressure in the group administered with dexmedetomidine which is in accordance with previously determined side effects of dexmedetomidine.[39] Data on the average heart rate of the patient and respiratory depression were not clear from most of the included studies. However, the cardiopulmonary effects following dexmedetomidine infusion were determined in the research by Deutsch et al., where results showed a lowered heart rate in patients but no significant respiratory depression.[40] The increased risk of PONV in morbidly obese who are also sensitive to opioids and laparoscopic surgery may be a reason to explore DX as a drug of choice for this population of patients. However, current RCTs do not explore the side effects of dexmedetomidine use enough, and more data should be obtained regarding the safety profile of the medication to be used as prophylaxis for PONV.

Limitations

Most of the included studies reported the efficacy of DX from many aspects of outcomes. Incidence of PONV was available in most of the studies but not all. Additionally, the type of NRS, use of opioids, and timing of administration were different. This could be a primary limitation of our report.

Secondly, we are aware that the incidence of reduction of PONV could be affected by the use of opioids. Thirdly, outcomes such as time to discharge from PACU could be confounded by other factors such as comorbidity, pain score, currently taking medications, etc. Lastly, this population's limited number of RCTs may have affected our analysis.

CONCLUSION

From this analysis, there is considerably sufficient evidence to prove that the administration of dexmedetomidine (DX) can reduce the incidence of postoperative nausea and vomiting (PONV) in patients undergoing laparoscopic bariatric surgery. The increased risk of PONV in morbidly obese who are also sensitive to opioids and laparoscopic surgery may be a reason to explore DX as a drug of choice for this population of patients with or without dexamethasone.

We also found that the additional analgesic effects of dexmedetomidine reduce postoperative opioid requirements, which can contribute to reducing the incidence of PONV as well. The use of DX appeared to significantly reduce the incidence of PONV when the duration of surgery was < 120 minutes.

Future trials should focus on NRS and its correlation with PONV using DX in laparoscopic bariatric surgeries, and the antiemetic properties of DX in different doses and regimens should be explored.

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SYSTEMATIC / NARRATIVE REVIEW ARTICLE

Normocytic Anemia in Pregnant Women: A Scoping Review

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ABSTRACT

Introduction: The iron supplementation program for pregnant women is the main program for tackling anemia in various countries, especially in developing countries in which daily diets may lack sufficient iron intake. In Indonesia, it is recommended that expectant mothers ingest 90 iron tablets during their pregnancy; however, the World Health Organization reports that 37% of pregnant women in the country continue to experience anemia. Iron deficiency anemia consistently emerges as the primary etiology for diagnosing anemia; however, it is important to recognize that anemia can stem from various factors beyond just lack of iron. In addition to iron deficiency, chronic illnesses and infections significantly contribute to the prevalence of anemia worldwide. Consequently, this literature review endeavors to uncover the underlying factors responsible for normocytic anemia among pregnant women, focusing on developing countries.

Materials and Methods: Eight search engines, specifically Proquest, EbscoHost, Scopus, Cochrane Library, Science Direct, Wiley Online Library, PubMed, Google Scholar, and Garuda, were utilized to identify primary articles. Three independent reviewers assessed abstracts and full articles based on specific inclusion and exclusion criteria. The data collected encompassed information regarding the population under study, research methods employed, and primary findings pertinent to the review's objectives. Fifteen studies, published between 2014 and 2023, that met the eligibility criteria outlined in the PRISMA-ScR.

Results: Among the 15 studies on normocytic anemia in pregnant women, malaria and HIV were the highest causes of normocytic anemia, followed by worm/intestinal parasite infections, chronic diseases, and bleeding.. In pregnant women, anemia of chronic disease and infection often coexists with iron deficiency anemia, both show decrease serum iron levels. Hence, other investigations need to be carried out to diagnose with certainty the cause of anemia in pregnant women.

Conclusion: Anemia is not a standalone disease but rather a symptom of various underlying diseases. Therefore, diagnosing anemia requires identifying the basic disease that causes anemia, rather than simply labeling it as anemia.

KEYWORDS:
Normocytic anemia, pregnant women, chronic disease, infection, bleeding

INTRODUCTION

Anemia is prevalent among pregnant women, particularly in developing countries, commonly attributed to insufficient iron levels.[1] The primary method for addressing anemia in these countries, particularly where daily iron intake through food is often inadequate, is the implementation of iron supplementation programs for pregnant women. For instance, in Indonesia, expectant mothers are advised to consume 90 iron tablets during their pregnancy. According to the World Health Organization (WHO), anemia affects a significant number of women between the aged of 15 and 49, as well as millions of children aged 6 to 59 months globally. It is estimated that anemia affects 40% of children aged 6 to 59 months, 37% of pregnant women, and 30% of women aged 15 to 49 years worldwide. In 2019, anemia affected 30% (539 million) of non-pregnant women and 37% (32 million) of pregnant women aged 15 to 49 years.[2] In Indonesia, the causes of anemia during pregnancy are multifactorial, but iron deficiency is generally considered the primary cause, as anemia diagnosis primarily relies on measuring hemoglobin levels. According to the 2018 Basic Health Research (Riskesdas) data, the prevalence of anemia in pregnant women in Indonesia has increased from 37.1% in 2013 to 48.9% in 2018, indicating a concerning annual rise in anemia cases among expectant mothers. Consequently, promptly addressing this issue is crucial, as maintaining good health is paramount.[3]

Normocytic anemia is characterized by red blood cells of normal size and shape and containing normal hemoglobin levels.[4] Despite this, individuals with normocytic anemia still experience anemia. The mean corpuscular volume (MCV) in normocytic anemia falls within the standard range of 80-100 fL. The primary cause of normochromic normocytic anemia is typically a chronic illness. The prevalence of anemia due to chronic diseases varies depending on the specific condition, with infection ranging from 18% to 95%, cancer from 30% to 77%, autoimmune disorders from 8% to 71%, and chronic kidney disease and inflammation from 23% to 50%.[1] In pregnancy, anemia is determined using the World Health Organization's classification, which considers a

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hemoglobin (Hb) level below 11 g/dl as indicative of anemia. The WHO classification further divides anemia into three degrees: mild anemia (Hb level 9.0-10.9 g/dL), moderate anemia (Hb level 7.0-8.9 g/dL), and severe anemia (Hb level less than 7.0 g/dL).[5]

Anemia is not a separate disease but a symptom of various underlying diseases.[6] Therefore, diagnosing anemia requires identifying the basic disease that causes anemia, rather than simply labeling it as anemia. This is important because the underlying disease is often hidden, so if this can be uncovered, it will lead clinicians to hidden dangerous diseases. Understanding the underlying cause is crucial for effective treatment. An approach to anemia patients requires an understanding of the pathogenesis and pathophysiology of anemia and skills in selecting, analyzing, and summarizing the results of anamnesis, physical examination, laboratory tests, and other supporting examinations.[6,7]

A scoping review was undertaken to enhance comprehension of the primary research domains about normocytic anemia in pregnant women, particularly in developing countries. The rationale for conducting a scoping review lies in the dearth of available data concerning normocytic anemia in pregnant women in developing countries such as Indonesia. This study aims to: 1) determine the prevalence of normocytic anemia in pregnant women, 2) determine the degree of normocytic anemia in pregnant women, and 3) identify the causes of normocytic anemia in pregnant women.

MATERIALS AND METHODS

The process of conducting this scoping review aligns with the framework proposed by Arksey H and O'Malley,[8] which serves as a methodological blueprint for conducting comprehensive reviews. This approach suggests that scoping reviews can effectively explore the breadth, depth, and characteristics of existing literature, thereby identifying research areas lacking sufficient attention. Additionally, this type of review can be utilized to inform future systematic reviews, synthesize and disseminate current knowledge, as well as identify gaps, and provide direction for future research endeavors.

The operational methodology described in the 2020 PRISMA ScR statement is utilized for reporting purposes.[9] This methodology outlines the most effective approach for identifying, selecting, evaluating, and synthesizing studies from both systematic and scoping reviews. The process consists of five stages: formulating research questions, identifying relevant studies, selecting studies, mapping data, compiling, summarizing, and reporting the findings.

Identify research questions

Our research questions were formulated based on the Population Concepts and Context (PCC) framework endorsed by the Joanna Briggs Institute.[10] The PCC framework is widely acknowledged for its efficacy in adequately addressing the specific requirements of a scoping review, offering a broader approach compared to a systematic review.[11]

There are three formulations of questions: 1) What is the incidence rate of normocytic anemia in pregnant women? 2) What are the causes of normocytic anemia in pregnant women?

Identify relevant studies

The first step is that determining the database:
There are a total of nine electronic databases commonly utilized in academic research, namely Proquest, EbscoHost, Scopus, Cochrane Library, Science Direct, Wiley Online Library, PubMed, Google Scholar, and Garuda (Digital Reference Garba), an online reference search platform curated by the Indonesian Ministry of Research, Technology, and Higher Education.

The second step is that determining inclusion and exclusion criteria
The screening process utilized in this study was based on the framework developed by Arksey H and O'Malley (2005) and further refined by Levac D.[8,12] The team conducted independent screenings of titles and abstracts using predetermined criteria outlined in Table I to determine inclusion or exclusion. Abstracts that passed this initial screening were then evaluated to assess their eligibility for detailed evaluation. Subsequently, four reviewers independently obtained and evaluated complete articles aligned with the eligible abstracts, ensuring they were pertinent to the research inquiries and adherence to the inclusion criteria (Table II).

The third step is namely the search strategy
The data search strategy consisted of primary studies published from 2014-2023 and the eight databases used. The search terms used were "anemia", "normocytic", "pregnant women", "chronic disease", "infection", and "bleeding". The most recent search was carried out on August 16, 2023.

Study selection

The selection and assessment of studies to determine the quality of the articles were carried out by four reviewers. 15 studies were evaluated from a rating scale of 0-3, based on the following criteria: 1) Study design: studies using cross-sectional, case-control, or cohort = 1, otherwise = 0; 2) Sample size: large = 1, small = 0; 3) there are supporting laboratory tests such as serum Fe, Ferriti, TIBC, peripheral blood smear, stool specimen examination etc = 1, otherwise = 0; 4) There is a degree of anemia and identify the cause of anemia = 1, if not = 0 (JBI, 2021). The average value of these scores was presented as the final score, the scores were then grouped as follows: 1=Poor; 2=Moderate; 3-4=High.

Charting and summarizing the data

Based on the 15 articles that met the inclusion criteria and were selected, data mapping was then carried out to determine the articles' important key points: author, year of publication, purpose, sample, participant characteristics, research design, causes of anemia, and research findings.

Compile, summarize, and report results

There are 15 pieces of literature used in this scoping review. Levac et al. (2010) employed a methodology that involves compiling, summarizing, and reporting review findings. This

Table I: PCC Framework (population, concept, and context)

Population (P)	Pregnant women
Concepts (C)	Causes of normocytic anemia (chronic disease, infection, bleeding)
Contexts (C)	The study was conducted in a developing country

Table II: Inclusion and Exclusion Criteria

Inclusion Criteria	Exclusion Criteria
Quantitative study human studies Original article Published between 2014-2023 Native language and English	Review articles, Case reports animal studies

Table III: Search strategies and research threads for databases

Search strategy	Search strategy
Keywords used: Anemia, normocytic, pregnant women, chronic disease, infection and bleeding	236 from primary sources and five from auxiliary databases
Example 1: A Scopus search using (anemia OR anemia) AND (Normocyte OR normocytic) AND infection AND (pregnancy OR pregnant OR gestation OR gestational) returns 78 records	
Example 2: A PubMed search using (anemia OR anemia) AND (Normocyte OR normocytic) AND ("infection OR malaria OR HIV OR typhoid OR hepatitis OR tuberculosis OR "post hemorrhagic" OR "acute bleeding" OR Hemolysis OR inflammatory OR bowel OR intestinal) AND (pregnancy OR pregnant OR gestation OR gestational) resulted in 125 records	
Duplicate records are removed	197 remaining after duplicates were removed
Number of studies deleted for not meeting study objectives (n=58)	139 remaining
Studies (n=118) were deleted for reasons	21 studies remaining
The study does not have full text (n=6)	15 studies were left for final analysis

was achieved through describing article characteristics and applying thematic analysis.

RESULTS

studies fail to provide information on the severity of anemia in their investigations. In comparison, four studies merely provide a general overview of the causes of normocytic anemia in pregnant women. Malaria infection is the predominant cause of normocytic anemia in pregnant women, followed by HIV, worm/intestinal parasite infections, chronic disease and bleeding, and urinary tract infections.

Quality assessment of study findings

Of the 15 studies reviewed, 12 studies[7,13–21,23,26], were rated as high quality, scoring between 3 and 4, which accounts for 80% of the total One study[22], 6.7% got a score of 2, indicating medium quality. The remaining two studies[24,25] representing 13.3%, were rates as low quality with a score of 1.

DISCUSSION

Significant factors leading to anemia in developing nations include deficiencies in micronutrients, infectious illnesses, hemoglobin disorders, and maternal hemorrhaging. Regarding morphological traits, iron deficiency anemia commonly exhibits microcytic characteristics, while anemia of chronic disease manifests as normocytic. Conversely, macrocytic anemia is commonly linked to vitamin B12 and folate deficiencies or the toxic effects of drugs and alcohol. (7). Normochromic normocytic anemia, the most prevalent form, is primarily associated with chronic diseases, with estimated prevalence rates of the underlying causes being infection (18%-95%), cancer (30%-77%), autoimmune disorders (8%-71%), chronic kidney disease, and inflammation (23%-50%).[1] In a comprehensive analysis of anemia's global burden from 1990 to 2010, hookworm, schistosomiasis, and malaria emerged as the top three causes.[27]

Of the 15 studies, there were seven studies[7,13,14,16,18,23,24] that have an incidence of normochromic normocytic anemia above 50%. This is in line with the findings in India

Table IV: Findings of Normocytic Anemia Study in Pregnant Women (2014-2023)

No	Study (year)	Objective	Sample size	Participant characteristics	Study design	Causes of Anemia	Results
1	Melku et al (2014)(13)	To evaluate the frequency and factors influencing maternal anemia, a study was conducted.	Of the 302 pregnant women, 50 (16.5%) pregnant women were diagnosed with anemia	Pregnant women receiving prenatal care at Gondar University Hospital in Ethiopia.	Cross-sectional	A significant occurrence of anemia was observed among mothers who were HIV-positive (38.7%), had hookworm infections (30%), and experienced chronic illnesses (27.3%).	Out of the 50 pregnant women diagnosed with anemia, the majority (76%) exhibited normocytic normochromic anemia, while 64% experienced mild anemia. Additionally, 30% of the women were classified as having moderate anemia, and a smaller proportion (6%) were diagnosed with severe anemia.
2	Alemayehu et al (2016)(14)	To ascertain the occurrence, severity, and factors influencing the presence of anemia in pregnant women.	Out of a total sample of 360 pregnant women, approximately 36.1% (130 individuals) were found to have anemia.	South Sudanese refugee pregnant woman, Pugnido, western Ethiopia	Cross-sectional	This study reveals that intestinal parasite infections accounted for 73% of anemia cases in pregnant women.	Among 130 pregnant women with anemia, the majority (56.2%) had normocytic normochromic anemia, while 89.2% experiencing mild anemia, 8.5% having moderate anemia, and 2.3% suffering severe anemia.
3	Adamu et al (2017) (7)	The objective of this study was to analyze the frequency and geographic distribution of various degrees and classifications of anemia, as well as investigate the potential risk factors associated with different levels of severity in anemia.	264 pregnant women with anemia	Pregnant women who live in rural and urban areas in Malawi, Africa	Cross-sectional	In this study, it was found that individuals with HIV infection experience the development of anemia at various levels of severity.	In a sample of 264 pregnant women, 61.7% of them were observed to have normocytic anemia. Within this group, 71.1% exhibited mild anemia, while the remaining 28.9% presented with moderate to severe anemia.
4	Anchang Kimbi J et al (2017)(15)	To examine the correlation between red blood cells anomalies and the etiology of anemia, a comprehensive assessment was required.	Out of the total population of 279 pregnant women, a significant proportion of 159 individuals (57%) were diagnosed with anemia during their pregnancy.	Pregnant women were recruited at the first antenatal visit at the Mutengene and Muea Integrated Medical Center, Cameroon.	Cross-sectional **Study design**	The research identified malaria infection as the cause of anemia in 2.3% of anemia cases in pregnant women.	Normocytic anemia was observed in 43.2 percent of pregnant women.

Table IV: Findings of Normocytic Anemia Study in Pregnant Women (2014-2023)

No	Study (year)	Objective	Sample size	Participant characteristics	Study design	Causes of Anemia	Results
5	Tunkyi K & Moodley J (2018)(16)	The objective of this study was to ascertain the frequency of anemia during the initial antenatal consultation and at 32-34 weeks of gestation, as well as to assess the impact of this condition on maternal and perinatal outcomes.	Out of the total sample size of 2000 pregnant women, 854 individuals (42.7%) were found to have anemia.	Pregnant women who visit African regional hospitals	Cohort Study	The occurrence of anemia in pregnant women with HIV is significantly higher compared to the uninfected population, with a prevalence of 64.6%.	In a study of 854 pregnant women with anemia, the majority (68.9%) displayed normocytic normochromic anemia, while 81.34% were diagnosed with mild anemia, 18.06% exhibited moderate anemia, and 0.6% had severe anemia.
6	Feleke and Feleke (2018)(17)	The objective of this study was to ascertain the prevalence and contributing factors of anemia in women during pregnancy and lactation.	Out of a total of 550 pregnant women, 187 individuals (34%) exhibited symptoms of anemia.	Pregnant and breastfeeding women who come to visit health facilities in the city of Bahir dar Etophia	Comparative cross-sectional	Pregnant women afflicted with malaria face a 3.61-fold increase in the likelihood of experiencing anemia, while those infected with hookworms face a 3.37-fold increase in the risk of developing anemia.	Among the population of pregnant women, approximately 34% were found to have anemia. Specifically, 7.45% exhibited normocytic hypochromic anemia, while 0.4%. had normochromic anemia
7	Adebo et al (2019)(18)	To ascertain the occurrence rate of anemia among pregnant women and elucidate its underlying causes.	Among the sample of 200 pregnant women, half of them (50%) were diagnosed with anemia.	pregnant women who carry out antenatal checks at the University Hospital of Abomey Calavi/So-Ava, Benin, West Africa	Cross-sectional descriptive analytic	Among a cohort of 200 pregnant women, half of them, or 100 individuals, were diagnosed with anemia.	A substantial portion of pregnant women, specifically 60%, experience normocytic anemia, while 83% exhibit mild anemia. Moreover, 15% of pregnant women experience moderate anemia, and a small proportion, specifically 2%, exhibit severe anemia.

Table IV: Findings of Normocytic Anemia Study in Pregnant Women (2014-2023)

No	Study (year)	Objective	Sample size	Participant characteristics	Study design	Causes of Anemia	Results
8	Okia et al (2019) (19)	A significant proportion of pregnant women, specifically 60%, exhibit normocytic anemia, while 83% experience mild anemia. Additionally, it should be noted that a considerable proportion of pregnant women, specifically 15%, are confronted with moderate anemia, while a negligible percentage of 2% endure severe anemia.	Out of the total sample of 163 pregnant women, a subset of 12 individuals (7.4%) were found to have anemia.	Pregnant woman having antenatal checkup at Itojo hospital, Ntungamo district, southwest Uganda	Cross-sectional	The present study found a significant positive association between urinary tract infection and anemia in pregnancy (p=0.002, CI 3.5-6.7). Furthermore, a history of postpartum hemorrhage was also found to be significantly associated with anemia in pregnant women (p=0.03).	The prevalence of anemia in the sample population was found to be 7.4%, with normochromic normocytic anemia accounting for 8.3% of cases. The majority of individuals (91.7%) presented with mild anemia, while 8.3% had severe anemia. Notably, none of the pregnant women in the study were found to have moderate anemia.
9	Schmiegelow et al (2019) (20)	To examine the potential links between preconception factors and hemoglobin (Hb) levels in the initial stages of pregnancy, a research study was conducted.	A total of 261 pregnant individuals were included in the study, with hemoglobin levels assessed in 226 of them.	The study was carried out in 48 rural communities located in the districts of Korogwe and Handeni in the northeastern region of Tanzania.	Cohort study	This study revealed that malaria infection accounted for 14.6% of anemia cases in pregnant women, while HIV and intestinal worm infection accounted for 2.4% and 6.7% respectively.	Among the cohort of 226 pregnant individuals, 46.5% of women experienced anemia during the initial stages of pregnancy, while 41.9% exhibited normochromic normocytic anemia.
10	Berhe, et al (2019)(21)	The aim of this study was to ascertain the incidence and etiology of anemia among expectant mothers.	Out of the total sample size of 304 pregnant women, a subset of 24 individuals (7.9%) were identified as having anemia.	Pregnant women who make antenatal visits at Adigrat General Hospital, northern Ethiopia	Cross-sectional	The presence of a history of bleeding has a notable correlation with the occurrence of anemia, as indicated by an odds ratio of 3.4 (95% confidence interval: 1.16-10.2, p=0.026).	Out of the total population of pregnant women, approximately 7.9% were diagnosed with anemia. Among these individuals, 25% exhibited normocytic anemia, while the remaining 75% were split between mild (62.5%) and moderate (37.5%) anemia.
11	Wirahartati, Herawati and Wande (2019)(22)	The categorization of anemia in pregnant women with consideration to hemoglobin levels and erythrocyte index.	A sum of 94 pregnant individuals experiences the condition of anemia.	The data obtained are secondary data from patient medical records from April to December 2016	Retrospective descriptive study	This paper addresses the topic of iron deficiency anemia, a form of anemia that can occur in various contexts.	A total of 34.04% of pregnant women were found to have normochromic normocytic anemia, while 29.8% exhibited mild anemia. Moreover, 61.7% of the pregnant population displayed moderate anemia, and 8.5% suffered from severe anemia.

Table IV: Findings of Normocytic Anemia Study in Pregnant Women (2014-2023)

No	Study (year)	Objective	Sample size	Participant characteristics	Study design	Causes of Anemia	Results
12	Waye et al (2020)(23)	To ascertain the frequency of anemia among pregnant women and identify associated factors, this study aimed to investigate the prevalence of this condition and its potential determinants.	Out of the total sample size of 312 pregnant women, 90 individuals, constituting 28.8 percent, were identified as having anemia.	Pregnant woman having antenatal checkup at Arba Minch Health Facility South Ethiopia	Cross-sectional	The prevalence of anemia was significantly higher among pregnant women who had experienced blood loss during childbirth, with an adjusted odds ratio (AOR) of 3.66 (95% confidence interval [CI]: 1.56-8.70). Similarly, pregnant women infected with malaria had a significantly higher likelihood of anemia, with an AOR of 6.10 (95% CI: 2.26-16.43).	Among the population of pregnant women, a total of 28.8% were found to have anemia. Within this subset, 75.5% of cases exhibited normochromic normocytic anemia, while 55.5% were classified as mild, 43.3% as moderate, and a mere 1.1% as severe.
13	Eunika Alicia Valentina (2021)(24)	To mitigate the occurrence of high-risk pregnancies in Indonesia in the future, it is crucial to have a comprehensive understanding of the prevalence of anemia and hemoglobin levels among multiparous pregnant women.	Out of a total of 50 pregnant women, 26 individuals (constituting 52% of the sample) were found to have anemia.	Medical record data for multiparous pregnant women at Citra Medika Hospital, Sidoarjo, Indonesia	Retrospective descriptive study	Hemodilution has been identified as the underlying factor contributing to normochromic normocytic anemia.	Among the cohort of pregnant women, a total of 52% were diagnosed with anemia. Within this group, 34.8% exhibited normochromic normocytic anemia, while mild anemia was observed in 46% of cases. Moderate anemia was identified in 50% of pregnant women, whereas severe anemia was present in only 4% of the individuals.
14	Princess Wande and Mahatini (2021)(25)	Knowing the description of the erythrocyte index in pregnant women with anemia	43 pregnant women with anemia	Data on medical records of anemic pregnant women at the Abiansemal I Community Health Center, Bandung Regency	Retrospective descriptive study	The causes of normochromic normocytic anemia are only described in general terms, possibly due to hemolytic anemia, anemia of acute renal failure, post-hemorrhage, and chronic disease.	There were 62,8% normochromic normocytic anemia, 72.1% mild degree, 27.9% moderate degree and no severe anemia
15	Bansal et al (2023)(26)	To investigate systematically the causes of anemia in pregnancy	Out of 2000 pregnant women, there were 500 (25%) pregnant women with anemia	Pregnant women having antenatal check up in North India	Cross-sectional	The examination of peripheral blood revealed that the primary cause of normochromic normocytic anemia among patients was predominantly attributed to anemia of chronic disease, accounting for 51.6% of cases.	Of the 25% of pregnant women with anemia, 24.4% were normochromic normocytic anemia,

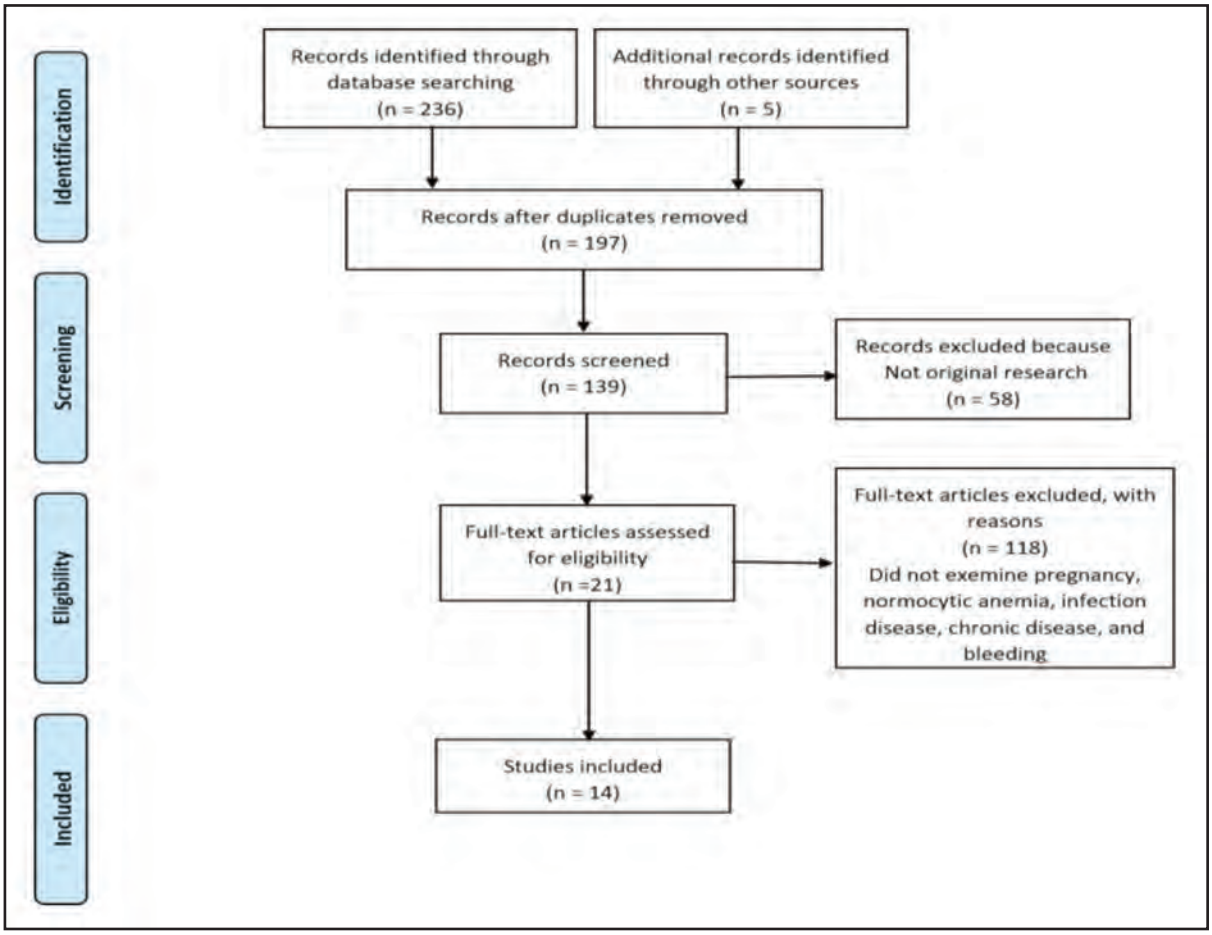

Fig. 1: The PRISMA flowchart shows the results of the search strategy, the inclusion and exclusion criteria of the articles

conducted by[28] And[29]. This is due to lack of health awareness, extreme poverty, a large number of families, and overcrowding which causes recurrent infections and antepartum bleeding. However, this contrasts with findings from[30] and[31], where microcytic anemia is more dominant; this is due to iron supplementation and slow early detection of anemia, which also causes a high incidence of anemia. This is in line with research conducted in[17,19–22,26].

For the degree of anemia from 15 studies, nine studies [7,13,14,16,18,19,21,23,24], in which most degrees of mild anemia are compatible with[32], and four studies did not include the degree of anemia[15,17,20,26]. Most types of normocytic anemia are mild. Physiologically, the lowest hemoglobin levels in pregnant women occur during the second trimester of pregnancy, averaging Hb 10.5 g/dL. In the first and third trimesters, the hemoglobin level is around 11 g/dL. Normocytic anemia is characterized by low Hemoglobin (Hb) levels but normal Mean Corpuscular Volume (MCV). In the third trimester, Hb levels tend to rise again after the decrease in the second trimester. This pattern means that women with normocytic anemia usually experience mild anemia, rather than moderate or severe levels.[22] Physiological anemia is a commonly employed term to denote the reduction in hemoglobin concentration during a typical pregnancy. This decrease is attributed to expanding plasma volume beyond normal levels towards the end of gestation, despite a concurrent increase in red blood cell mass. As a result, normocytic anemia is manifested.[24] In pregnancy, anemia can also be associated with the cause of normocytic anemia.

Malaria

According to five studies, normocytic anemia is primarily attributed to malaria infection, with a prevalence of 33.3% [15,17,18,20,23], all of which are in the countries of the African continent, namely Cameroon, Ethiopia, Benin, Tanzania, and Africa. The anemias associated with malaria discussed in this review demonstrated a notable reduction in the hematological index. Malaria-induced inflammatory anemia leads to alterations in iron absorption and distribution, leading to prolonged iron storage in a form that restricts its availability for maternal use and potentially hinders its transfer to the fetus.

Mothers infected with malaria have a 3.61 times higher risk compared to mothers who do not have a history of malaria infection.[17] The reduction in red blood cell count results from Plasmodium species engulfing the host red blood cells. Malaria, caused by the Plasmodium parasite, is predominantly prevalent in Africa and contributes significantly to the mortality rates in this region. Conversely, Plasmodium vivax is primarily observed outside sub-Saharan Africa, such as Cameroon, Ethiopia, and Tanzania.[15,17,20] According to Basic Health Research[3] in Indonesia, the most

severe prevalence of anemia caused by malaria infection is observed in Papua New Guinea (89.7%). In particular, the island of Papua has the most severe prevalence of anemia compared to other islands in Indonesia. The prevalence of malaria infection in Indonesia is 0.37%.[3]

Based on a study conducted in Mumbai, India, pregnant women show a higher prevalence of malaria compared to other groups. This condition can lead to various adverse outcomes, including abortion, intrauterine fetal death, premature delivery, and even maternal death.[33] The susceptibility of pregnant women to malaria infection can be attributed to changes in their immune system during pregnancy, specifically alterations in cellular and humoral immunity, potentially influenced by elevated cortisol levels. In malaria-endemic regions[15,20], many pregnant women infected with malaria parasites do not exhibit typical disease symptoms (asymptomatic). Yet, it still poses risks to both the mother and the developing fetus. Moreover, deficiencies in essential micronutrients such as iron and folic acid exacerbates malaria infection among pregnant women. The Plasmodium parasite resides within red blood cells, utilizing hemoglobin for its growth and replication, subsequently rupturing the host's erythrocytes. Infected erythrocytes with surface changes and deformities are easily recognized and cleared in the spleen. In addition, malaria can cause digestive system inflammation, interfering with iron absorption in the digestive tract and the release of iron from hepatocytes.[27,34]

Human Immunodeficiency Virus (HIV)

After malaria, HIV stands as the second most common cause, comprising 26.6% of the review findings across several African continent including Tanzania, Ethiopia, Malawi, and Africa[7,13,16,20], with the highest prevalence in Africa at 64.6%. Anemia is the strongest predictor of mortality within the first year post-HIV diagnosis. The risk of death is higher with increasing severity of anemia, as evidenced by studies conducted in developing countries like Africa.[7,16] A study conducted in Indonesia revealed that the average prevalence of anemia in individuals with HIV/AIDS is 57.5%. However, at DR. Wahidin Sudirohusodo Hospital in Makassar, Indonesia, the prevalence of anemia in HIV/AIDS patients was notably higher at 89.6%. This higher prevalence can be attributed to the generally severe nature of the disease among patients referred to the hospital. Among the 58 HIV/AIDS patients studied, 52 (80%) were found to have anemia. Out of the cases examined, the majority (80.7%) showed normochromic normocytic anemia. A smaller percentage exhibited hypochromic microcytic anemia (9.6%), macrocytic hypochromic anemia (3.8%), normochromic microcytic anemia (3.8%), and normocytic hypochromic anemia (1.9%). These results are consistent with international studies, suggesting that normochromic normocytic anemia is the most commonly observed form of anemia among individuals with HIV/AIDS.[1]

Anemia is a prevalent hematological complication in individuals with HIV infection. Typically, the condition is characterized by normochromic normocytic features, including a low count of immature red blood cells, normal iron levels, and a compromised response to erythropoietin.[35]

The etiology of anemia in HIV-infected individuals can be broadly classified as a result of an inefficient hematopoiesis process, which can be attributed to factors such as malnutrition, co-infections, neoplasms, reduced erythropoietin production, and the use of antiretroviral drugs. Other mechanisms contributing to anemia may involve heightened erythrocyte destruction and blood loss from gastrointestinal or genitourinary bleeding.[36] The pathogenesis of anemia associated with HIV infection is intricate and multifaceted. Notably, opportunistic infections or malignancies commonly associated with HIV infection can further induce anemia. Diagnosing anemia in regions where infectious diseases like malaria and helminthiasis are prevalent poses a challenge, as these conditions can independently cause anemia without HIV infection, complicating the diagnostic process.[37]

The real impact of anemia is fatigue. This is exacerbated by pregnancy. Fatigue in HIV infection is associated with physical functional impairment, psychological distress, and decreased quality of life. Although the cause of fatigue in anemia is multifactorial, it is suspected that anemia is the most influential cause of fatigue. Fatigue is seen in disruptions of daily routines, work productivity, and sleep pattern.[36]

Intestinal worm and parasitic infections

Apart from HIV, infections with worms and intestinal parasites are also the most common cause after malaria, according to the review[14,17,20] by 26.6% This occurs in African countries like Ethiopia, West Ethiopia, and Tanzania, with the highest prevalence in West Ethiopia, as high asa 73%. According to the World Health Organization, worms are infested with one or more intestinal parasitic roundworms belonging to the intestinal nematode class, including whipworms, hookworms, and Ascaris.[38] Intestinal nematodes responsible for causing helminthiasis typically belong to the Transmitted Helminths (STH) group, which consists of worms that require specific soil conditions for their infective stage to occur. Examples of STH nematode species that contribute to helminthiasis include roundworms (Ascaris lumbricoides), hookworms (Ancylostoma duodenal and Necator americanus), threadworms (Strongyloides stercoralis), and whipworms (Trichuris trichiura). The pinworm (Oxyuris vermicularis) is another non-STH nematode that commonly infects individuals.[39]

Helminthiasis remains highly prevalent worldwide, especially in tropical and sub-tropical climates, including Indonesia. Worm disease, categorized as one of the 17 Neglected Tropical Diseases (NTDs), pertains to tropical illnesses that receive inadequate attention from the government. The prevalence of helminthiasis fluctuates between 40% and 60% across all age groups. Alarmingly, a substantial population of 195 million individuals in Indonesia reside in areas endemic to worm infestation. Moreover, the overall prevalence of worm infections remains remarkably elevated in Indonesia, particularly among socioeconomically disadvantaged groups with heightened susceptibility to this ailment.[40,41] The high prevalence of helminthiasis does not only occur in Indonesia. Other countries with conditions similar to Indonesia also

experience the same thing as research in North West Ethiopia, with a prevalence of helminthiasis in pregnant women of 32% in the Dembecha District[42] and 70.6 % in the Mecha District.[43]

The presence of intestinal worms exacerbates anemia by increasing blood loss. This disruption in iron equilibrium occurs due to the release of a greater amount of iron compared to the amount supplied.[44] Consequently, alterations in intestinal iron absorption, iron metabolism, and intestinal bleeding can result in iron deficiency anemia. Furthermore, the impairment of the intestinal mucosa obstructs the absorption of essential nutrients, specifically micronutrients like iron, thereby detrimentally affecting the host's physical condition, nutritional status, and immune system.[45]

The presence of anemia in pregnant women contributes to an elevated susceptibility to complications throughout pregnancy and delivery. Anemia in expectant mothers is closely linked to heightened rates of mortality and morbidity among both the maternal and neonatal populations, encompassing the likelihood of spontaneous abortion, fetal demise, preterm birth, and lower birth weight.[2] Worm infestations can be contracted via the consumption of improperly washed food contaminated with worm eggs, the ingestion of water containing worm eggs, the influence of socioeconomic and environmental factors, and inadequate personal hygiene practices.[46]

Chronic Disease

After the prevalence of HIV and intestinal worm and parasite infections, a review conducted in Ethiopia and India found that chronic disease accounted for 13.3% of the findings in Ethiopia and 27.3% in India[13,26]. Anemia of Chronic Disorder (ACD), also known as anemia of chronic disease or chronic inflammation, is identified as the second most common type of anemia globally, following iron deficiency anemia.[47] Typically lasting over three months, the chronic disease contributes to anemia through three main mechanisms. Firstly, the production of red blood cells in the bone marrow is suppressed due to inflammatory mediators impacting iron homeostasis, resulting in limited iron availability for erythropoiesis and subsequent development of anemia. Secondly, inflammation affects the production and activity of erythropoietin, the hormone responsible for regulating red blood cell formation, primarily through cytokine inhibition and reduced expression of erythropoietin receptors on erythroid progenitors, as well as limited iron availability. Thirdly, impaired iron utilization in the body prevents stored iron in the bone marrow from effectively producing new red blood cells. Anemia of chronic disease often progresses slowly and mildly, leading to few or no noticeable symptoms. When symptoms do arise, such as fatigue, weakness, or pallor, they are typically attributed to the underlying disease rather than the anemia itself.[48,49] As a result, laboratory tests are necessary for a definitive diagnosis of Chronic Disease Anemia.

Hepcidin, a hormone synthesized by the liver, is crucial in maintaining iron balance within the body. Its synthesis is elevated in Anemia of Chronic Disease (ACD) cases and reduced in instances of Iron Deficiency Anemia (IDA). Frequently, ACD and IDA occur simultaneously, and their manifestations can be indistinguishable upon visual examination of the peripheral blood sample. Furthermore, the diagnosis of IDA and ACD is commonly conducted through laboratory tests such as measuring serum iron levels, Total Iron Binding Capacity (TIBC), transferrin saturation, and ferritin concentrations.[50]

Anemia in chronic diseases,whether infectious or non-infectious diseases, is the result of a combination of several factors, including genetics, behavior, and the environment.[1] According to a study in India[26], Chronic diseases as comorbidities among pregnant women include chronic liver disease, chronic kidney disease, heart disease, essential hypertension, diabetes mellitus, tuberculosis, and autoimmune disorders. The same study reported that half of pregnant women in India experience chronic diseases such as diabetes, hypertension, tuberculosis, respiratory disease, malaria, and cardiovascular disease. Studies show that mothers who have two or more chronic diseases during pregnancy have a higher chance of experiencing delivery-related complications such as seizures and excessive vaginal bleeding.[33]

Bleeding

The next cause of maternal health issues is bleeding or post-hemorrhagic events, 13.3% of cases found in the African continent, including Uganda, both southern and northern Ethiopia.[19,21,23] This high percentage is often due to a history of previous postpartum bleeding, abortion, and bleeding during pregnancy, all of which cause anemia in pregnant women.

Based on the World Health Organization (WHO) findings, approximately 40% of maternal fatalities in developing nations can be attributed to anemia during pregnancy. Most instances of anemia in pregnancy result from acute hemorrhaging and inadequate nutritional conditions.[51] Field[52–54] research in Indonesia has demonstrated that pregnant women with suboptimal nutritional status are prone to experiencing chronic energy deficiency (CED). Furthermore, anemia during pregnancy can contribute to postpartum hemorrhage, a leading cause of maternal mortality, with a staggering mortality rate of 58%, particularly prevalent in developing countries.[2] Although women survive after experiencing postpartum hemorrhage, they can later experience severe blood loss (severe anemia) and prolonged health problems. This is what will affect anemia in women in subsequent pregnancies. Anemia that occurs during pregnancy will likely impact the process of childbirth, the postpartum period, and the health of the newborn.

Acute or rapid blood loss can give rise to severe initial symptoms, particularly when anemia occurs abruptly due to sudden blood loss from various causes such as injury, surgical procedures, childbirth, or the rupture of blood vessels. The sudden depletion of significant quantities of blood can lead to two major complications: First, a decrease in blood pressure arises due to insufficient fluid volume within the blood vessels. Second, the body experiences a sharp decline in its oxygen supply, owing to the rapid reduction in the

number of red blood cells responsible for carrying oxygen. Consequently, these circumstances can precipitate adverse events, such as heart attacks, strokes, or even death.[55]

Chronic blood loss is a more prevalent occurrence compared to sudden blood loss. Chronic bleeding refers to the long-term and ongoing bleeding from any part of the body. While significant bleeding events like nosebleeds and hemorrhoids are easily noticeable, smaller blood losses might go unnoticed. For instance, it may be difficult to detect small traces of blood in the stool, referred to as occult or hidden blood loss. Prolonged and gradual bleeding can lead to substantial blood loss over time if left unaddressed. This gradual bleeding is commonly associated with gastrointestinal or urinary tract disruptions, as well as heavy menstrual periods.[19] This type of chronic bleeding typically results in low iron levels, exacerbating the severity of anemia.[55]

CONCLUSION

Anemia is not a standalone disease but a symptom of various underlying conditions. Therefore, diagnosing anemia requires more than just identifying its presence; it necessitates determining the root cause. This review article explores five causes of normocytic anemia in pregnant women, most of which occur in African continent countries. The most common causes include malaria, HIV, worm infections and intestinal parasites, chronic disease, and bleeding.

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SHORT COMMUNICATION

Presentation skills teaching in anaesthesia

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SUMMARY

Presentation is a communication method to convey information within a specific time, involving judgment, decision-making and critical thinking. Incorporation of teaching- learning-assessment of presentation skills is essential in medical curriculum because medical education involves presentations such as case reports, seminar, and conferences. The presentation skills equip 'the future doctors' to be at par with the ever-advancing world of technology, artificial intelligence and globalisation. The presentations should involve effective constructive feedback to enhance the effectiveness of presentation skills in medical curriculum.

The 2nd edition of Malaysian Qualification framework (MQF) incorporates communication skills as an essential functional work skill included in the five clusters of learning outcomes for the undergraduate medical programme (Malaysian medical council). As per the 'standards for undergraduate medical education', communication skills refer to the ability to convey information/ideas/reports cogently and professionally in appropriate language. In addition, the curriculum framework for core skills in communication includes a. Effective doctor-patient relationship, b. communication about the patient, c. communication about medicine and science.[1]

A. Communication Skills for Effective Doctor-Patient Relationship

The New Integrated Curriculum (NIC), followed in Malaysia aims at producing a competent doctor with a holistic approach to the practice of medicine[2] for which effective communication skills leading to effective doctor-patient relationship are pivotal. The communication skills essential for the effective doctor-patient relationship have been well researched and emphasised, evidenced from the teaching-learning-assessment methods incorporated in the medical curriculum.[3,4]

Presentation skills

Presentation is a communication method to convey information within a specific time, involving judgment, decision-making and critical thinking.[5] As evidenced from the literature, the emphasis on communication from the perspective of presentation skills in medical education is scanty as compared to patient-doctor communication skills.[6] Presentation skills are an important educational content because medical education incorporates presentations such as case reports, seminars, and conferences.[5]

B. Communication About the Patient

Effective case reports' presentations convey and transfer information about the patient among the medical fraternity essential for effective learning, interprofessional patient management and ultimately leading to improved patient outcomes. The oral case presentation is one of the primary avenues for physician-to-physician communication.[7] A well-done case presentation has the potential to facilitate patient care, improve efficiency on rounds, serve as a stimulus for individual and group learning, and allow for student and resident evaluation. Medical students present mostly clinical case presentations.

C. Communication about Medicine and Science

Seminars and conferences presentations convey and disseminate information about medicine and science essential for continuing medical education and practicing evidence-based medicine (EBM) concept.

Inculcating and encouraging research from undergraduate level, medical students are involved in paper presentation at seminars and conferences from an early stage of their career preparing them for future. Park and Park[5] suggested development of a robust program for medical students to improve presentation skills.

Teaching and incorporating the presentation skills at undergraduate level equips the medical students for the internet era of information and technology as well because the presentations involve not only the oral presentation skills but also the use of information technology.

The authors suggest an example of incorporating presentation skills at undergraduate level in Anaesthesia teaching.

Example of incorporating presentation skills in anaesthesia teaching: presentation by students using PowerPoint slides

The students in anaesthesia posting are asked to prepare and present a preassigned topic using PowerPoint slides. The topic chosen can be the, 'must know component' for undergraduate anaesthesia teaching like Mendelson

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syndrome. The students receive guidance on the resource materials and basic PowerPoint slides preparation by the respective lecturer. The time required for the preparation of PowerPoint slides is part of the non-face to face student learning time.

The goal of student presentation is to focus on presentation skills including – a. Clarity of presentation, b. confidence of the presenter, c. content of the presentation, d. creative and innovative skills to make the slides interesting, e. use of information technology (IT) skills, e. appropriate referencing of the resources. The aim and objectives of the student's presentation are communicated well in advance to the students.

The presentation must be followed by feedback from the facilitator and the peers. As evidenced from the literature, effective feedback improves the quality of presentations and enhances students' performance.[5]

In addition to improve the presentation skills this exercise exposes the students to opportunities to enhance and practice the literacy skills which are the essential 21st century skills.8 The literacy skills include: (1) Information, (2) media, (3) technology referred as IMTs. The IMTs equip to discern the facts, the sources of the information, and the technology involved. A study by Nurjahan et al. suggests that in order to increase the level of computer literacy among medical students, positive steps need to be taken, involving the formal inclusion in the teaching of undergraduate medical students. Thereby, enhancing the medical students' ability to acquire, appraise and use information technology in the course of their studies, and more importantly after graduation.[9]

Additionally, by emphasising the importance of citing the resources appropriately, the students learn and practice the concept of intellectual property rights (IPR). IPR refers to legal protection available in relation to certain property that is intangible (intellectual) and created by individuals.[10]

For the assessment of presentation skills, the authors suggest relevant preassigned subject topic students' PowerPoint presentation as part of clinical assessment at the end of the clinical posting.

To conclude, student presentations must be incorporated into the undergraduate medical education curriculum to improve the presentation skills which are essential skills for future doctors to be at par with the ever-advancing world of technology, artificial intelligence, and globalisation. The presentations should involve effective constructive feedback to enhance the effectiveness of presentation skills in medical curriculum.

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