Official Journal of the
Malaysian Medical Association

The Medical Journal of Malaysia

Volume: 79

Issue No: 2

March 2024

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

MJM

Official Journal of the Malaysian Medical Association

Volume 79 Number 2 March 2024

EDITORIAL BOARD

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

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

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Subscription Rates:
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Printed by: Digital Perspective Sdn. Bhd.
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Risk factors of emerging multidrug resistant *Acinetobacter baumannii* in burn patients at Burn Unit of Dr. Soetomo Hospital during January 2020 to December 2021

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ABSTRACT

Introduction: Burn injury patients are at high risk of infection as a result of the nature of the burn injury itself, including prolonged hospital stays, antibiotics use, treatment procedures, etc. In this era, nosocomial infections caused by *Acinetobacter baumannii (A.ba)* have increased significantly. This study was conducted to investigate the micro-organism pattern and the risk factors for burn patients with multi-drug resistant (MDR) *Acinetobacter baumannii (A.ba)* in the Burn Unit at Dr. Soetomo Hospital.

Materials and Methods: We conducted a retrospective, observational study among burn patients with *A.ba* admitted to the Burn Unit at Dr. Soetomo Hospital from January 2020 to December 2021. Potential risk factors for MDR-*A.ba* were analysed by univariate and multivariate analysis. The patients diagnosed with MDR-*A.ba* wound infection were included in the case group. The patients diagnosed with non MDR, these are: (1) the patients isolated micro-organisms other than *A.ba*, (2) sterile isolates, and (3) the patients isolated as *A.ba* but not MDR, were included in the control group.

Results: A total of 120 burn patients were included in this study. During this study, 24% burn patients were found to have *Acinetobacter baumannii* and 79% (from 24% of *Acinetobacter baumannii*) had MDR-*A.ba*. According to univariate analysis, risk factors that significant were: Abbreviated Burn Severity Index (ABSI) (p = 0,002; OR: 6.10; CI: 1,68 - 21,57); hospital Length Of Stay (LOS) (p < 0,000; OR: 6.95; CI: 2,56 - 18,91) and comorbid (p = 0,006; OR: 3,72; CI: 1,44 - 9,58). But, after analysed by multivariate analysis, only ABSI was the significant factor (p = 0,010; OR: 1,70; CI: 1,23 - 2,36).

Conclusion: Based on univariate analysis, the significant risk factors for MDR-*A.ba* were: ABSI, hospital length of stay and comorbid. But after adjusted by multivariate analysis, only ABSI was the significant factor.

KEYWORDS:
Burns, Acinetobacter baumannii, multidrug resistance

INTRODUCTION

One of the major functions of the body skin is to ensure protection against microorganisms in the external environment. The burn wound can be considered as one of the major health problems in the world.[1]

Patients who are hospitalised after having a major burn injury are at high risk of developing hospital-acquired infections.[2] If patients survive in the initial 72 hours after a burn injury, infections are the most common cause of death.[2] In burn injuries, the most frequent and devastating pathogens are *Acinetobacter baumannii, Pseudomonas aeruginosa, Klebsiella pneumoniae* and *Staphylococcus aureus. Acinetobacter spp.* are the most common gram negative MDR nosocomial agents.[3]

Recently, multidrug-resistant *Acinetobacter baumannii* (MDR-*A.ba*), defined as bacteria resistant to three or more classes of antibiotics including carbapenem, has arisen as a major causes of infection related healthcare.[4] MDR-*A.ba* are difficult to treat and high in mortality and morbidity, it is also associated with increasing in hospital stays.[4] Therefore, identifying risk factors for these nosocomial infections is needed to help reduce their occurence.[4]

The aim of this study was to investigate the micro-organism pattern and to assess the risk factors for burn patients with multidrug resistant *Acinetobacter baumannii* in the Burn Unit.

MATERIALS AND METHODS

Patients' Selection and Study Design

We conducted a retrospective and observational study of burn patients that were admitted to the Burn Unit of Dr. Soetomo Hospital, Surabaya, Indonesia from January 2020 to December 2021.

During the study period, wound cultures were routinely taken from all patients within 48 hours after hospitalized in Dr. Soetomo Hospital. Other cultures were collected from blood, urine and sputum/endotracheal aspirate for all patients admitted to the Burn Unit as indicated.

This article was accepted: 29 January 2024
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Table I: Univariate analysis of risk factors for burn patients between MDR-A.ba vs non MDR

Risk factors	MDR-Ab (n = 23)	Non MDR (n = 97)	Total	R squared	OR (CI 95%)	*p*-value
Sex						
● Male	17	68	85	0.001	0.83 (0.29 -2.31)	0.476
● Female	6	28	35			
Age (years)						
● <=60	21	89	110	0.000	1.06 (0.21 - 5.36)	0.608
● >60	2	8	10			
% TBSA						
● <=3 (<30%)	0	6	6	0.012	1.25 (1.14 - 1.37)	0.271
● >=4 (> 31%)	23	91	114			
ABSI						
● <=7	3	46	49	0.092	6.10(1.68- 21.57)	0.002
● >=8	20	51	71			
Length of stays (days)						
● <=20	7	73	80	0.177	6.95 (2.56 - 18.91)	0.000
● >=21	16	24	40			
Duration of previous antibiotics (days)						
● <=10	8	37	45	0.036	1.44 (0.05 - 1.98)	0.060
● >=11	15	20	35			
Cause						
● Fire	18	61	79	0.016	0.47 (0.16 - 1.38)	0.123
● Others	5	36	41			
Inhalation injury						
● Yes	7	23	30	0.004	1,408 (0.516 - 3.841)	0.336
● No	16	74	90			
Comorbid						
● Yes	12	22	34	0.066	3.72 (1.44 - 9.58)	0.006
● No	11	75	85			

TBSA: Total body surface area, ABSI: Abbreviated Burn Severity Index, MDR-A.ba: Multidrug resistance Acinetobacter baumannii, OR: Odds ratio

Table II: Multivariate analysis for risk factors in burn patients between MDR-A.ba vs non MDR.

Risk factors	Multivariate analysis		
	OR	95% CI	p value
ABSI	1.70	1.23 - 2.36	0.010
Length of stay (days)	3.03	0.24 - 37.90	0.390
Comorbid	2.00	0.68 - 5.911	0.210

ABSI: Abbreviated Burn Severity Index, OR: Odds ratio, CI: Confidence interval

The risk factors for MDR-*A.ba* in burn patients were identified as sex, age, inhalation trauma, comorbid diseases, causes of burn injuries, hospital length of stay, day of exposure to antibiotics, Abbreviated Burn Severity Index (ABSI) and Total Body Surface Area (TBSA).

Patients were excluded from this study if they did not undergo bacterial culture, died before 48 hour and had incomplete dat.

Burn patients were divided into two group, case and control groups. The patients diagnosed with MDR-*A.ba* wound infection were included in the case group. Patients diagnosed with non MDR, such as those who isolated micro-organisms other than *A.ba*, (2) sterile isolates and(3) those who isolated as A.ba but not MDR, were included in the control group.

Multidrug-resistant MDR-*A.ba*, defined as strains resistant to three or more classes of antibiotics including carbapenem, has emerged as a major cause of healthcare associated infection.

Statistical Analysis

Numeric data were presented with standard deviation (SD). Continuous variables were analysed using Student's t-test. The Mann-Whitney U test is used when the data in not normally distributed. Potential risk factors for MDR-*A.ba* were analysed by univariate and multivariate analysis. Odds ratio (OD) and 95% confidence intervals (CI) were calculated using binary logistic regression for each model. p value < 0.05 represented statistical significance. Statistical analysis was calculated using SPSS version 15.0.

RESULTS

During the period of this study, from January 2020 to December 2021, a total number of 143 burn patients were admitted to the Burn Unit.

Of the 143 burn patients, 120 patients were included, and 23 patients were excluded because of incomplete data and no isolates culture (Figure 1). There were 23 MDR-*A.ba* burn patients and 97 non MDR burn patients. Of the 97 non-burn

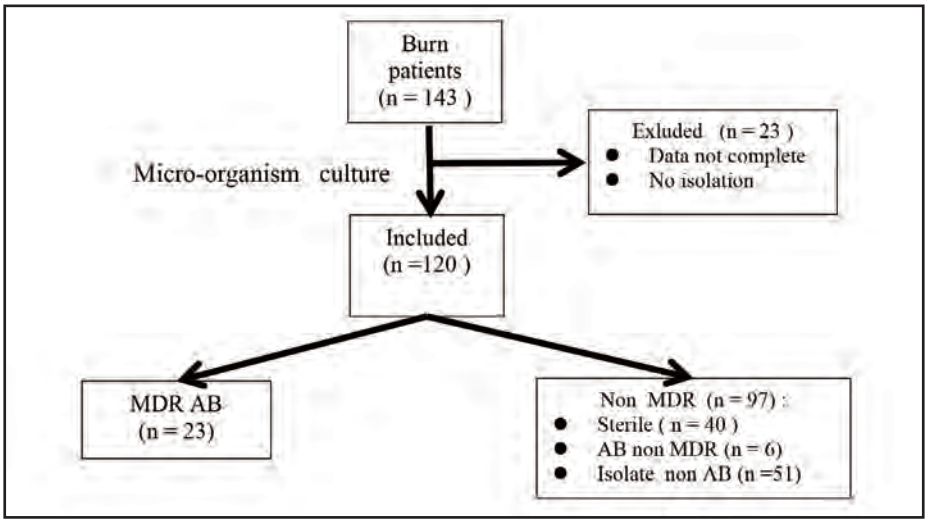

Fig. 1: Selection process in burn patients. MDR multi-drug resistant. A.ba Acinetobacter baumannii

patients, 40 patients (41%) had sterile isolate culture, six patients (6%) had Acinetobacter baumannii non MDR and 51 patients (53%) had positive isolate non *Acinetobacter baumannii*.

Table I showed the causative agents isolated from burn patients. Of the 120 burn patients, there were 80 patients (67%) with positive culture and 40 patients (37%) with negative cultures.

The most frequently isolated pathogens were *Pseudomonas aeruginosa* (35), *Staphylococcus sp* (30), *Acinetobacter baumannii* (29) and *Klebsiella* (20). Of the 29 patients with Acinetobacter, 23 patients (79%) were MDR-*A.ba*, and only six patients were *Acinetobacter* non MDR.

Univariate analysis of baseline and risk factors associated with MDR-A.ba infection is presented in Table I. According to the univariate analysis, there were no significant difference associated with risk factors, such as sex, age, TBSA and cause of burns and inhalations injury. But, there were significant difference associated with ABSI (p = 0,002; OR: 6.10; CI: 1,68 - 21,57), hospital length of stay (p < 0,000; OR: 6.95; CI: 2,56 - 18,91) and comorbid (p = 0,006; OR: 3,72; CI: 1,44 - 9,58). But, after analysed by multivariate analysis, only ABSI was the significant factor (p = 0,010; OR: 1,70; CI: 1,23 - 2,36) (Tabel II).

Of the 120 burn patients, there were 44 patients (37%) death and 76 patients (63%) discharged alive. In MDR-A.ba group, there were nine patients (20%) death and 35 patients (80%) in non MDR. But, there was no significant difference between MDR-A.ba and non MDR group (p = 0.784).

DISCUSSION

Infection become a major cause of morbidity and mortality in patients with burn injury.[2] The Infectious Diseases Society of America (IDSA) identifies *Acinetobacter baumannii* as one of the seven pathogens that threaten the health system because of its ability to survive on patient skin and environmental surfaces, this pathogen transmits and spreads very quickly.[5] Likewise in the burn unit, this pathogen often causes extraordinary events.[4]

Acinetobacter baumannii, previously categorised as a low pathogenicity bacterium, has evolved into a high pathogenicity bacteria because it is resistance to more than one type of antibiotic (multi drug resistance/MDR to extremely drug resistance *Acinetobacter baumannii*/XDR-*Ab*) which causes world health problems due to nosocomial outbreaks in hospitals throughout the world.[5]

During hospital treatment, the spread of this pathogen can occur from invasive medical devices used, such as intravenous lines, catheters, endotracheal tubes, ventilators, ward bed, to objects carried by medical personnel, such as trolleys, food, and direct contact from medical personnel.[6,7] We didn't investigate the source of pathogen in our hospital. However, in our burn unit, we have limitation of isolation room, therefore, in a very large number of patients were placed in the same room which increase the risk of cross contamination.

In this study it was found that the incidence of *Acinetobacter baumannii* were quite high, counted as 29%. Another study conducted by Song et al and Atilla & Kilic each reported almost the same results 21% and 30%.[7,8]

Acinetobacter baumannii microbes were found, 23 (79%) were categorised as MDR-*A.ba*. Likewise, the results of research by Song et al. and Atilla & Kilic, namely 59% and 88%, respectively.[7,8]

In this study, burn patients with *Acinetobacter baumannii* ranked third after Pseudomonas and Staphylococcus. Meanwhile, according to the results of a study by Song et al., *Acinetobacter baumannii* is in second place after *Staphylococcus Microbes*. Meanwhile, the results of Atilla & Kilic's study show that Acinetobacter baumannii ranks first.[7,8]

Certain risk factors increase the incidence of Acinetobacter baumannii. In our study, it was found that significant risk factors for the occurrence of MDR-*A.ba* were ABSI (p = 0.002),

length of stay (p = 0.000) and comorbid factors (p = 0.006). However, after multivariate analysis, ABSI was the only significant risk factor. Statistically, this means that when all variables are analysed simultaneously, length of stay and comorbidities do not play a role in increasing the risk of MDR-*A.ba*. Multivariate analysis allows for the examination of the combined effects of multiple variables, which can lead to different result than univariate analysis. The possibilities of confounding factors which can affect the result in this study are medication and treatment in previous hospital, since our hospital is the last referral hospital in Eastern Indonesia.

ABSI is an assessment to predict the survival rate in burn patients in arrival. This scoring consists of five variables, namely gender, age, presence/absence of inhalation trauma, full thickness burns and extent of burns.[9] Tsolakidis, et al showed that patients who developed infections tended to have higher TBSA, higher ABSI score and longer hospital stays. In this study, a retrospective study was conducted on 252 burn patients. In our study, the small population size of patients may limit the clinical applicability of the data.[10]

Jung et al. reported the results of his research regarding risk factors for MDR-*A.ba*, such as the use of endotracheal tubes, central venous catheters and previous use of antibiotics. Given this, they suggest that clinicians minimize the use of invasive devices and remove them as early as possible.[11]

Song et al. conducted a study by comparing the MDR-A.ba vs. Non-MDR-*A.ba* groups (non-*Acinetobacter* positive cultures, sterile culture and culture of *Acinetobacter* non MDR-A.ba).[7] From the results of this study, it was concluded that the significant risk factors for the occurrence of MDR-*A.ba* were length of stay, TBSA, intubation and causes of burns. However, after multivariate analysis, only length of stay and TBSA were significant.

Meanwhile, according to the results of Wong et al.'s study, the independent risk factors for causing MDR-A.ba were the acute physiology and chronic health evaluation (APACHE) II score at hospital admission and the number of invasive devices installed.[12]

Atilla & Kilic reported the results of their research, namely that significant risk factors contributing to Acinetobacter baumannii were the use of invasive devices, length of stay in hospital, length of stay in ICU and TBSA.[8]

Based on the research results of Munier et al. It can be concluded that the incidence of nosocomial MDR-*A.ba* infection in the burn unit is very high. The increased risk of nosocomial infection in MDR-*A.ba* burn patients is associated with factors: simplified acute physiology score (SAPS II), ABSI, *Acinetobacter baumannii* colonisation, invasive procedures and more than two skin grafts.[4]

CONCLUSION

In conclusions, this retrospective-observational study found a moderate high incidence of MDR-*A.ba* nosocomial infection in burn patients. A univariate analysis showed that Abbreviated Burn Severity Index (ABSI), hospital length of stay and comorbid, were statistically significant. But, after multivariate analysis was adjusted, ABSI was the only significant factor.

Due to increased drug resistance, wider research and further studies are necessary to control hospital infections.

ACKNOWLEDGEMENTS

We gratefully acknowledge the Burn Unit and Microbiology department of Dr. Soetomo Hospital, Surabaya, Indonesia for providing patient medical record.

CONFLICT OF INTEREST

The authors declare that they have no competing interests.

FUNDING

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

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Tracheostomy decannulation readiness: A cross sectional study comparing standardised evaluation for tacheostomy decannulation to flexible endoscopic evaluation of swallowing examination

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ABSTRACT

Introduction: Tracheostomy is a procedure commonly performed in neurocritical and mechanically ventilated patients in the intensive care unit. Dysphagia and impaired airway protection are the main causes for a delay in tracheostomy decannulation in patients with neurological disorders. Endoscopic evaluation is an objective examination of readiness for tracheostomy decannulation with flexible endoscopic evaluation of swallowing (FEES) as the most commonly used method, yet it requires special expertise and is heavily dependent on its operator in assessing the parameters. A relatively new method for assessing decannulation readiness in neurologic disorder, the Standardized Endoscopic Swallowing Evaluation for Tracheostomy Decannulation (SESETD) was introduced in 2013 by Warnecke, et al. This method includes stepwise evaluation of secretion management, spontaneous swallowing and laryngeal sensitivity. This study aims to find conformity between the SESETD and FEES in assessing readiness for tracheostomy decannulation in patients with neurologic disorders.

Materials and Methods: This study is a cross-sectional study conducted on 36 neurologic patients at Cipto Mangunkusumo General Hospital which was aimed to find the agreement between two modalities for tracheostomy decannulation readiness, FEES and SESETD based on parameters, standing secretion, spontaneous swallowing and laryngeal sensitivity.

Result: A total of 36 subjects were examined and 22 of them underwent successful tracheostomy decannulation. The agreement between FEES and SESETD showed significant results with p-value <0.0001 and Kappa value = 0.47.

Conclusion: There was conformity between FEES and SESETD in evaluating tracheostomy decannulation readiness based on three parameters: standing secretion, spontaneous swallowing and laryngeal sensitivity.

KEYWORDS:
Decannulation, dysphagia, FEES, neurologic disorders, tracheostomy

INTRODUCTION

Tracheostomy is a common procedure performed in critically ill patients who require prolonged mechanical ventilation.[1,2] It involves the creation of an opening in the trachea to facilitate breathing and airway management.[3] However, tracheostomy is not without complications, and one of the most significant challenges is the process of decannulation, which involves the removal of the tracheostomy tube while maintaining spontaneous breathing and airway protection.[4] The importance of tracheostomy decannulation cannot be overstated, as it represents a crucial milestone in the recovery and rehabilitation of patients with tracheostomy.[1,2,5] Successful decannulation not only signifies the restoration of natural airway function but also reduces the risk of complications associated with prolonged tracheostomy tube placement, such as infection, granulation tissue formation and tracheal stenosis.[2]

The main causes of delayed tracheostomy decannulation are impaired airway protection and dysphagia. In neurologically ill patients, the prevalence of oropharyngeal dysphagia is 23.2 to 84%.[6,7] Decannulation is a critical step in the management of patients with tracheostomy, as it can significantly impact their quality of life and reduce the risk of complications.[5] Therefore, the accurate assessment of swallowing function and airway protection is paramount in determining the appropriateness of decannulation.

Only a number of studies brought up the optimal timing and procedure of tracheostomy decannulation.[1,4] Furthermore, no gold standard protocol was offered for heavily neurologically ill patients with dysphagia.[1,8,9] Flexible endoscopic evaluation of swallowing (FEES) is the diagnostic tool used to assess swallowing function in patients with tracheostomy. FEES is a well-established method for evaluating swallowing function, providing valuable information on the safety and efficiency of swallowing, aspiration risk, and laryngeal sensitivity and had served as an objective protocol to evaluate decannulation readiness, yet had not been officially determined to be used as standard protocol in clinical settings.[1,2,5] On the other hand, Standardized Endoscopic Swallowing Evaluation of Tracheostomy Decannulation (SESETD), introduced by Wernecke et al.[5] in 2013, is a relatively new technique that has shown promise in assessing

This article was accepted: 06 February 2024
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the readiness for tracheostomy decannulation, particularly in critically ill neurologic patients.[2]

FEES has been widely utilised in the assessment of swallowing function in patients with tracheostomy, providing valuable insights into the presence of pharyngeal residue, penetration, aspiration and laryngeal sensitivity.[10,11] However, it is heavily dependence on its operator, and in the context of critically ill neurologic patients, the assessment of swallowing function regarding tracheostomy decannulation is particularly challenging due to the underlying neurologic deficits and the increased risk of aspiration.[1,2,5] SESETD presents an opportunity to enhance the assessment process by providing a standardised and objective evaluation of swallowing function through three parameters: 1) secretion management, 2) spontaneous swallowing and 3) laryngeal sensitivity, which can surpass or complement the information obtained from FEES.[2,5]

In this study, we aim to investigate the effectiveness of SESETD in assessing swallowing function and its conformity to FEES particularly in critically ill neurologic patients, so that it could serve as an alternative examination that provides an objective, practical and efficient result to assess tracheostomy decannulation readiness.

MATERIALS AND METHODS

This study was a cross-sectional study conducted at the Department of Otorhinolaryngology-Head and Neck Surgery, Faculty of Medicine, Universitas Indonesia/Dr. Cipto Mangunkusumo National General Hospital. The study included 36 patients with tracheostomy who underwent both SESETD and FEES examinations. Sample size was determined using paired two different proportion test. The patients were assessed for their readiness for tracheostomy decannulation based on the parameters of standing secretion, spontaneous swallowing and laryngeal sensitivity.

The inclusion criteria for this study were patients with tracheostomy who were at least 18 years old and had been on mechanical ventilation for at least 7 days. The general condition of these patients varies, as they had different neurological disorder diagnosis. However, those with a history of head and neck surgery, radiation therapy, or oesophageal disease was excluded from the study. Patients who were unable to tolerate the SESETD or FEES examination were also excluded.

The SESETD and FEES examination were performed at the same time, first SESETD then followed by FEES. The examination was conducted by a trained junior otorhinolaryngologist. The recording of SESETD and FEES examination was then assessed by a trained senior otorhinolaryngologist who was blinded to the results of the prior SESETD and FEES examination.

The FEES examination was performed using a flexible endoscope with a diameter of 3.4 mm. It consisted of the evaluation of swallowing function, including the presence of pharyngeal residue, penetration, aspiration and laryngeal sensitivity.

The SESETD examination was also performed using a flexible endoscope with a diameter of 3.4 mm. This examination consisted of three stages, management of standing secretion, spontaneous swallowing and laryngeal sensitivity. The standing secretion was assessed by observing the patient's ability to manage secretions without the aid of suction. If massive pooling was seen in hypopharynx, on vocal cord, aspiration and or silent aspiration was found, then the patient got 0. Spontaneous swallowing was assessed by observing the patient's ability to swallow saliva. If patient swallowed less than two times in two minutes, then patient got 0. Laryngeal sensitivity was assessed by observing the patient's response to laryngeal touch with the endoscope. If no reaction was found, patient got 0. Patients who scored on all three parameters were considered ready for tracheostomy decannulation. Patients who failed one of these parameters were considered not ready.

Data were collected and analysed using SPSS version 25.0. Descriptive statistics were used to summarize the demographic and clinical characteristics of the study population. Kappa test was used to analyse interrater and intrarater agreement according to the three parameters: standing secretion, spontaneous swallowing, and laryngeal sensitivity. In order to find a conformity between SESETD and FEES, the McNemar test and Kappa assessment were used.

RESULTS

The study included a total of 36 subjects with tracheostomy who underwent both SESETD and FEES examinations to assess their readiness for tracheostomy decannulation. The demographic and clinical characteristics of the study population are summarized in Table I. The mean age of the subjects was 45.06 $\pm$ 15.64 years. The most common underlying neurologic condition necessitating tracheostomy was stroke, accounting for 63.9% of the cases. Most subjects used tracheostomy for 3 months – 1 year range (41.7%).

The interrater agreement between two otolaryngologists for SESETD was listed as Kappa score of 0.737 to 1 for three parameters, which showed good reliability. The intrarater agreement for one otolaryngologist at different times was listed as Kappa score 1, which also showed good reliability.

The results of the SESETD and FEES examinations are presented in Table II. The assessment of standing secretion, spontaneous swallowing, and laryngeal sensitivity using SESETD revealed that 16 subjects were ready for decannulation with total score of 3 (41.7%), and 20 weren't ready (58.3%). Meanwhile, the assessment using FEES with swallowing reflex initiation, epiglottic retroflexion, penetration-aspiration, and residue parameters revealed that 26 subjects (72.8%) were deemed ready for tracheostomy decannulation (PAS 1-6) and subjects were not (27.2%). Hence, there were 10 subject discrepancies for decannulation readiness between SESETD and FEES, where they were deemed ready according to FEES but not according to SESETD.

Further analysis of the discrepancies between SESETD and FEES examinations are presented in Table III and IV. It showed that the majority of discrepancies were related to the

Table I: Characteristics of study population

Characteristics	Number (n = 36)
Age (Mean)	45,06 ± 15,64
Age group	
18 – 40 years old	13
41 – 73 years old	23
Gender	
Male	17 (47.2)
Female	19 (52.,8)
Neurologic disease	
Central nervous system lesion	23
Peripheral nervous system lesion	8
Dysphagia due to prolonged intubation	5
Tracheostomy indication	
Prolonged intubation	35
Not prolonged intubation	1
Tracheostomy duration of use	
< 3 Months	8
3 months – 1 year	15
> 1 Year	13
History of dysphagia therapy	
Yes	14
No	22

Table II: Conformity between SESETD and FEES examination.

SESETD conclusion	FEES conclusion		Total
	Ready	Not ready	
Ready	16	10	0
Not ready	10	1620	
Ready	26	10	36
Annotation: Mc Nemar test p = 0.001. Kappa (κ) = 0.47 p = 0.002			

Tabel III: Subjects not ready for decannulation according to SESETD (n = 10)

SESETD readiness	Frequency
Standing secretion	
Score 0	7
Score 1	3
Spontaneous swallowing	
<2	7
>2	3
Laringoreflex	
Present	5
Not present	5

Tabel IV: Subjects not ready for decannulation according to SESETD, but ready according to FEES (n = 10).

FEES readiness	Frequency
Swallowing initiation	
Normal	5
Delayed	5
Epiglottic retroflexion	
Normal	5
Delayed	5
Penetration	
Present	4
Not present	6
Aspiration	
Present	0
Not present	10
Residue	
Present	4
Not present	6

assessment of spontaneous swallowing and laryngeal sensitivity. Specifically, on all 10 subjects there was no aspiration found and four subjects had PAS 2-5, which might still be considered to undergo decannulation. Based on the 10 subjects' difference, six underwent successful tracheostomy decannulation while the other four failed due to subglottic stenosis and no adequate cough reflex.

Tracheostomy decannulation was successful in 22 subjects (61%) where no complication and recanulation occurred. From the remaining 14 subjects with unsuccessful decannulation, 10 didn't pass SESETD nor FEES examination, three were found to have granulation and subglottic stenosis and 1 was found to have no adequate cough reflex. In addition, the concordance between SESETD and FEES in determining the readiness for tracheostomy decannulation was evaluated using the McNemar test and kappa statistics. The Kappa value for the concordance between SESETD and FEES was 0.47, suggesting moderate agreement.

DISCUSSION

The assessment of tracheostomy decannulation readiness is a critical step in the management of critically ill neurologic patients. The decision to decannulate a tracheostomy tube is based on the patient's ability to manage secretions, swallow safely and protect their airway.

The method used in this study, SESETD, had interrater κ = 0.737 and intrarater κ = 1.0 which showed moderate and very strong agreement according to McHugh's Cohen kappa classification.12 Hence, the data taken for this study are valid according to statistical analytics.

In this study, we found that SESETD and FEES had a moderate level of agreement in their assessments of tracheostomy decannulation readiness. Specifically, we found that 61.1% of the patients were deemed ready for decannulation based on both SESETD and FEES examinations. As stated earlier, there are three parameters assessed: standing secretion, spontaneous swallowing and laryngeal sensitivity.

Standing secretion evaluation is the main parameter used for assessment using endoscopy. The accumulation of secrete is associated with an increasing risk of aspiration pneumonia and breathing distress. The second parameter is spontaneous swallowing, which is a protective aerodigestive reflex to prevent penetration and spiration. In normal individuals, spontaneous swallowing should happen 1 to 2 times in 1 minute.[13] A study by Murray et al.[14], found that the frequency of spontaneous swallowing in patients with aspiration is significantly lower than those without aspiration. Most subjects (18 out of 36) didn't pass this 'spontaneous swallowing' parameter in the SESETD examination, hence, scored <3 for SESETD. However, when screened using FEES they acquire PAS 2-5 which show no aspiration and might still considered to undergo decannulation.[15,16] The difference might happen due to the amount difference of stimulus to initiate swallowing reflex, whether spontaneous or voluntary. Spontaneous swallowing in SESETD is assessed without any bolus given, while it is in FEES. The food administration stimulates the initiation of swallowing reflex, resulting in a 'conscious' process that influence the swallowing process, voluntarily or spontaneously.[13]

The evaluation using both FEES and SESETD showed moderate agreement (κ = 0.47). The SESETD examination has several advantages which require less examination time, no food preparation, and could be performed by otorhinolaryngologists without in-depth comprehension of FEES.[17] According to Muhle et al.[2], the three SESETD parameters can predict the ability to protect the airway, as seen in this study. Therefore, SESETD has shown good performance in evaluating the readiness of tracheostomy decannulation in neurologically ill patients or patients with neurogenic dysphagia.

This study successfully performed decannulation on 61% of subjects. Most subjects in this study have haemorrhagic stroke, ischemic stroke, and brain tumour. Dysfunction in swallowing and airway protection is related to the degree of neurologic disease and the breadth of damage found in the brain of the subjects. This study result is in line with Muhle et al.[2] population study in which most subjects had ischemic (58.1%) and haemorrhagic (17.2%) strokes. This study also stated that with heavier neurologic disorders, the swallowing function might need a longer time to recover in comparison to breathing function. Another study, DECAST, by Schenider et al.[18] also stated that 26% with brain injury are ready for tracheostomy decannulation after 3 months, while other studies, SETPOINT, by Bosel et al.[19] only 47% of stroke patients can be decannulated in 6.6 to 7.5 months period. The main reason for this difference is the pathophysiology complexity of dysphagia with the heavy neurologic disorder which might induce central or peripheral swallowing organ dysfunction.

In addition to the discrepancies between SESETD and FEES, this study also identified several limitations that should be considered when interpreting the results. First, the sample size was relatively small, which may limit the generalisability of the findings. Second, the study was conducted at a single centre, which may limit the generalisability of the findings to other settings.

This study also had some limitations which should be address in future studies. First, prior airway patency should be determined before FEES and SESETD examination using flexible endoscope to exclude those without patent airway. If airway is not patent, like those with subglottic stenosis, hence SESETD is not needed. Second, general condition of the patients including GCS should be provided to get a more extensive view of the study population.

CONCLUSION

In conclusion, this study demonstrates that Standardized Endoscopic Swallowing Evaluation for Tracheostomy Decannulation (SESETD) is an effective method for assessing swallowing function in patients with tracheostomy. The conformity between SESETD and flexible endoscopic evaluation of swallowing (FEES) was moderate agreement (κ = 0.47). Patients assessed as not ready through SESETD should be further evaluated using FEES. But those assessed ready,

should not. Further studies with bigger samples are needed to eliminate sample bias and to achieve better agreement between the two modalities.

ACKNOWLEDGEMENTS

Our study has received approval from the Ethics Committee of the Faculty of Medicine Universitas Indonesia and permission to do the research from Cipto Mangunkusumo General Hospital. Informed consent has been obtained from each patient before the initiation of data collection. The authors declare no conflict of interest and no source of funding for this research.

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ORIGINAL ARTICLE

Comparison of adverse effects following immunisation degree after the administration COVID-19 vaccine of different platforms

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ABSTRACT

Introduction: Vaccination is an effective way to overcome the spread of Coronavirus Disease 19 (COVID-19). However, it can give rise to adverse event following immunisation (AEFI). AEFI is an important aspect that is assessed in vaccine safety standards. It is assumed that different vaccine platforms can give rise to different degrees of AEFI severity, but so far there have been no studies that discuss the differences in the degree of AEFI on each type of COVID-19 vaccine platform. Aim: Evaluate the differences in the degree of AEFI on each type of COVID-19 vaccine platform.

Materials and Methods: The research used a quantitative analytical observational design with a cross sectional approach. Data collection from participants was carried out by filling out questionnaires. The collected data was tabulated and statistical analysis was carried out.

Results: A total of 217 respondents who received three doses of vaccine participated in the study. Of the 651 vaccine doses studied, the results showed that there were significant differences in the degree of AEFI between the three types of vaccine platforms. The degree of AEFI was significantly different ($p < 0.05$) between each type of vaccine platform, with the degree of AEFI starting from the lowest, namely inactivated vaccine, then viral vector vaccine and the highest was nucleic acid vaccine.

Conclusion: The degree of AEFI differs significantly between each COVID-19 vaccine platform. The degree of AEFI, from the mildest to the most severe, was inactivated vaccine, viral vector vaccine and nucleic acid vaccine. No serious AEFI was reported.

KEYWORDS:
Vaccine, COVID-19, adverse effect

INTRODUCTION

Since the end of December 2019, Coronavirus Disease 19 (COVID-19), an infectious disease caused by the SARS-COV2 virus, has rapidly spread from Wuhan, China, throughout the world and caused a pandemic.[1] WHO designated COVID-19 as a public health emergency of international concern (PHEIC) from 30 January 2020 to 5 May 2023.[2,3] To date (24 September 2023), the number of COVID-19 cases has reached 770 million cases and has resulted in almost seven million deaths.[4]

One way to overcome the impact of COVID-19 is by vaccination. Vaccination aims to form specific immunity against the SARS-COV2 virus, so it is hoped that it can reduce virus transmission, illness and death rates. Apart from that, vaccination is expected to form herd immunity in protecting groups that have contraindications to vaccination. According to a study, COVID–19 vaccination has prevented 14.4 to 19.8 million additional deaths in 185 countries from December 8, 2020 to December 8, 2021.[5]

However, like other vaccines, COVID-19 vaccination are associated with adverse effects following immunisation (AEFI).[1] World Health Organization defines AEFI as any untoward medical occurrence which follows immunisation and which does not necessarily have a causal relationship with the usage of the vaccine. AEFI can be caused by immune reactions to vaccine components, procedural errors, anxiety reactions or coincidences with things that are not related to vaccination.[6,7]

In the COVID-19 AEFI vaccination, various types of reactions can occur, starting from no reaction, local reactions such as pain, redness, swelling at the injection site, and severe reactions such as cellulitis, and systemic reactions, namely fever, muscle pain throughout the body (myalgia), joint pain (arthralgia), body weakness, headache. Other reactions can include allergic reactions such as urticaria, edema, anaphylactic reactions and syncope.[8] Severe AEFI can cause morbidity and death for vaccine recipients, and community resistance to vaccination.[9]

Until now, the COVID-19 vaccine circulating in Indonesia can be divided into three based on platform type, namely inactivated vaccine (Sinovac), viral vector vaccine (AstraZeneca) and nucleic acid vaccine (Moderna, Pfizer).[10] These three types of platforms have different types of vaccine

This article was accepted: 21 February 2024
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ingredients and additional components, so they have different reactogenicities, and of course this will influence the incidence of AEFI. Until now, the differences in the severity of AEFI on different vaccine platforms circulating in Indonesia are still not clear yet, even though this is an important issue because the presence of AEFI affects vaccine safety and the level of community participation in the COVID-19 vaccination program. Therefore, this study aims to evaluate the differences in the degree of AEFI on each type of COVID-19 vaccine platform.

MATERIALS AND METHODS

Study Design and Population

This research used a quantitative analytical observational design with a cross sectional approach. The population studied was all Indonesian people who had received the COVID-19 vaccine, with the sample being population that met the inclusion criteria, namely: (1) had been administered with two doses of COVID-19 vaccine and (2) filled out the questionnaire completely. The sampling technique in this research was snowball sampling, where participants were recruited online using social media.

A previous study reported AEFI prevalence of about 17% in Jakarta, Indonesia.[11] We used this prevalence data to calculate the sample size in OpenEpi web-based program, using theformula n = [DEFF*Np(1-p)]/ [(d2/Z21-α/2*(N-1) + p*(1-p)] and taking 95% confidence level. This resulted in a requirement of 217 participants.

Respondents submitted the data using an online Google Forms questionnaire (docs.google.com/forms). Before filling out the questionnaire, respondents received an informed consent form provided in Google Forms. By filling in the questionnaire the respondent is deemed to agree to participate in this research. Data collection was carried out in the period from 21 September 2022 to 26 October 2022.

Variables

The variables studied consisted of vaccine platform type and the degree of AEFI. The independent variable was vaccine platform type, which includes inactivated vaccine, nucleic acid vaccine and viral vector vaccine with a nominal measuring scale. The independent variables were the degree of AEFI, which includes no complaints, local AEFI (pain at the injection site) and systemic AEFI (headache or muscle pain, joint pain, chills, fever (body temperature > 37.5°C, fatigue and nausea or vomiting) with an ordinal measuring scale. An online questionnaire was used to measure the two variables.

Statistical Analysis

Data were extracted from Google Forms to Microsoft Excel 2019 for cleaning and coding. Statistical analysis for the data was carried out using SPSS 24.0. Kruskal-Wallis test (p = 0.05) was perfomed to test whether there was a significant difference of the degree of AEFI on different platforms. If there was a significant difference, analysis continued with a post hoc test to assess the differences between different groups.

RESULTS

Demographic Characteristic of Participants

A total of 217 participants were included in this study. A majority of the participants were female (67.3%), and most have education level of diploma/bachelor degree (60.3%). Age varied between participants, from 18 to 65 years old, with a median age of 35 years (IQR: 22-44). Most participants were in the 21 to 30 years age group (32.7%). The demographic characteristic of participants is presented in Table I.

All the respondents received three doses of vaccine, with three different types of vaccine platforms used, inactivated vaccine (Sinovac), nucleic acid vaccine (Moderna, Pfizer) and viral vector vaccine (AstraZeneca), with the number of recipients for each type of vaccine are shown in Table II.

A comparison of AEFI degrees between platforms, along with the results of the Kruskal Wallis test, are shown in Table III. No serious AEFI was reported in our study. The lowest AEFI degrees were found in the inactivated vaccine, while the highest were found in the nucleic acid vaccine. It can be seen that the p-value of the Kruskal Wallis test is less than 0.05, which indicates that there was a significant difference between the degrees of AEFI on the three types of platforms. Since there were significant differences in the degree of AEFI, a post hoc test was done and its results are shown in Table IV.

The post hoc test results showed significant differences ($p < 0.05$) in the degree of AEFI between the three types of vaccine platforms compared to other vaccine platforms.

DISCUSSION

Vaccination is one way to deal with COVID-19, but just like the vaccination of other diseases, it is associated with adverse effects (AEFI). In this study, AEFI from 651 vaccine doses was studied and the results showed that there were significantly different in the degree of AEFI in the three vaccine platforms. The difference in the incidence of AEFI between each type of vaccine platform can be explained by differences in the reactogenicity of the immune system to vaccines.[12]

The lowest degree of AEFI was found after the administration of inactivated vaccine and the majority of inactivated vaccines administration were not followed by AEFI. Majority of viral vector vaccine recipients also did not report AEFI, however the degree of AEFI on this type of vaccine platform was higher than the inactivated vaccines. Administration of nucleic acid had the highest incidence of AEFI among the three vaccine platforms studied, with the majority of vaccine recipients experiencing systemic AEFI. In this study, there were no respondents who reported serious, life-threatening AEFI.

AEFI in COVID-19 vaccination is very common in all types of currently available vaccines,[13] and AEFI can appear in a matter of minutes – days.[14] The results of this study are in accordance with several previous studies, where the incidence of AEFI in the inactivated vaccine and viral vector vaccine was lower than that on the nucleic acid vaccine, and there were more moderate-severe AEFIs after administration of the

Table I: Demographic characteristic of participants (n = 217)

Variable	n	(%)
Sex		
Male	71	32.7
Female	146	67.3
Age (years)		
< 21	25	11.5
21-30	71	32.7
31-40	32	14.7
41-50	62	28.6
51-60	22	10.1
> 60	5	2.3
Level of education		
Primary school	1	0.05
Secondary school	46	21.2
Diploma/bachelor degree	131	60.4
Master degree	39	18.0

Table II: Number of administered vaccine doses

Vaccine platform	1st dose n (%)	2nd dose n (%)	3rd dose n (%)	Total n(%)
Inactivated vaccine	188 (86.6)	181 (83.4)	15 (6.9)	384 (60.0)
Nucleic acid vaccine	8 (3.7)	10 (4.6)	155 (71.4)	173 (26.6)
Viral vector vaccine	21 (9.7)	26 (12.0)	47 (21.7)	94 (14.4)
Total	217	217	217	651

Table III: Comparison of AEFI degrees between different vaccine platforms

Vaccine platform	AEFI degree	n	(%)	*p*-value
Inactivated vaccine	No AEFI	228	59.4	0.000
	Local AEFI	100	26.0	
	Systemic AEFI	56	14.6	
Nucleic acid vaccine	No AEFI	44	25.4	
	Local AEFI	49	28.3	
	Systemic AEFI	80	46.2	
Viral vector vaccine	No AEFI	39	41.5	
	Local AEFI	21	22.3	
	Systemic AEFI	34	36.2	

Table IV: Post hoc test results

Variable comparation	*p*-value
Inactivated vaccine – nucleic acid vaccine	0.000
Inactivated vaccine – viral vector vaccine	0.000
Nucleic acid vaccine – viral vector vaccine	0.012

nucleic acid vaccine.[12,15] A meta-analysis study revealed that administration of nucleic acid vaccine produces more and more severe side effects compared to other platforms.[1,16] However, another study stated that systemic AEFI occurred more often when administering the viral vector vaccine compared to the nucleic acid vaccine.[17] This is because these differences can be caused by the factors of the vaccine itself (such as differences in vaccine components and route of vaccine administration) and other factors (age, race, gender, comorbidities, etc.).[8,17,18] Of these factors, the number of doses administered has the greatest influence on the incidence of AEFI following COVID-19 vaccination.[18]

Even though it causes more severe AEFI, administration of a nucleic acid vaccine is considered safer than the the inactivated vaccine because it is not infectious, so there is no risk of infection and is safe for people with immunocompromised diseases.[12] After the administration of viral vector vaccines, most AEFIs are mild and systemic and very rarely can cause serious side effects in the form of thromboembolism and thrombocytopenia.[13,19] Nucleic acid vaccine may be associated with allergic reactions, which may be caused by the pegylated lipid component used to transport the vaccine's mRNA components into cells.[20] Severe AEFIs was not reported by respondents in this study.

To the extent of the author's knowledge, there has been no similar research discussing AEFI on different types of vaccine platforms in Indonesia. Another interesting thing about this research is that no serious or life-threatening side effects were reported. Severe side effects have been reported in some cases of COVID-19 vaccine administration, these events are very rare when compared with the total dose injected.[11] There are several limitations in this research. The sample used in this

study was small, and dominated by women, so there are limitations in generalisation to the general population. We have a small number of respondents who are over 60 years old. The participants were recruited using social media, which is infrequently used by older people, thus only a few respondents were over 60 years old. Another study conducted in Jakarta, Indonesia, showed that there was no correlation between the adults and elderly age group with the incidence of AEFI.[11] Until today, there were very few serious AEFI recorded in Indonesia and there was no mortality linked to COVID-19 vaccination in Indonesian adults and elderly.[21,22] Thus, we think the result will not be significantly different if more elderly respondents were participating in this study.

In addition, this study compared different types of vaccine platforms as a determinant of the degree of AEFI, but did not assess the existence of other factors that could influence the incidence of AEFI. In this study, the effect of the order and number of vaccine doses received by respondents on the incidence of AEFI was also not assessed. In addition, the use of a cross-sectional approach in this study limits drawing causal relationships between the two variables. Further research is needed to answer issues related to the limitations of this research, and open a wider horizon of knowledge regarding AEFI in vaccination.

CONCLUSION

There are differences in the degree of adverse event following immunisation (AEFI) for each COVID-19 vaccine platform in Indonesia, starting from the lowest inactivated vaccine, then viral vector vaccine and the highest nucleic acid vaccine, and this difference is related to difference in vaccine reactogenicity. Most inactivated vaccine administration caused no AEFI, but viral vector and nucleic acid vaccine receiver reported AEFI, with systemic AEFI more prevalent than local AEFI. Our study found that COVID-19 vaccines used in Indonesia are safe to use, with no serious AEFI reported. Further research is required to find other factors that influence the AEFI of the COVID-19 vaccine in Indonesia.

CONFLICT OF INTEREST

Protocol used in this study has been ethically approved by the Health Research Ethics Committee of Universitas Nahdlatul Ulama Surabaya (No 243/EC/KEPK/UNUSA/2022).

ACKNOWLEDGEMENTS

The authors would like to thank the Universitas Nahdlatul Ulama Surabaya for the support of this research.

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ORIGINAL ARTICLE

Unmasking domestic violence: Examining victim and perpetrator characteristics and injury patterns in Kuching, Sarawak

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ABSTRACT

Introduction: Domestic violence (DV) is a pervasive social and public health issue affecting millions globally, regardless of age, gender or socioeconomic background. Understanding victim and perpetrators' characteristics as well as the DV injury patterns are essential for developing targeted interventions and prevention strategies. Although past DV studies have often focused on female victims, it is increasingly recognised that DV affects a significant proportion of male victims as well. This study aimed to comprehensively examine both male and female DV victims and perpetrators, as well as the anatomical regions affected in DV cases in Kuching, Sarawak, so that a deeper understanding of DV within this community can be enhanced.

Materials and Methods: This prospective, observational study was conducted from March 2021 to March 2023, involving adult DV victims aged 18 years and above admitted to the One Stop Crisis Center (OSCC) of Sarawak General Hospital. Data were collected from the OSCC clerking sheet, focusing on the victims, perpetrators and the violence characteristics.

Results: A total of 133 DV victims were analysed, with 25.6% being male victims. Although majority of the perpetrators in cases involving male victims were male perpetrators, there was a significantly higher number of female perpetrators in these male DV cases (i.e., 5 out of 34 cases,14.7%) compared to in female DV cases (4 out of 99 cases, 4.0%) ($p = 0.05$). The commonest type of relationship between the victims and perpetrators was spouses or ex-spouses (56.4%). Male victims had more cases involving weapons (67.6%) compared to female victims (26.3%), $p < 0.001$. The most affected anatomical region was the head and neck (63.9%) region although no significant differences were observed.

Conclusion: The study reveals that DV affects individuals across all societal classes and income groups. Although weapons were used more frequently in male DV cases, other injury characteristics and affected anatomical regions were not significantly different between genders, suggesting female perpetrators can inflict similar injuries as male perpetrators. Subgroup analysis showed that the majority of male victims faced abuse from their children or grandchildren, hinting at hidden geriatric abuse, that should be unmasked and treated as a separate entity.

KEYWORDS:
Domestic violence, victim-perpetrator relationships, male victims, victim characteristics, perpetrator characteristics

INTRODUCTION

Domestic violence (DV) is a pervasive and devastating social and public health issue that affects millions of individuals worldwide, regardless of age, gender, race, religion or socioeconomic background.[1-3] Despite the growing awareness and efforts to address DV, it remains a complex and often hidden problem that lurks frequently behind closed doors.[1] The consequences of DV may extend beyond the immediate victims, impacting family members, children, friends and even employers and co-workers as well.[1]

Understanding the characteristics of victims and perpetrators in DV cases, as well as the anatomical regions where the injuries are inflicted, is crucial for developing targeted interventions, support services and prevention strategies tailored to victims' specific needs. Raising societal awareness of the negative consequences of DV for example, can help survivors, not only to openly discuss their experiences and seek support, but can also encourage those who are suffering in silence to recognise the abuse they are experiencing.[3] Indeed, the World Health Organisation (WHO) emphasises the critical role that the healthcare providers play in DV prevention and education.[3] Unfortunately, comprehensive information on the profiles of victims and perpetrators as well as the associated DV injury patterns are not readily available in many regions, including in Malaysia.[4]

In the Malaysian context, Awang and Hariharan[5] had examined the socioeconomic characteristics of DV victims and perpetrators, the nature and types of violence as well as the frequency of incidents based on secondary data obtained from the Women's Aid Organisation (WAO) Malaysia from 2002 to 2005. Their findings revealed that out of the 162 cases analysed, nearly half of the victims were in their 30s, while 33% were 29 or younger. Similarly, over half of the

This article was accepted: 18 February 2024
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perpetrators were in their 30s. However, the study by Awang and Hariharan[5] only focused on female DV victims and did not include male victims in its analysis.

Indeed, DV narrative has often been viewed from a female-gendered lens.[6,7] In reality, however, it is increasingly recognised that DV can affect a substantial proportion of male victims as well. For example, Truman and Morgan[8] reported that, whilst the frequency of severe DV involving female victims can be as high as 25%, one in nine men were also reported to have experienced some forms of DV with serious consequences including injury, fearfulness and post-traumatic stress disorder. Despite that, in contrast to cases involving female DV victims, cases involving male DV victims are rarely researched.

Hence, there is an urgent need for a comprehensive study examining the characteristics of victims and perpetrators in DV cases across both genders, as well as the anatomical regions affected by these injuries. This study aimed to address this literature gap in order to contribute to a deeper understanding of DV within our community in Kuching, Sarawak.

MATERIALS AND METHODS

This was a prospective, observational design conducted from March 2021 to March 2023 in One Stop Crisis Center (OSCC) of Sarawak General Hospital (SGH). OSCC is defined as a multidisciplinary, health-system oriented centre that delivers healthcare services as well as a combination of social, legal and shelter support services to victims of domestic violence, child abuse, rape and sexual abuses.[9]

Participants

Participants of this study were all adult DV victims aged 18 years and above admitted to the OSCC of SGH during the study period. Victims who were haemodynamically unstable at the time of admission and cases involving rape or statutory rape, as defined under Section 375 of the Malaysian Penal Code (and not under the Domestic Violence Act or Act 521), were excluded.

Materials

All data needed in this study were obtained from the OSCC clerking sheet. The data can be categorised in to three sections, i.e., (1) characteristics of victims, (2) characteristics of the main perpetrator and (3) characteristics of the violence.

For the characteristics of victims, the variables obtained were the gender, age, monthly income and educational level. For the characteristics of the main perpetrator (defined as the individual perceived by the victim to have inflicted the most significant injuries and trauma, in instances involving multiple perpetrators), the data obtained were the gender of the main perpetrator and their relationship to the victim, such as spouse or ex-spouse, parent, child or grandchild, other relatives, or non-spousal intimate partners. For the characteristics of the abuse, data obtained were: (1) whether the victim was restrained or not, (2) whether the victim put up resistance or not and (3) whether a weapon was used or not during the violence. The anatomical regions inflicted during the violence were categorised as head and neck, trunk, right and left upper limbs and right and left lower limbs regions.

Procedure

Upon obtaining informed consent from the DV victims, data from the OSCC clerking sheet at SGH were manually entered into a separate data collection form specifically designed for this study. No additional face-to-face interview was necessary. The medical research ethics approval from the Malaysian Medical Research and Ethics Committee (NMRR-20-1437-5483; https://nmrr.gov.my/) was obtained before starting this study.

RESULTS

A total of 133 DV victims in OSCC of SGH between March 2021 to March 2023 were included in the analysis. Of these, 34 (25.6%) were male and 99 (74.4%) were female victims. The median age of the entire cohort of victims was 35 years. Mann-Whitney U test revealed that the median age for male victims (42.5 years) was statistically higher than that for female victims (34.0 years), $U = 1151.5$, $z = -2.74$, $p = 0.01$.

Regarding perpetrators' gender, majority were male perpetrators (124 or 92.8%), while only nine (6.8%) were female perpetrators. Similar to cases involving female victims, majority of the perpetrators in male victim cases were also caused by male perpetrators (with 96.0% and 83.5%, respectively). However, the number of female perpetrators in cases of male victims was statistically higher than the number of female perpetrators in cases of female victims, i.e., five out of 34 cases (14.7%) and four out of 99 cases (4.0%), respectively, $p = 0.05$.

The relationships of the main perpetrator with the victim were as follows: the majority of these perpetrators were: (1) spouses or ex-spouses (75 cases or 56.4%), followed by their (2) siblings (20 cases, 15.0%), (3) children or grandchildren (18 cases, 13.5%), (4) relatives (8 cases or 6.0%), (5) non-spousal partners (such as cohabiting boyfriends, girlfriends, fiancé, etc) (7 cases, 5.3%) and (6) parents (5 cases, 3.8%).

Fisher's exact test was used to analyse the relationships of the main perpetrator with the victims according to the victims' gender, revealing statistically significant differences between the groups ($p < 0.001$). Post hoc analysis involved pairwise comparisons using multiple Fisher's exact tests (2×2), and statistically significant differences were noted between (1) the 'spouse/ex-spouse' and 'siblings' groups, (2) the 'spouse/ex-spouse' and 'children or grandchildren' groups, (3) the 'spouse/ex-spouse' and 'relatives' groups, (4) the 'siblings' and 'non-spousal partners' groups and (5) the 'children or grandchildren' and 'non-spousal partners' groups, all with $p < 0.001$.

With regards to whether the perpetrator had used weapons during the abuse, significantly more cases with weapons were observed in male victim cases (23 out of 34, 67.6%) than in female victim cases (26 out of 99, 26.3%), $p < 0.001$.

The most affected anatomical region was the head and neck region (happened in 85 out of 133 cases or 63.9%), followed

Table I: Analysis of relationships of main perpetrators with victim according to victim's gender

	Victim's gender		*p*-value
	Male (n = 34)	Female (n = 99)	
Victim's age in years (range)	42.5 (19 - 66)	34.0 (18 - 73)	0.01**
Victim's income level			0.32
Median income (RM per month)	RM1150	RM1000	
Income range (RM per month)	RM0 – RM5000	RM0 – RM21000	
Victim's educational level	0.33**		
No formal education	0	1 (1.0%)	
Primary school	7 (21.2%)	9 (9.3%)	
Secondary school	22 (66.7%)	62 (63.9%)	
Pre-university/diploma	2 (6.1%)	17 (17.5%)	
Bachelor degree and above	2 (6.1%)	4 (4.1%)	
Postgraduate degree	0	2 (2.1%)	
Professional qualification	0	2 (2.1%)	
Missing data	1	2	
Number of perpetrators			0.23**
1	31 (91.2%)	96 (97.0%)	
2	3 (8.8%)	2 (2.0%)	
3	0	0	
4	0	1 (1.0%)	
Main perpetrator's gender			0.05**
Male	29 (85.3%)	95 (96.0%)	
Female	5 (14.7%)	4 (4.0%)	
Perpetrator who used alcohol/illicit drug during the abuse	1 (2.9%)	1 (1.0%)	0.45**
Relationship of main perpetrator with the victim			<0.001**
Spouse	4 (11.8%)	71(71.7%)	
Parents	1 (2.9%)	4 (4.0%)	
Sibling	13 (38.2%)	7 (7.1%)	
Children or grandchildren	12 (35.3%)	6 (6.1%)	
Relatives	4 (11.8%)	4 (4.0%)	
Non-spousal partners	0	7 (7.1%)	
Characteristics of abuse			
Weapons used during abuse	23 (67.6%)	26 (26.3%)	<0.001***
Put up resistance during abuse	25 (73.5%)	57 (57.6%)	0.10***
Victim was restrained during abuse	2 (5.9%)	3 (3.0%)	0.60**
Injury patterns:			
Anatomical regions of injuries			
Head and neck	21 (61.8%)	64 (64.6%)	0.84***
Trunk (front)	3 (8.80%)	6 (6.10%)	0.69**
Trunk (back)	4 (11.80%)	12 (12.10%)	0.99**
Left upper limb	12 (35.30%)	27 (27.30%)	0.39***
Right upper limb	10 (29.40%)	27 (27.30%)	0.81***
Left lower limb	2 (5.90%)	10 (10.10%)	0.73**
Right lower limb	4 (11.80%)	8 (8.10%)	0.52**

*Note: As one or more cells have expected count of less than 5, Fisher-exact test was used for this analysis.

by the left upper limb (39 out of 133 cases, 29.3%) and the right upper limb (37 out of 133 cases, 27.8%). No statistically significant differences were observed in all anatomical regions when analysed according to the victims' gender as well as the perpetrators' gender.

Subgroup analysis of the 34 male DV victims revealed that in merely four out of 34 cases (11.8%), the perpetrators were their spouses. Surprisingly, majority of these cases involved siblings (13 out of 34 cases, 38.2%) as well as children or grandchildren (12 out of 34 cases, 35.3%) as the perpetrators. In another four cases (11.8%), the perpetrators were relatives of the victims, and in one case (2.9%), the perpetrator was the parent. Among these 12 cases of male DV abused by their children or grandchildren, the youngest of these victims is 40 years old, while the oldest victim is 66 years old. The detailed results of the victims' characteristics, perpetrators' characteristics and injury patterns analysed according to victim's gender are given in Table I.

DISCUSSION

Findings from this study suggest that DV can affect individuals from all societal classes, transcending income groups and educational backgrounds. This is evidenced from the fact that although the median income of DV victims in this study (RM 1150 per month for male victims and RM 1000 per month for female victims) was below the minimum wage of Malaysia in 2022 (i.e., RM 1500 per month),10 the range of income of our victims varied considerably from no income at all to earning more than RM20,000 per month for female victims and RM5,000 per month for male victims. In other

words, although lower-income earners are more likely to suffer from DV,[11] in reality, DV victims can be found in all socio-economic classes.[12]

Other than the findings that weapons were significantly used in male DV victims, other characteristics (i.e., whether the victim was restrained during abuse or not and whether the victim put up resistance or not during abuse) as well as the anatomical regions affected were not significantly different between the gender of the victims, suggesting that the female perpetrators are capable to inflict similar intensity and pattern of injuries compared to male perpetrators. Indeed, only a few past studies have been published comparing male and female perpetrators. In the review by Swan et al,[13] it was shown that women can be just as likely as men to perpetrate physical violence, and some studies even reported a higher prevalence of physical aggression committed by women. Unfortunately, male victims tend to underreport violent offenses due to feelings of shame, fear, perceptions that the injuries were minor enough to be ignored, as well as a lack of information and appropriate support rendered to them.[14] Consequently, we believe that the cohort of our DV cases in Sarawak may also contain underreporting from male victims who might be reluctant to report incidents due to feelings of shame and embarrassment. Unsurprisingly, the head and neck region, due to its exposure and vulnerability, was found to be the most commonly inflicted region in DV, a finding that was also identified in a systematic review on the anatomical regions of elderly abuse.[15]

Another key insight that can be gleaned from this study is the finding that as many as one in four DV victims in our population were male victims. Unfortunately, many past research on DV had predominantly focused on female victims despite the fact that men can also be DV victims, experiencing both physical and psychological abuse caused their female partners as the perpetrators.6 In fact, one of the main reasons men do not report abuse is the belief that the authorities such as the police would downplay its severity and would not take any serious action.16 Hence, there is a need for society to be aware that DV cases affecting, as well as avoiding judgmental attitudes so that male victims may feel safe to report such incidents.[6]

More importantly, the subgroup analysis performed on the male victims of DV alone revealed that the majority of perpetrators were not their spouses, but rather their children or grandchildren. This suggests that cases of geriatric abuse may be hidden under the facade of DV. This possibility was further indicated by the fact that the age of male and female victims in this study was as old as 66 and 73 years old, respectively. The global prevalence of geriatric abuse is estimated to be around 15.7%.[17] In Malaysia it was found that the mean age of elder abuse victims was 70 years[18] whilst specifically for Sarawak, it was most prevalent among those aged 60 to 69 years,[19] both of which are consistent with the finding of this current study.

This study has several pertinent limitations that should be mentioned. First, the participants in this study were recruited exclusively from DV victims admitted to OSCC, SGH. Hence, our sample may only be representative of DV cases from the Kuching and Kota Samarahan divisions and may not be reflective of DV cases from the entire state of Sarawak nor Malaysia as a whole. Second, the study only included DV victims who were admitted the OSCC, potentially overlooking those who suffered in silence and did not report their experiences. Furthermore, DV encompasses not only physical violence but also psychological, sexual and now even include economic abuse as well. Therefore, our data may not capture cases primarily characterised by psychological violence or economic abuse (with less physical violence), as victims who step forward to seek assistance are primarily doing so due to the perceived severity of the physical violence that they experience. Additionally, the study may also have excluded cases where the violence was predominantly sexual in nature, as sexual abuses particularly for rape, statutory rape, and sodomy are legally classified as separate entities in Malaysia. Another limitation of the study is that it only collected personal details of the main perpetrator, neglecting information on secondary, tertiary or other additional perpetrators. Furthermore, we only captured data on whether weapons were used or not, but we did not capture the specific details regarding the types of weapons used (e.g., blunt or sharp objects). Lastly, our study also did not record the specific types of wounds (bruises, abrasions, haematomas, lacerations, etc.) sustained by the victims, as we focused only on the anatomical regions affected.

Despite its limitations, we believe that the findings from this study call for the implementation of comprehensive strategies to improve our support systems, awareness education initiatives as well as reporting mechanisms for all DV victims in Malaysia. Notably, as it is revealed that as one in four DV victims in our study population were male, this emphasises the need for increased awareness and support for male victims. Additionally, the fact that there were no significant differences in terms of the anatomical regions affected between male and female perpetrators suggests that both genders are capable of inflicting similar patterns of injuries. This underscores the necessity of addressing DV issue inclusively, regardless of the perpetrator's gender.

CONCLUSION

This study highlights the importance of recognising domestic violence (DV) as a complex issue affecting individuals across all the societal classes, income groups and educational backgrounds. As such, inclusive support services and educational programs that address the diverse backgrounds of DV victims are needed. Furthermore, this sutdy also sheds light on the potential prevalence of geriatric abuse hidden within these DV cases, as the majority of male victims were abused by their children or grandchildren rather than spouses. Inclusive awareness campaigns that can challenge stereotypes about DV victims, are needed.

ACKNOWLEDGEMENT

The authors acknowledged the support from the Ministry of Higher Education Malaysia through Fundamental Research Grant Scheme (FRGS) (no: FRGS/1/2020/SKK06/UNIMAS/01/1). The authors also acknowledged the help given by Miss Mandy Jing Ying Ang in formatting the manuscript.

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Endoscopic sphincterotomy with balloon dilatation versus sphincterotomy alone for common bile duct stones removal: a randomised controlled trial

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ABSTRACT

Introduction: Endoscopic sphincterotomy (EST) plus endoscopic papillary large balloon dilatation (EPLBD) has been reported as a valid alternative to EST alone in removing common bile duct (CBD) stone. The aim of this study is to compare efficacy, and safety of these two groups of patients in removing CBD stone in Hospital Universiti Sains Malaysia (HUSM).

Materials and Methods: This is a prospective single centre randomised single blinded comparative study conducted in HUSM. The primary endpoints for this study are the overall complete stone clearance rate and complication rate, while the secondary outcome for this study are duration of procedure and rate of usage of adjunct methods. Objective data analysis is conducted using independent sample t-test and chi-squared test.

Results: A total of 66 patients underwent endoscopic retrograde cholangiopancreatography (ERCP) for choledocholithiasis which is CBD stone. 34 patients were allocated to EST plus EPLBD arm (n=34), and 32 patients were in EST alone arm (n=32) using randomisation method. For intention to treat, patients from EST alone arm that unable to achieve complete stone clearance will be switched to EST plus EPLBD arm. The overall complete stone removal rate for both groups were comparable (EST plus EPLDB: 100% versus EST alone: 93.8%; p= 0.139). The two patients from EST alone group (6.2%) that unable to achieve complete stone clearance were converted to EST plus EPLBD group for intention to treat and able to achieve complete stone clearance by EST plus EPLBD. For procedural time, both arms are comparable as well (EST plus EPLDB: 15.8 minutes vs EST alone: 15.5 minutes; p= 0.860). Complications such as pancreatitis occurred in one patient in EST plus EPLBD arm (EST plus EPLDB: 2.9 % vs EST alone: 0 %; p= 0.328), and bleeding occurred in one patient in EST alone arm (EST plus EPLDB: 0 % vs EST alone: 3.1 %; p= 0.299) , but it is not statistically significant. No perforation or cholangitis complication occurred in both groups. No adjunct usage was observed in both groups.

Conclusion: In this study with limited sample size, both EST plus EPLBD and EST alone are effective and has comparable procedural time in removing CBD stone. Even though both methods are equally effective, EPLBD plus EST is an alternative solution if complete stone clearance is unable to achieve via EST alone.

KEYWORDS:
Endoscopic sphincterotomy; balloon dilation; common bile stone; choledocholithiasis

INTRODUCTION

Endoscopic sphincterotomy (EST) is the most widely used procedure during endoscopic retrograde cholangiopancreatography (ERCP) to remove the common bile duct (CBD) stone and considered as a standard therapy for treatment of choledocholithiasis. However, in view of EST requires an adequate incision on major duodenal papilla to achieve biliary cannulation, it can potentially cause damage to biliary sphincter during the procedure and potentially increased risk of some complications such as bleeding and biliary reflux.[1] This procedure carries risk of complications such as haemorrhage, perforation and long-term effect like sphincter dysfunction.[2]

Staritz et al.[3] introduced a method called endoscopic papillary large balloon dilatation (EPLBD) in 1983 as an alternative to EST in clearing CBD stone. EPLBD can reduced the risk of bleeding and perforation post procedure, but it carries higher risk of post-ERCP pancreatitis.[4-6]

About 10 to 15% of CBD stone are unable to be extracted by both EST or EPLBD alone, especially in those patients with big and difficult stone (size bigger than 10 to 15mm, numerous, barrel-shaped, and impacted stones).[7] Besides that, other factors that can contribute to failure of stone extraction are periampullary diverticulum or post operative variation, tortuosity and tightening of distal common bile duct.[8]

In 2003, combination of EST and EPLBD was introduced as an alternative method.[9] It can reduce the risk of complications through avoiding a complete sphincterotomy, shortened procedure time and reducing the need of usage of mechanical lithotripsy.[10]

A study in 2007 showed that EST plus EPLBD had comparable efficacy and safety when compared to conventional EST

This article was accepted: 18 February 2024
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alone and both groups had similar complication rate.[10] Besides that, in a recent study in 2020, it was shown that EST plus EPLBD had a comparable efficacy when compared with EST alone in clearing CBD stones and EST plus EPLBD required shorter procedural time when compared with EST alone.[11] While, a randomised controlled study in 2017 showed that EST plus EPLBD is more effective than the EST alone in clearing large CBD stones and is equally safe compared to EST alone.[12] In another randomised controlled trial in 2013, the study showed that the success rate for complete CBD stone removal in first session is higher in EST plus EPLBD group than the EST alone and it was statistically significant.[13] Apart from that, there are many other studies have suggested EST plus EPBD as a safe and promising alternative to conventional EST or EPLBD.[14-16] In a published meta-analysis, accumulated data showed that EST plus EPLBD is a safe and effective procedure in removing large or difficult CBD stone without any additional risk of complications.[17]

There is still no definite conclusion in evaluating superiority of EST plus EPLBD vs EST alone in term of efficacy in removing CBD stone.

Thus, in this study, our primary outcome is to compare the overall complete stone clearance rate and complication rate for both arms, while the secondary outcomes are the duration of procedure and rate of usage of adjunct methods.

MATERIALS AND METHODS

This is a single centre, randomised controlled trial that was conducted in Hospital Universiti Sains Malaysia (HUSM). Patient with CBD stone who seek treatment at HUSM from June 2021 to June 2022 and fulfilled the inclusion criteria will be recruited into the study.

This study had obtained approval from ethical committee board (JEPEM) from Universiti Sains Malaysia.

The inclusion criteria for this trial are patients with CBD stone as evidenced on imaging studies who are more than 18 years old. While the exclusion criteria are CBD stone size exceeding 15mm, number of CBD stone exceeding three, concurrent hepatobiliary tumour, patient with intrahepatic stone, patient with bleeding tendencies (coagulopathy, thrombocytopenia, patient on anticoagulant medication), patient in sepsis, cholangitis patient, patient with concurrent acute pancreatitis and history of patient with Bilroth II or Roux-en-y surgery.

Sample Size Estimation

Assuming a 22.1% difference in CBD stone clearance rate in one endoscopic session with 74% in conventional group (EST alone) and 96.1% in EST plus EPLBD based on the previous positive series by Karsenti et al.[12] in 2017, with the usage of power and sample size programme, under Dichotomous test for sample size Design: independent, prospective, two proportion study, uncorrected chi-square test, with type 1 error of 0.05 (2-sided) and a power of 80%, P0 of 0.74, P1 of 0.961 and m=1, the sample size needed is 40 for each arm.
Add on 10% dropout : 40 +4 = 44 for each arm.

Final sample size = 88

Randomisation and Data Collection

Based on the sample size calculation, our required sample size was 88. But we were not able to achieve sample size of 88 on designated timeline (June 2021 to June 2022) due to inadequate number of patients undergone elective ERCP for choledocholithiasis in view of Malaysia movement control order (MCO) due to Covid-19 pandemic situation in Malaysia during that time. We managed to recruit 66 patients with CBD stone who meet all the inclusion criteria from period of June 2021 to June 2022. Written consent was taken from each of the patient.

A computer software for sequence generation was used and applied with 1:1 allocation using random block sizes of 6 and 8 to Group A: EST plus EPLBD or Group B: EST alone. The allocation concealment mechanism was developed by preparing equal numbers of sealed and opaque envelopes. Each envelop contain one allocation sequence which is generated by computer software. Data collection officer will randomly open one of the envelop each time one patient recruited and will need to follow the allocation sequences inside the envelop to determine whether the patient to be Group EST plus EPLBD or Group EST alone. This is single blinded study whereby the participant is blinded but the endoscopist is not blinded.

On the designated timeline, we are only able to recruit 66 patients out of 88 patients. As randomisation were already completed previously using computer software for sequence generation and allocation concealment mechanism for 88 patients with 88 sealed opaque envelopes, there were only 66 envelopes used. Thus, based on the randomisation method used above, there were 34 patients in EST+EPLBD arm and 32 patients in EST alone arm.

There is possibility of crossover of both arm in this study in which failure to clear all stone in EST alone will be proceeded with EST+EPLBD.

Participants were admitted 1 day prior to the procedure and were monitored in ward for at least 1 day after the procedure for any complication post procedure. Total duration of involvement were at least 72 hours.

Procedure/Intervention

All the cases were done by one consultant hepatobiliary surgeon, with more than 5 years of experience in the field. ERCP was achieved with endoscopic side-viewing (Olympus Optical Co). Medications was given according to type of anaesthesia (local anaesthesia/monitored anaesthesia care/general anaesthesia) with or without the help of anaesthetist. In case of patient for ERCP under local anaesthesia, midazolam and pethidine and/or fentanyl were the preferred medications in our centre.

The initial cholangiogram was taken after cannulation of CBD.

In EST alone group: EST was extended to the full length of major duodenal papilla, but not exceeding the major duodenal horizontal fold avoiding crossing the intramural part of the CBD.

In EST plus EPLBD group: The length of the sphincterotomy was limited to one third the length of sphincterotomy of EST alone group. EPLBD with a balloon catheter (controlled radial expansion (CRE) wire-guided biliary dilation balloon catheter, Boston Scientific) was performed. The extent of balloon dilation was determined according to the size of the stones. The balloon was inflated slowly (1 – 2 minutes) under endoscopic and fluoroscopic guidance and was deflated immediately after the disappearance of the balloon waist.

After intervention done in both groups, conventional extraction balloon was trawled, and stone was removed from the bile duct.

Operational Definition
CBD complete stone clearance: no residual stone on cholangiogram in one endoscopic session (either via EST alone or EST plus EPLBD)

Duration of procedure: Defined as the duration of time from starting of intervention (EST alone or EST +EPLBD) until complete stone clearance as evidenced in cholangiogram.

Number of attempts: Defined as number of attempts of trawling that conventional retrieval balloon needed after intervention done (EST alone or EST +EPLBD) to remove CBD stone.

Post ERCP pancreatitis: Persistent abdominal pain more than 24 hours after ERCP and associated with rise of serum amylase more than three times of the upper normal limit.[18]

Haemorrhage: Evidence of bleeding such as melena or hematemesis with drop in at least 2g/dl of haemoglobin concentration or need for a blood transfusion.[1]

Cholangitis: Fever in which temperature > 38°C accompanied by leucocytosis and right upper quadrant abdominal pain after the procedure, without concomitant evidence of acute cholecystitis.[1]

Statistical Analysis
Statistical analysis was performed using SPSS version 26.0. Comparison of primary and secondary endpoints was done using independent t test and chi-square test. P-value of <0.005 is considered significant.

RESULTS

A total of 66 patients were recruited and successfully randomised using computer software into two groups, group A for EST+EPLBD arm and group B for EST alone arm.

For baseline characteristics and demographic date of patient, mean age of study participants was 46.7 years, with group A patients had mean age of 45.5 years, while group B had mean age of 48 years. In term of gender, group A: EST+EPLBD arm included 24 female patients (70.6%) and 10 male patients (29.4%), while for group B: EST alone arm included 23 female patients (71.9%) and 9 male patients (28.1%). In group A, 15 patients (44.1%) had history of laparoscopic cholecystectomy, while, in group B, 16 patients (50%) had history of laparoscopic cholecystectomy. In term of previous history of ERCP, in group A, 28 patients (82.4%) had previously undergone ERCP, while in group B, 23 patients (71.9%) had previously undergone ERCP.

The demographic data of all the participants are summarised in Table I.

For pre-ERCP blood investigations, both arms of patients had normal blood investigations in full blood count, renal function test, coagulation profile and liver function test.
The pre-ERCP blood investigations result is summarised in Table II.

For the post ERCP data, 44 study participants (66.7%) had procedure (EST plus EPLBD or EST alone) done via local anaesthesia, while 22 study participants (33.3%) had procedure done via general anaesthesia. In terms of ampulla anatomy, 27 patients (79.4%) in group A: EST plus EPLBD had normal ampulla anatomy, while 26 patients (81.3%) in group B: EST alone arm had normal ampulla anatomy (p: 0.524). In terms of mean common bile duct (CBD) diameter, there is noy statistically difference in mean CBD diameter in both groups. Group A patients had mean CBD diameter of 9.4 mm as compared to group B patient which had mean CBD diameter of 9.6 mm (p = 0.862). In terms of number of CBD stone, 55.9% of patients in group A had three CBD stone, while 40.6% of patients in group B had two CBD stone (p = 0.113). In addition, there is not statistically difference in largest size of CBD stone in both groups. Group A patients had largest CBD stone size of 7.6mm while group B patients had largest CBD stone size of 7.0 mm (p = 0.445).

Comparison of overall complete stone clearance rate in Group A: EST plus EPLBD versus Group B: EST alone arm
Group A patients achieved overall 100% complete stone clearance rate (n = 34), while group B patients achieved 93.8% overall stone clearance rate (n = 32), but it is not statistically significant (p = 0.139). Two patients from group B: EST alone arm unable to the had complete stone clearance thus, was being converted to EST plus EPLBD with intention to treat and able to achieve complete stone clearance. In term of number of attempts of trawling for conventional balloon retrieval needed for complete stone clearance, 41.2% of patient from group A required single trawling attempt of conventional balloon retrieval while 28.1% of patients from group B required two trawling attempts of conventional balloon retrieval to remove the CBD stone completely after the intervention (p = 0.523).

Comparison of Duration of Procedure in Group A: EST plus EPLBD versus Group B: EST Alone Arm
The duration for both procedures is almost similar, with 15.8 minutes for EST+ EPLBD and 15.5 minutes for EST alone (p= 0.860).

Comparison of Rate of Adjunct Usage Among Patients in Group A: EST plus EPLBD versus Group B: EST Alone
There was no usage of adjunct in both groups of study.
Post ERCP data of both groups of study are summarised in Table III.

Table I: Demographic data among patients with common bile duct stone in Hospital Universiti Sains Malaysia (n=66)

Characteristics	Frequency (%)			*p*-value[a]
	All (n=66)	Group A EST + EPLBD (n=34)	Group B EST only (n=32)	
Age (years)*	46.7 ± 13.57	45.5 ± 12.64	48.0 ±14.46	0.462[b]
Gender				
Male	19 (28.8)	10 (29.4)	9 (28.1)	0.908
Female	47 (71.2)	24 (70.6)	23 (71.9)	
Ethnicity				
Malay	62 (93.9)	31 (91.2)	31 (96.9)	0.332
Chinese	4 (6.1)	3 (8.8)	1 (3.1)	
History of cholecystectomy				
Yes	31 (47.0)	15(44.1)	16 (50.0)	0.632
No	35 (53.0)	19 (55.9)	16 (50.0)	
History of ERCP				
Yes	51 (77.3)	28 (82.4)	23 (71.9)	0.310
No	15 (22.7)	6 (17.6)	9 (28.1)	

*Presented in mean ±SD, SD= standard deviation
[a]Chi-square test was applied, bIndependent t test was applied, significant set at 0.05

Table II: Pre-ERCP lab investigation among patients with CBD stone in HUSM (n=66)

Characteristics	Mean (SD)			*p*-value[a]
	All (n=66)	EST + EPLBD (n=34)	EST only (n=32)	
TWC	8.6 ±2.15	8.6 ±2.13	8.5 ±2.21	0.966
Platelet	269.2±78.78	283.0 ±74.56	254.9 ±81.61	0.152
INR	1.1 ±0.35	1.0 ±0.08	1.1 ±0.50	0.142
APTT	38.1 ±7.50	38.7 ±10.04	37.4 ±3.16	0.515
Serum urea	7.0 ±15.35	7.1 ±19.28	7.0 ±9.92	0.983
Serum creatinine	69.6 ±17.48	70.7 ±15.34	68.3 ±19.67	0.578
Total bilirubin	15.4 ±18.80	12.8 ±13.05	18.2 ±23.51	0.267
Albumin	41.2 ±3.79	41.5 ±4.29	40.8 ±3.22	0.466
ALP	125.8 ±63.8	126.6 ±59.63	125.0 ±68.96	0.920
AST	38.8 ±44.26	41.6 ±51.95	35.7 ±34.86	0.588
ALT	60.3 ±97.88	71.1 ±118.14	48.7 ±70.44	0.357

All data presented in mean± SD, SD= standard deviation
[a] Independent t test was applied, significant set at 0.05

Table III: Post-ERCP among patients with CBD stone in HUSM (n = 66)

Characteristics	Frequency (%)			*p*-value[a]
	All (n=66)	EST + EPLBD (n=34)	EST only (n=32)	
Type of anaesthesia				
LA	44 (66.7)	22 (64.7)	22 (68.8)	0.728
GA	22 (33.3)	12 (35.3)	10 (31.3)	
Ampulla anatomy				
Normal	53 (80.3)	27 (79.4)	26 (81.3)	0.524
Floppy	12 (18.2)	7 (20.6)	5 (15.6)	
Diverticulum	1 (1.5)	0 (0.0)	1 (3.1)	
CBD diameter (mm)*	9.5 ±3.49	9.4 ±3.66	9.6 ±3.36	0.862[b]
Number of stones				
1	16 (24.2)	9 (26.5)	7 (21.9)	0.113
2	19 (28.8)	6 (17.6)	13 (40.6)	
3	31 (47.0)	19 (55.9)	12 (37.5)	
Largest size of stone (mm)*	7.3 ±2.78	7.6 ±2.61	7.0 ±2.97	0.445[b]
Stone clearance				
Complete	64 (97.0)	34 (100.0)	30 (93.8)	0.139
Incomplete	2 (3.0)	0 (0.0)	2 (6.3)	
Number of attempts				
1	22 (33.3)	14 (41.2)	8 (25.0)	0.523
2	15 (22.8)	6 (17.6)	9 (28.1)	
3	14 (21.2)	7 (20.6)	7 (21.9)	
More than 3	15 (22.7)	7 (20.6)	8 (25.0)	
Duration of the procedure (minutes)*	15.6 ±6.75	15.8 ±5.58	15.5 ±7.89	0.860[b]

*Presented in Mean ±SD, SD= standard deviation
[a]Chi-square test was applied, [b]Indipendent t test was applied, significant set at 0.05

Table IV: Complications Among Patients with CBD stone in HUSM (n=66)

Complications	Frequency (%)		*p*-value[a]
	EST + EPLBD (n = 34)	EST only (n = 32)	
Pancreatitis			
Yes	1 (2.9)	0 (0.0)	0.328
No	33 (97.1)	32 (100.0)	
Bleeding			
Yes	0 (0.0)	1 (3.1)	0.299
No	34 (100.0)	31 (96.9)	

[a]Chi-square test was applied, significant set at 0.05

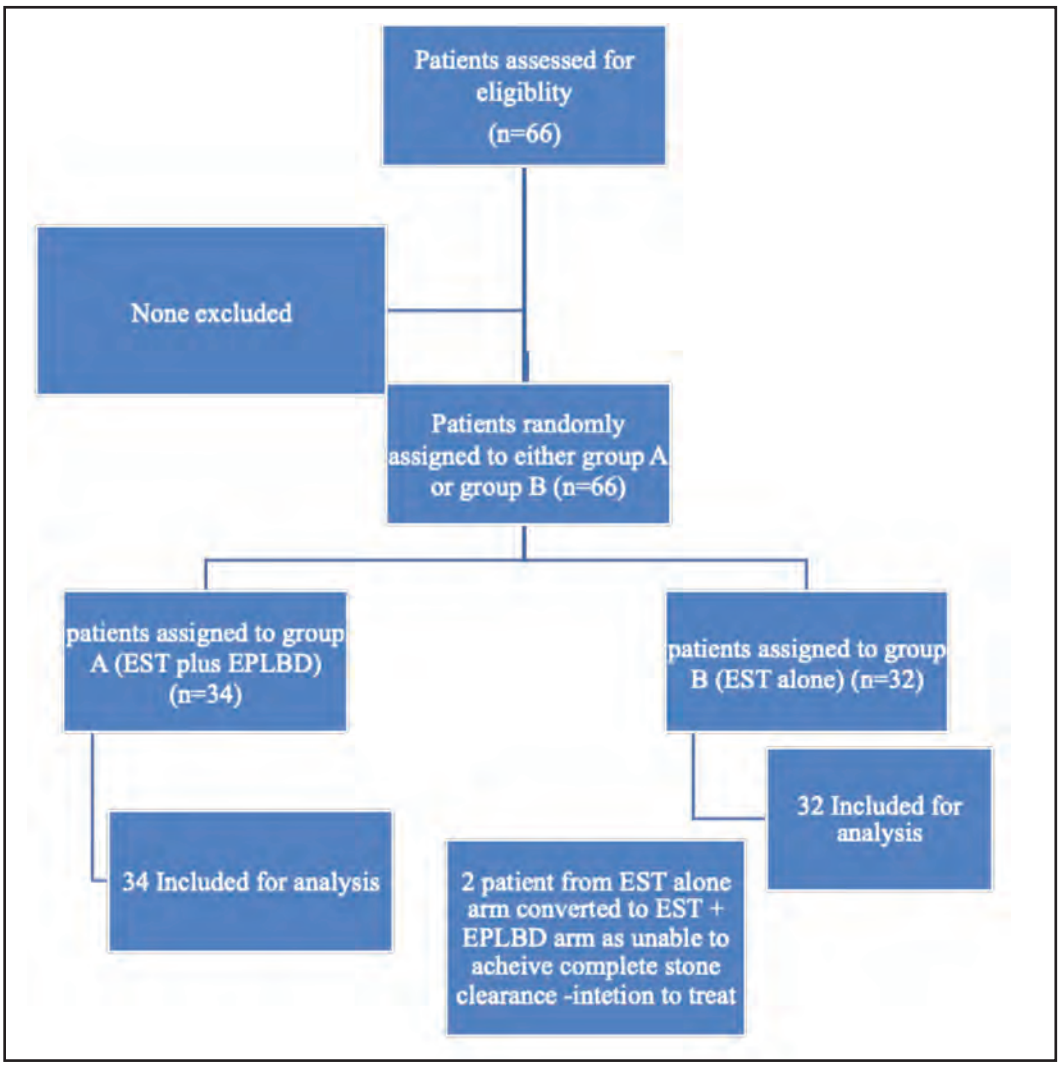

Fig. 1: Consort flowchart

Comparison of complications among patients in Group A: EST plus EPLBD versus Group B: EST Alone

In general, there were only two cases of complication reported among patients in both groups of study. One patient from group A (2.9%) developed pancreatitis, while one patient from group B (3.1%) developed bleeding post procedure. There was no significant difference of complication between EST+ EPLBD and EST alone (p value >0.05).

There was no cholangitis or perforation complication happened in both groups.

Complications rate of both groups of study are summarised in Table IV.

DISCUSSION

Gallstone is a worldwide clinical problem which is affecting most of the populations with incidence of 15 to 20% in west

and 10% in Asians.[19] About 5 to 15% of patients with gallstones will go on to develop bile duct calculi.[20] Complications of bile duct stone can be devastating including pain, complete or partial biliary obstruction leading to obstructive jaundice, cholangitis, hepatic abscess, pancreatitis, and secondary biliary cirrhosis.[21] Thus, due to these serious complications, there are several endoscopic strategies developed for treatment of common bile duct stone that are EST alone, EPLBD and combination of EST plus EPLBD.

The development of EST occurred in 1974.[22] It is the most common procedure used during ERCP to remove CBD stone and is considered as standard therapy for treatment of choledocholithiasis.

EST requires an adequate incision on major duodenal papilla to achieve biliary cannulation and thus it can potentially cause damage to biliary sphincter during the procedure and can increase risk of some complications such as bleeding and biliary reflux.[1] Apart from that, it can potentially carry long term effect like sphincter dysfunction.[2] With the loss of sphincter function, it can cause enteric biliary reflux with bacterial colonisation and thus lead to cholangitis and stone formation.[4]

In 1983, a method called EPLBD was introduced and it is an alternative to EST in clearing CBD stone.[3] EPLBD can reduce the risk of bleeding and perforation post procedure, but it carries higher risk of post-ERCP pancreatitis.[4-6] EPLBD is usually only useful in extracting small to moderate sized stone which is less than 10mm.6 About 10 to 15% of CBD stone was unable to be extracted by either EST nor EPLBD alone, especially in patients with large and difficult stone.[7]

In 2003, another method called combination of EST plus EPLBD was introduced as an alternative method to EST alone and EPLBD.[9] It can reduce the risk of complications through avoiding a complete sphincterotomy, shortening procedural time, and reducing the need of usage of mechanical lithotripsy.[10]

As mentioned above, EPLBD alone carries higher risk of post-ERCP pancreatitis.[4-6] EST alone carries higher risk of post-ERCP bleeding.[1] While EST plus EPLBD is useful in dealing with patient with flat ampulla where small sphincterotomy only can be performed.[10]

A meta-analysis done at 2013 to compare efficacy and safety of EST plus EPLBD and EST alone in removing large CBD stone (>15 mm in size), and this study had shown that EST plus EPLBD is equally effective as EST alone in removing large CBD stone and at the same time had lesser perforation risk.[23] However, in this meta-analysis, one of the limitations is this study included two low quality trials and thus vulnerable to bias. Apart from that, one systemic review and network meta-analysis done on 2020, comparing efficacy and safety of EST alone, EST plus EPLBD and EPLBD alone in managing CBD stone and the result showed that EPLBD has highest successful rate in removing CBD stone.[24] So, there is still no definite conclusion based on these two meta-analyses.
Thus, in our study, we aim to compare effectiveness and safety of both arm in removing CBD stone (<15mm in size) as previous meta-analysis only conducted for large CBD stone and still no definite conclusion whether both method is equally effective, or one arm is more effective than another arm.

In our study, EST plus EPLBD group had higher percentage of overall complete stone clearance rate when compared to EST alone group (100% vs 93.8%), but it is not statistically significant (p = 0.139). Our study is in agreement in many other studies in which both EST plus EPLBD groups and EST alone groups have comparable efficacy in removing CBD stone.

In a study conducted in 2007, it was found that EST plus EPLBD had comparable efficacy and safety when compared to conventional EST alone.10 In another study in 2020 by Mustafa et al,[11], it was found that EST plus EPLBD had a comparable efficacy when compared with EST alone. While in another study in 2017 by Karsenti et al,[12], it was found that EST plus EPLBD groups had higher success rate of complete CBD stone removal in first session when compared to EST group alone, but the overall complete stone clearance rate and complication rate were similar in both groups. In our study, those patients who failed to achieve complete stone clearance via EST alone were converted to EST plus EPLBD arm and able to achieve complete stone clearance.

While in terms of procedural time, our study showed that there is no difference in duration of procedure for both EST plus EPLBD and EST alone groups (p = 0.860). This contrasts with the study in 2020 by Mustafa et al,[11] in which in the study, EST plus EPLBD required shorter procedural time.

For this study, it was noted that 77.3% of patient had previous ERCP before, which indicate likely sphincterotomy done during previous ERCP. There is no study done to compare the efficacy of EST plus EPLBD or EST alone in removing CBD stone for patients with prior sphincterotomy versus patient with no prior history of sphincterotomy. However, another study done in 2022 to quantify the effect of previous sphincterotomy on post-ERCP pancreatitis, showed that that the risk of post-ERCP pancreatitis is halved by prior sphincterotomy.[25] In our study, there is one patient from EST plus EPLBD group (2.9%) developed post-ERCP pancreatitis while there is no patient from EST alone group developed post ERCP pancreatitis, however it is not statically significant (2.9% vs 0 ; p = 0.328). This is same with the study by Mustafa et al.[11], in which EST plus EPLBD group did not have increased risk of post-ERCP pancreatitis. In fact, EST plus EPLBD may have a lower chance of post ERCP pancreatitis as EST done prior to EPLBD will cause the separation of biliary orifice from pancreatic duct and can lead the path of balloon dilatation towards CBD rather than pancreatic duct.[26,27]

In addition, none of our patients from EST plus EPLBD group developed post-ERCP bleeding complications as compared to EST alone group in which one patient developed post-ERCP bleeding (0 vs 3.1%; p = 0.299). However, it is not statically significant. In recent randomised controlled trial in 2019, the trial showed that EST alone group have higher post-ERCP bleeding rate compared to EST plus EPLBD.28 In the EST

group, the bleeding rate was like the 1 to 3.0% rates reported by Cotton et al.[1] We believe that the decrease in bleeding episodes in EST plus EPLBD group may be caused by the balloon tamponade placed at the sphincterotomy site during EPLBD.

There is no cholangitis/perforation complication occurred in both groups of study.

LIMITATIONS

One of the limitations of our study is the small sample size that might be too small to detect difference in clinical outcomes such as total procedural time and stone extraction between endoscopic sphincterotomy (EST) plus endoscopic papillary large balloon dilatation (EPLBD) group and EST alone group. Small sample size might also decrease the validity of the study.

Another limitation is the single-centre clinical trial design may produce potential bias.

Besides that, another limitation in the study is only short-term complications was being studied, but not long-term complications such as recurrent common bile duct stone.

Another limitation of this study is cost of study. The cost of EPLBD is higher than EST alone as EPLBD will need a balloon catheter (Controlled Radial expansion (CRE) wire-guided biliary dilation balloon catheter, Boston Scientific).

Perhaps a future study with larger sample size and focusing of comparing long term complications such as recurrent CBD stone in both groups of patients should be carried out.

CONCLUSION

In summary, endoscopic sphincterotomy (EST) plus endoscopic papillary large balloon dilatation (EPLBD) had comparable efficacy rate of removing common bile duct stones when compared with EST alone group, without increasing the procedural time and adverse events. EPLBD plus EST should be considered as an alternative solution if complete stone clearance unable to achieve via EST alone.

ACKNOWLEDGEMENT

All the authors would like to thank the endoscopic staffs, radiographers, operating theatre staff and anaesthesiology department Hospital Universiti Sains Malaysia for their help in completing the study.

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Optimising care: Impact of regular nephrologist appointments on clinical outcome for chronic kidney disease patients in primary care

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ABSTRACT

Introduction: The rise in the cases of chronic kidney disease (CKD) with the increasing prevalence of non-communicable diseases such as type 2 diabetes mellitus and hypertension is a major public health concern in Malaysia. This results in the many cases of chronic kidney disease being managed in primary healthcare clinics. This study examines the pre- and post-clinical outcomes of scheduled nephrologist visits on CKD patients in a primary health care clinic in Ipoh, Perak.

Materials and Methods: This is a retrospective cross-sectional study reviewing the medical records of patients seen by visiting nephrologists from January 2019 to December 2021 in Greentown Health Clinic. The study population are patients with CKD stage 3b, 4 and 5 who are followed up in Greentown Health Clinic. Universal sampling was done, a total of 87 patients reviewed at least once by the visiting nephrologist and with retrievable medical records were included in the study. Those whose medical records were irretrievable were excluded. Blood pressure, urine protein, fasting blood sugar (FBS), glycated haemoglobin (HbA1c), serum creatinine, eGFR and fasting lipid profile (FLP) pre- and post-visits were collected by reviewing patient medical records and laboratory results. The results were then analysed and compared using SPSS version 26.

Results: The median age of patients in this study was 66 years of age, the majority were male patients (54%) and Malay ethnicity (62.1%). Absence of urine microalbuminuria pre and post referral remain the same (n = 11). During pre-nephrologist visits, a higher percentage of patients exhibited moderate (30-300 mg/g) and severe (>300 mg/g) increase in urine albuminuria (15.7% and 7.2%, respectively) compared to the post-referral period. In patients with significant urine protein pre-referral, patient group with urine protein 3+ showed the highest increment of 30.1% (n = 22), in comparison to 19.3% (n = 16) observed during pre-referral. Statistically significant clinical outcomes between pre- and post-referral to the nephrologist include reduction of systolic blood pressure [141±15 mmHg versus 135 ±12 mmHg, p = 0.001] and diastolic blood pressure [median = 80 mmHg (IQR: 10) versus median=71 mmHg (IQR: 17), p < 0.001]. Similarly, total cholesterol [median = 4.4 mmol/L (IQR: 1.4) versus median = 4.0 mmol/L (IQR: 1.5, p = 0.001] and LDL [median = 2.5 mmol/L (IQR: 1.2) versus median = 2.2 mmol/L (IQR: 1.2), p < 0.001)] exhibited statistically significant differences between pre- and post-referral. However, HDL remained unchanged and other outcome variables showed no significant differences.

Conclusion: Incorporating nephrologist visits in primary care seems to have positive impact towards patient clinical outcomes. Results shown in this study can aid other primary care clinics in the decision to initiate nephrologist services in the primary care setting as a multidisciplinary approach to managing CKD patients.

KEYWORDS:
Nephrologist, primary care, chronic kidney disease, blood pressure, cholesterol

INTRODUCTION

Chronic kidney disease (CKD) is a leading public health problem and burden on the healthcare system. The global estimated prevalence of CKD is 13.4% and patients with end-stage kidney disease (ESKD) needing renal replacement therapy are estimated to be between 4.902 and 7.083 million.[1] In Malaysia, a population-based study in 2011 reported that 9.1% of Malaysians have CKD[2] however, by 2018 this figure has rapidly increased to 15.48%.[3] The prevalence of CKD is expected to further rise in the future due to the increasing prevalence of diabetes mellitus, hypertension and the ageing population in Malaysia.[4] A time-series analysis published in 2017 projected the estimated incidence of new dialysis patients in Malaysia from 10,208 in the year 2020 to 19,418 in 2040. Meanwhile, the prevalence of ESKD is estimated to be 51,269 in 2020 and 106,249 in 2040.[5] This is quite worrying as managing CKD will have a significant socioeconomic burden on the national healthcare system.

In Malaysia, the majority of CKD patients are managed at primary healthcare centres under the Ministry of Health (MOH). Early detection of CKD and timely intervention are two important strategies in retarding the disease progression.[4] Studies have shown that early referral to a nephrologist can be lifesaving and also improves patients' quality of life.[6]

An established patient-primary care practitioner-nephrologist relationship can ease the transition to renal replacement therapy in future. One such intervention by MOH Malaysia is the National Action Plan for Healthy Kidneys (ACT-KID) which was developed in 2018. The main

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aim of ACT-KID is to prevent or delay the onset of CKD, improve its management, and establish multidisciplinary collaboration between primary care and nephrologists. These outreach services were made available at 17 primary care clinics nationwide, with Greentown Health Clinic the only centre in Perak state providing this service.[4]

A retrospective study was done in 2020 at Greentown Health Clinic, to evaluate the outcome of patients with CKD under the visiting nephrologists' follow-up.[7] However, this study only had a small sample size of 35 patients.

The objectives of this study are to look at the impact of scheduled nephrologist visits on the clinical outcomes of CKD patients in primary care by comparing blood pressure readings, urine albumin and blood investigations (FBS, HbA1C, RP and FLP) pre- and post-referral to visiting nephrologist.

MATERIALS AND METHODS

Study Design

This study is a retrospective cross-sectional study by reviewing the medical records of patients seen by visiting nephrologists from January 2019 to December 2021.

Study Setting and Population

This study was conducted in Greentown Health Clinic, a government health clinic located in Ipoh, Perak. There are about 4000 diabetics and 5200 hypertensive patients on follow up in this clinic with two Family Medicine Specialist. The study population are patients with CKD stage 3b, 4 and 5 who are followed up in Greentown Health Clinic. Underlying comorbidities include hypertension, diabetes, ischemic heart disease and other renal related conditions. The role of the family medicine specialist is to optimise blood pressures, sugar and lipid levels by various measures. These would include lifestyle measures of dietary and exercise counselling, regular diabetes self-management education group classes to empower patients to control their diabetes, medication optimisation and pre dialysis counselling where appropriate. Patients seen in the visiting nephrologist clinic are all seen by or co-managed with a family medicine specialist to optimise their disease control at the primary care level in hope to slow down kidney disease progression prior to escalating care to the visiting nephrologist.

Inclusion and Exclusion Criteria

All patients who have been seen by visiting nephrologist at least once were included in the study. Patients whose medical records were not retrievable were excluded from the study.

Sample Size and Sampling Method

Universal sampling was done in this study. The number of patients referred to the visiting nephrologist in the year 2020 has reduced in comparison to 2019 due to the COVID-19 pandemic movement control order. An average of 2 to 6 patients are seen by the visiting nephrologist in a month. Taking into consideration that the number of patients attending the clinic is reduced, all patients who were eligible were included in the study.

A total of 94 patients were seen at least once by visiting a nephrologist at Greentown Health Clinic during the study period. Seven patients were excluded as their medical records were not found. A total of 87 patients were included in the final analysis.

Data Collection

The medical records of 87 CKD patients were reviewed retrospectively. CKD definition in this study is defined as eGFR <60 ml/min/1.73m² present for more than 3 months with or without evidence of kidney damage.[10] The variables for comparison in this study include pre and post-visit systolic blood pressure (SBP) and diastolic blood pressure (DBP), urine protein, fasting blood sugar (FBS), glycated haemoglobin (HbA1c), serum creatinine, eGFR and fasting lipid profile (FLP). The baseline blood investigations used will be the latest available investigations taken before the nephrologist visits. Investigations after nephrologist visit will be the earliest investigations taken after nephrologist visit.

The variables were compared and analysed using Statistical Package for Social Sciences (SPSS) version 26. Data that were normally distributed were reported as mean and standard deviation (SD), and those not normally distributed were reported as median and interquartile range (IQR). Paired T-test was used for the analysis of normally distributed variables. Wilcoxon signed-rank test was used for the analysis of non-normally distributed data. A value of $p<0.05$ is considered statistically significant (confidence interval 95%).

RESULTS

Among the 87 patients analysed, the median age was 66 years (range 31 to 90 years). There were more male patients (54%) than female (46%) with the majority being Malays (62.1%). Eighty two (94.2%) had hypertension and 79 (90.8%) of the patients were non-smokers. (Table I).

Referring to the urine profiles of 83 patients before referral, 13.3% (n = 11) exhibited no signs of albuminuria. Conversely, post-referral, 15.1% (n = 11) of the 73 patients showed an absence of albuminuria. During pre-nephrologist visits, a higher percentage of patients exhibited moderate (30 300 mg/g) and severe (> 300 mg/g) increase in urine albuminuria (15.7% and 7.2%, respectively) compared to the post-referral period. In patients with significant urine protein pre-referral, patient group with urine protein 3+ showed the highest increment of 30.1% (n = 22), in comparison to 19.3% (n = 16) observed during the pre-referral (Table II).

The comparison of clinical outcomes between pre- and post-referral to the nephrologist reveals statistically significant differences in the reduction of systolic blood pressure [141±15 mmHg versus 135 ±12 mmHg, p = 0.001] and diastolic blood pressure [median = 80 mmHg (IQR: 10) versus median=71 mmHg (IQR: 17), p < 0.001]. Similarly, total cholesterol [median = 4.4 mmol/L (IQR: 1.4) versus median = 4.0 mmol/L (IQR: 1.5, p = 0.001] and LDL [median = 2.5 mmol/L (IQR: 1.2) versus median = 2.2 mmol/L (IQR: 1.2), p<0.001)] exhibited statistically significant differences between pre- and post-referral. However, HDL remained unchanged and other

Table I: Characteristics of patients referred to visiting nephrologist

Patient demographics	Total (n=87)
Age in years, Median (IQR)	66 (16)
Gender, n (%)	
Male	47 (54.0)
Female	40 (46.0)
Ethnicity, n (%)	
Malay	54 (62.1)
Chinese	22 (25.3)
Indian	10 (11.5)
Others (Foreigner-Taiwanese)	1 (1.1)
Smoking, n (%)	
No	79 (90.8)
Yes	8 (9.2)
Comorbids (can be more than one)	
Hypertension	82 (94.2)
Diabetes	69 (79.3)
Hyperlipidaemia	65 (74.7)
Ischemic Heart Disease	12 (13.7)
Benign Prostate Hypertrophy	7 (7.8)
Gout	5 (5.7)
Renal calculi	2 (2.3)

Table II: Urine profile

	Pre-referral, n = 83 Frequency/%	Post-referral, n = 73 Frequency/%
Urine albuminuria		
Normal, < 30mg/g	11 (13.3)	11 (15.1)
Moderately increased, 30-300mg/g	13 (15.7)	6 (8.2)
Severely increased, >300 mg/g	6 (7.2)	4 (5.5)
Urine FEME		
Trace	3 (3.6)	4 (5.5)
1+	11 (13.3)	10 (13.7)
2+	23 (27.7)	16 (21.9)
3+	16 (19.3)	22 (30.1)

Table III: Clinical outcomes

Variables	n	Pre-referral median (IQR) or mean (SD)	n	Post-referral median (IQR) or mean (SD)	*p*-value
Systolic blood pressure (mmHg), mean (SD)	87	141 (15)	78	135 (12)	0.001#
Diastolic blood pressure (mmHg), median (IQR)	87	80 (10)	78	71 (17)	<0.001*
Creatinine (mmol/L), Median (IQR)	87	183.0 (92.0)	80	185.5 (134.0)	0.122*
eGFR (ml/min/1,73 m^2), median (IQR)	87	27.8 (19.5)	80	29.5 (21.6)	0.340*
Urine protein (normal), n(%)	83	11(13.3)	73	11(15.1)	>0.95∧
HbA1c (%), median (IQR)	73	6.7 (2.3)	59	6.6 (2.1)	0.233*
FBS (mmol/L), median (IQR)	87	6.3 (2.9)	74	6.2 (2.8)	0.730*
Total cholesterol (mmol/), Median (IQR)	87	4.4 (1.4)	72	4.0 (1.5)	0.001*
Triglyceride (mmol/L), Median (IQR)	87	1.5 (0.9)	72	1.4 (0.7)	0.062*
HDL (mmol/L), median (IQR)	87	1.1 (0.4)	72	1.1 (0.4)	0.006*
LDL (mmol/L), median (IQR)	87	2.5 (1.2)	72	2.2 (1.2)	<0.001*

Paired t-test with a mean difference of -5 (95% CI -7.77, -2.17)
* Wilcoxon signed-rank test
∧ McNemar test- urine protein is re-categorized to normal (urine albuminuria < 30 mg/g) and abnormal (urine albuminuria 30 to 300mg/g, >300 mg/g, proteinuria trace/1+/2+/3+)

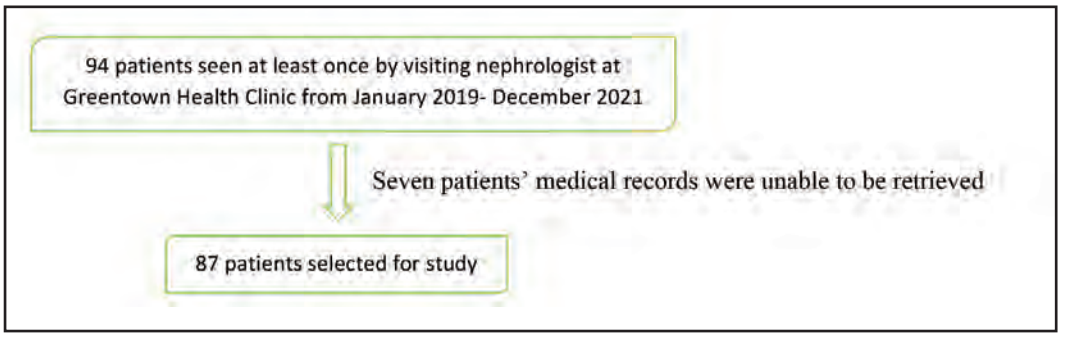

Fig. 1: Flow chart of sampling.

outcome variables showed no significant differences (Table III).

Post-referral data were missing in all variables as some patients defaulted follow-up visits. Several patients referred to the nephrology clinic in the tertiary centre did not have investigations ordered after their transfer out, while two patients were transferred to other local clinics.

DISCUSSION

The results of this 3-year retrospective study further amplify the results of the previous study done in 2020.[7] We managed to include 87 patients in this study. Results which were consistently seen is the significant reduction in both systolic and diastolic blood pressure pre- and post-referral to nephrologist. This could be attributed to reinforcement on dietary changes and compliance to medication, optimisation of therapy and minimizing exposure to nephrotoxins that potentially lead to deterioration of renal function. The Clinical Practice Guidelines (CPG) on management of chronic kidney disease in 2018 targets blood pressure for patients with diabetic kidney disease to be ≤130/80 mmHg.[8] In this study, blood pressure post-nephrologist referral was reduced to a median of 135/71 mmHg.

Other significant biochemical improvements post-referral was the reduction in total cholesterol and LDL levels. The LDL- cholesterol, an important modifiable risk factor in the incidence of revascularizations, ischemic stroke, atherothrombotic process and cardiovascular death has also improved post-nephrologist referral. A mean reduction to 2.2 (IQR: 1.2) drastically reduces the risk of developing atherosclerotic events in patients with CKD, though the effects of treatment on the progression of CKD remain uncertain.[9]

Urine protein levels did not show significant improvement post-referral. This is expected as patients included in this study were patients with CKD stages 3b, 4 and 5 who have glomerular hyperfiltration, hypertrophy and sclerosis. Though there was no improvement in eGFR levels, it seems to have stabilized and the deterioration is lesser than expected for patients with CKD. The reduction in HbA1c was not significant but it is important to highlight the median levels of HbA1c pre-referral were 6.7, which reduced to 6.6 post-referral. This shows the majority of the patients had acceptable glycaemic control.

To our knowledge, this is a novel study in Malaysia to evaluate the impact of scheduled nephrologist visits among CKD patients in primary care and can be used as a comparison for future studies. In addition to improving patient care and outcome, these patients also had better collaboration between primary and tertiary care. All the positive findings from this study are very promising and further consolidates the importance to establish a multidisciplinary collaboration and community health approach to meet the needs of CKD patients, in line with the National Action Plan for Healthy Kidneys.[4] Literature review on related or similar studies globally shows mixed results but prior contact with a nephrologist was not significantly associated with CKD progression, incidence of CVD or death.[10-13]

LIMITATIONS

This study had a small sample size over a span of 3 years. Covid restrictions and cancellation of appointments were one of the factors resulting in lesser referrals to visiting nephrologists. For this study, we defined investigations post-referral as the earliest investigations taken post nephrologist visit, hence, investigations are sometimes taken at the earliest at 1-month post-visit. However, HbA1c investigations should be taken 12 weeks after the initial test for comparison. In subsequent studies, we hope to have a larger sample, with standardized criteria for post-referral blood investigation schedules and follow-up visits. Furthermore, without controls, there is potential for bias and confounding factors in this study (e. g., effect of treatment and patient characteristics) which may affect the results beyond or independent of the care and management by nephrologist. Ideally, this should be an interventional study with controls, which we propose for future studies.

CONCLUSION

Nephrologists' visits to primary care seems beneficial and this study shows significant blood pressure reduction and cholesterol improvement among of chronic kidney disease (CKD) patients. This initiative should be expanded where feasible if there are adequate nephrologists available in tertiary centres for such visits.

Another important factor to be considered would be cost effectiveness of such an initiative, as it would be preferable if it's more cost effective than patients visiting them at the tertiary level. Additionally, tertiary referral of all identified

patients would lead to a non-sustainable overload of nephrology care resources. Nephrologist can help strengthen and assist family medicine specialists in primary care to co-manage patients with chronic kidney disease and further enhance multidisciplinary collaboration to meet the needs of CKD patients. We hope to have a multicentred, prospective study with a larger sample size in future with controls and standardized post-visit blood and urine investigation timings for a more robust study finding.

ACKNOWLEDGEMENT

We would like to thank Clinical Research Center (CRC) Hospital Raja Permaisuri Bainun Ipoh for their assistance in proposal editing and input in drafting results.

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ORIGINAL ARTICLE

Role of colchicine to reduce NLRP3 marker in STEMI patients undergo primary PCI: A randomised controlled clinical trial

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ABSTRACT

Introduction: ST-segment elevation myocardial infarction (STEMI) is a fatal disease with significant burden worldwide. Despite advanced medical treatment performed, STEMI-related morbidity and mortality remains high due to ischemia reperfusion injury after primary angioplasty mediated by NLRP3 inflammasome. Adding colchicine expected to reduce inflammation both in vitro and in vivo. We want to evaluate the effect of colchicine administration on the NLRP3 level of STEMI patient who undergo primary cutaneous intervention (PCI).

Materials and Methods: Randomised controlled trial was conducted on STEMI patients who undergo PCI in two hospitals in Jakarta, 104 patients enrolled to this study, and 77 patients completed the trial. 37 patients were randomly assigned to receive colchicines (2 mg loading dose; 0.5 mg thereafter every 12 hour for 48 hours) while 40 patients received placebo. NLRP3 level was measured from venous blood at baseline (BL), after procedure (AP), dan 24-hour post procedure (24H).

Results: No NLRP3 difference was observed initially between colchicine arm and placebo arm 38,69 and 39,0138, respectively (p >0.05). Measurement conducted at 24H, patients received colchicine demonstrate reduction in NLRP3 level (37.67), while placebo arm results increase in NLRP3 level (42.89) despite not statistically significant (p >0,05).

Conclusion: Colchicine addition to standard treatment of STEMI patients undergo PCI reduce NLRP3 level despite statistically insignificant.

KEYWORDS:
STEMI, inflammasomes, colchicine, acute coronary syndrome, reperfusion injury

INTRODUCTION

STEMI, ST-segment elevation myocardial infarction, is an urgent and potentially life-threatening medical emergency. STEMI occurs when there is a complete blockage of the coronary artery supplying blood to the affected area of the heart. STEMI patients manifested as intense chest pain and have a substantial portion of their heart muscle at risk. Swift access to procedures aimed at restoring blood flow to the coronary arteries is the gold-standard treatment, with a continued focus on minimising the time from admission to balloon angioplasty.[1] Myocardial infarct is still a major global health issue. In 2015, there was an estimated 7.4 million deaths due to coronary heart disease. Prevalence of myocardial infarct varies from 0.06% in men <45 years to 2.46% in men ≥75 years old.[2] However, despite adequate management in the form of percutaneous coronary intervention 3.4% of patients experience mortality within 7 days and up to 12.6% within 1 year after primary PCI conducted.[3,4] Restoring blood flow to previously blocked artery can induce ischemia reperfusion injury, which is attributable to an increased rate of major adverse cardiac events.[5] NLRP3, a crucial component of inflammasome, plays an important role in mediating ischemia reperfusion injury and serve as a potential therapeutic target.[6] Colchicine exhibits inhibition of inflammation in the NLRP3 associated pathway in COVID-19 and has been shown to reverse atherosclerosis mediated by NLRP3.[7,8] However, study assessing the effect of colchicine on the NLRP3 in STEMI patients who undergo primary PCI has not been studied yet. This study aims to address that matter.

MATERIALS AND METHODS

Study Setting

Study was conducted from December 2022 and April 2023 in Cipto Mangunkusumo National Referral Hospital and Jakarta Heart Centre. Study performed according to the Declaration of Helsinki and its 64th World Medical Assembly, Fortaleza, Brazil, 2013 amendments. Study was implemented corresponding to Good Clinical Practice guideline from ICH Tripartite Guideline. Ethical approval was issued by Ethical Committee of Faculty of Medicine University of Indonesia/Cipto Mangunkusumo National Referral Hospital (Ethical Approval Number, KET-1057/UN2.F1/ETIK/PPM.00.02/2022). This study also registered in www.clinicaltrials.gov with identification

This article was accepted: 20 February 2024
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number NCT05734612. Written informed consent was obtained from every study participant.

Population

Eligible patients are defined as those aged 18 to 80 years who have been diagnosed with STEMI and meet diagnostic criteria including typical chest pain, recorded ST-segment elevation and increased cardiac biomarker. Patients were enrolled to either colchicines arm or placebo arm which undergoes primary percutaneous coronary intervention and agree to participate in this study. Exclusion criteria encompass history of malignancy, allergy to colchichine, intolerance to contrast material, type 2 myocardial infarct, severe systolic dysfunction, stroke within 3 months, CABG within 3 years, inflammatory bowel disease, eGFR <30 mL/minute, chronic liver disease, autoimmune and long usage of corticosteroid, or abdominal pain with VAS score >5.

Protocol

This study is double blinded. Randomisation and allocation were made by third parties that didn't participate in data collection. Participants were divided into two groups, colchicine arm and placebo arm. Colchichine arm received loading dose of 2 mg before primary PCI procedure and 0.5 mg thereafter every 12 hour for 1 days. Placebo arm received same amount of glucose as a placebo. Both arm received standard medication for STEMI management. Venous blood sample was obtained before primary PCI and 24 hours after primary PCI procedure.

The samples used for NLRP3 examination is whole blood EDTA or PBMC. The selection of the best sample type is carried out by optimising examination of two samples using whole blood or PBMC. The sample used will be selected based on the most optimal results. The examination method used was flow cytometry with the Facs Canto BD® tool. CD14+-tagged monocytes have intracellular NRLP3. PBMC/whole blood samples will be given a marker for monocytes, namely CD14+. Cells that have CD14+ will be given a permeabilising agent to create pores on the cell surface, in order to the markers NRLP3 is able enter the cells. Cells that have CD14+ and ASC+, NRLP3+, Caspase 1+ markers will be read on a flow cytometry tool.

Data Analysis

Demographic data retrieved include age, sex, onset duration of chest pain, STEMI type and history of risk factors (smoking, hypertension, diabetes mellitus type 2, obesity, coronary artery disease, chronic kidney disease). Results from coronary angiography and primary PCI were collected regarding the number of vessels affected and the artery related to infarct. Ejection fraction was obtained after procedure. Data analysis was carried out using the SPSS version 20 (IBM).

Descriptive data will be arranged in table form. If the numerical data is normally distributed, it will be presented in the form of a mean with a standard deviation, and if it is not normally distributed, it will be presented in the form of a median with a interquartile range. Categorical data is presented in percentage form. The Kolmogorov-Smirnov test was carried out to determine the normality of the data. Analysing differences observed NLRP3 levels between the two intervention groups, independent T test used if the data was normally distributed or the Mann-Whitney test if the data was not normally distributed. Repeated measurement of NLRP3 concentration was done using generalised linear model. P value <0.05 was considered statistically significant.

RESULTS

A total of 104 STEMI patients were screened to participate in this study. 20 patients met exclusion criteria, three patients refused to participate and attending physician of one patient refused to participate. 80 patients were randomised evenly to each group (intervention arm n = 40; placebo arm n = 40). However, three of the intervention group received wrong drugs. 37 patients in intervention arm and 40 patients in placebo arm completed the study with zero dropout. This study recruitment, allocation, follow-up and analysis flow chart was summarised in Figure1.

The mean age of this study participants was 55.22 ± 9.9 years and majority of sex was male (76.6%) (Table I). There was no statistically significant difference of subject characteristics between intervention and control arm. Every study participant has comorbidities, including diabetes, hypertension, dyslipidaemia, history of smoking, obesity, chronic kidney disease and coronary artery disease. The most prevalent comorbidity is history of smoking (71.42%). Larger part of the study participants experienced three vessel disease (3VD; n = 44.15%) with the most frequent infarct-related artery was left anterior descending (LAD; n = 53.24%).

Measurement of NLRP3 concentration from baseline (BL), after procedure (AP) and 24-hour post procedure (24H) shows no statistically significant difference (p >0.05), was observed between colchicine and placebo arm (Table II). However, NLRP3 concentration measured in colchicine arm shows a trend of decrease from BL (38.69) to 24H (37.67) compared in placebo arm (39.01 vs 42.89), despite statistically insignificant.

Neither comparison of NLRP3 median delta (Δ) between colchicine arm and placebo arm yielded statistically insignificant results, whether comparison measured on AP-BL, 24H-BL or 24H-AP (Table III). Observation of median concentration of NLRP3 shows declining concentration in colchicine arm from BL to 24H, meanwhile placebo arm NLRP3 concentration shows increase (Figure 2).

DISCUSSION

Initial assessment of NLRP3 levels in the two intervention groups found no statistically significant difference (p = 0,950). Subsequent comparison of absolute concentrations reveals no significant difference. However, NLRP3 concentration in the colchicine arm decreased from baseline to 24H post primary PCI while the NLRP3 concentration in the placebo arm steadily increased. Comparisons of delta concentrations between AP and BL, 24H and BL, 24H and AP, shows no significant differences. On the other hand, comparison of absolute median between colchicine arm and placebo arm shows that Δ is always smaller or negative in the colchicine arm. Observations at 24H after primary PCI

Table I: Baseline subject characteristics

Subject characteristics	Colchicine N=37	Placebo N=40	*p*-value
Age (Mean ± SD)	55.3 ± 10.01	55.15 ± 9.88	0.930*
Sex, n (%)			
Male	27 (72.9)	32 (80)	0.467†
Female	10 (22.1)	8 (20)	
STEMI nset, (Mean ± SD)	6.0 ± 2.78	7.19 ± 3.34	0.10*
Comorbidities n (%)			
DM	15 (40.5)	13 (32.5)	0.464†
Dyslipidaemia	22 (59.4)	29 (72.5)	0.227†
Hypertension	23 (62.1)	25 (62.5)	0.976†
Smoking	25 (67.6)	30 (75.0)	0.471†
Obesity	17 (45.9)	23 (57.5)	0.311†
Chronic kidney disease	1 (2.7)	1 (2.5)	0.733†
Coronary artery disease	2 (5.4)	1 (2.5)	0.470†
Ejection fraction (Median ± IQR)	54.5% ± 10.70	55.0% ± 10.08	0.756†
Coronary angiography, n (%)			
CAD 1VD	7 (18.91)	14 (35.00)	0.260*
CAD 2VD	11 (29.72)	11 (27.5)	
CAD 3VD	19 (51.35)	15 (37.50)	
Infarct location, n(%)			
LAD	18 (48.64)	23 (57.5)	0.388*
LCx	6 (16.21)	2 (5.00)	
RCA	13 (35.13)	15 (37.5)	

*= Chi quare test, †= Independent t-test

Table II: Comparison of absolute NLRP3 concentration

Measurement	NLRP3 concentration		*p*-value*
	Colchicine arm (n = 37)	placebo arm (n = 40)	
Baseline (BL), mean (SD)	38,69 (16,59)	39,0138 (29,77)	0,950
After procedure (AP), mean (SD)	38,30 (19,91)	38,04 (28,05)	0,938
24 Hour post procedure, mean (SD)	37,67 (17,48)	42,89 (28,39)	0,276

*=Independent T-test

Table III: Comparison of NLRP3 concentration delta

Comparison	Difference in NLRP3 concentration		*p*-value*
	Colchicine arm (n = 37)	placebo Arm (n = 40)	
AP-BL Δ, median (IQR)	-2,86 (16,82)	3,88 (16,71)	0,378
24H-BL Δ, median (IQR)	-0,125 (26,85)	0,415 (38,45)	0,370
24H-AP Δ, median (IQR)	1,415 (26,19)	3,045 (38,3)	0,396

showed that the NLRP3 concentration decreased in the colchicine group while it increased in the placebo group.

Based on the literature exploration by researchers, there has been no previous research examining the effect of administering colchicine on reducing NLRP3 levels in STEMI cases in humans. Similar research conducted by Bakhta et al, conducted using mice subjects who were induced to undergo IMA-EST, found that administration of colchicine could reduce NLRP3 mRNA expression compared to without administration of colchicine.[9] Research on COVID-19 patients showed that administration of colchicine could significantly reduce NLRP3 activity, Measured by a decrease in the final synthesis of the cytokine IL-18.[7] A prospective cohort study assessing the effect of colchicine administration in chronic coronary syndrome patients showed a decrease in the synthesis of NLRP3 end products, namely IL-18, IL-6 and the IL-1 receptor agonist.[10]

Several mechanisms hypotheses to explain colchicine role in reducing NLRP3. Colchicine demonstrated inhibition of pyrin gene expression, thus preventing NLRP3 assembly.[11] Misawa, et al shows that colchicine inhibits transport of apoptosis-associated speck-like protein containing a caspase recruitment domain (ASC), component of NLRP3, resulted in blocked colocalisation of NLRP3.[12] Colchicine also act as inhibitor of P2X7 induced pore formation, crucial steps in NLRP3 inflammasome response to ATP, which resulted in lower levels of ROS and IL-1β.[13]

The main possible reason that this study yet to achieve statistically significant result is the level of inflammation occurs in STEMI higher than in NSTEMI.[14] Thus, colchicine administered in this study unable to achieve significant reduction in NLRP3 concentration. These data show that the cardioprotective mechanism of colchicine in inhibiting acute or chronic processes when STEMI occurs due to NLRP3 also occurs *in vivo*.

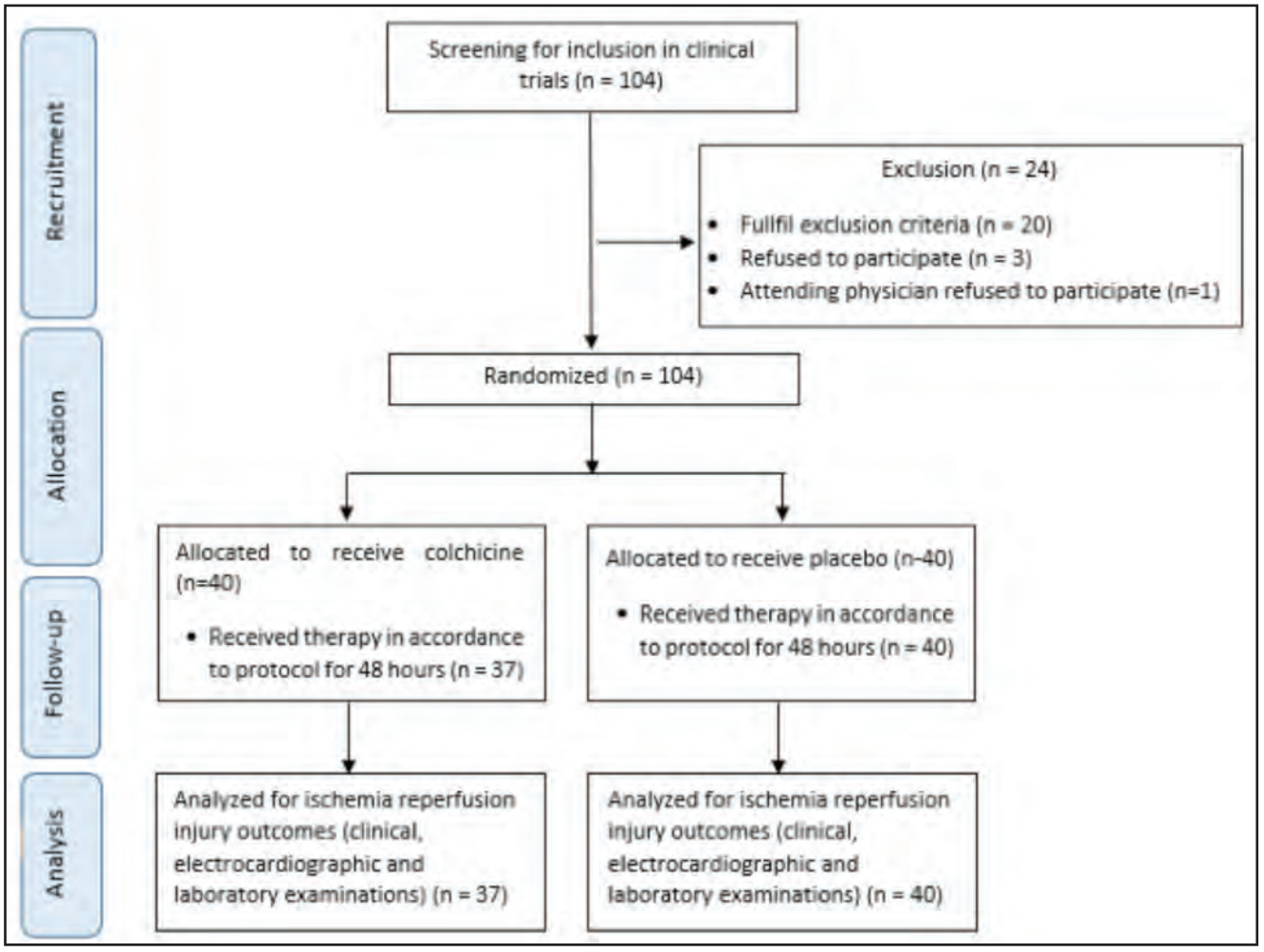

Fig. 1: Study flow chart

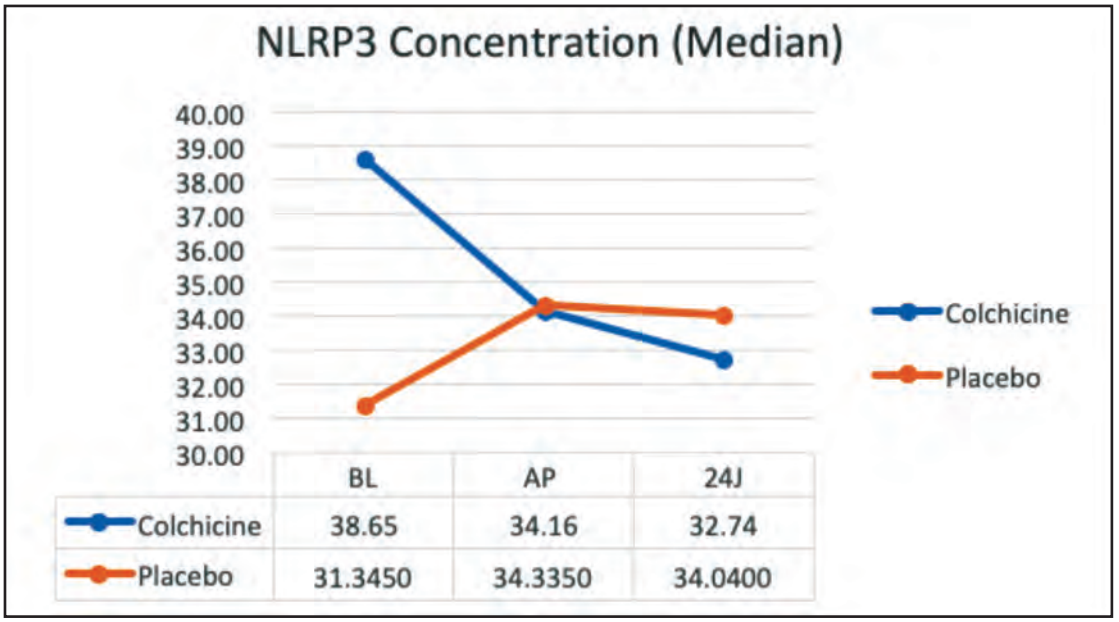

Fig. 2: Comparison of NLRP3 median

ACKNOWLEDGMENTS
All related parties who contributed to this study has been included in the authors list.

FUNDING
No external funding or research grant was awarded to this study.

CONFLICT OF INTEREST
No conflict of interest arises during this study.

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Scoring systems, expert assessment, and identification of risk factors for the emergence of delirium in paediatric patients: Prospective cohort study

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ABSTRACT

Introduction: Emergence delirium (ED) is a transient irritative and dissociative state that arises after the cessation of anaesthesia in patients who do not respond to calming measures. There are many risk factors for ED, but the exact cause and underlying mechanism have not been determined because the definition of ED is still unclear in consensus. This study aims to determine ED incidence, identify ED risk factors and external validation of Watcha, Cravero and expert assessment to Pediatric Anesthesia Emergence Delirium (PAED) scoring system in ED prediction.

Materials and Methods: This study is a prospective cohort study on 79 paediatrics who underwent elective surgery with general anaesthesia. Parameter measures include the incidence of ED, ED risk factors, and the relationship between PAED, Watcha, Cravero score and expert assessment. The ED risk factor was analysed using univariate and multivariate analysis. The relationship between PAED, Watcha, Cravero score, and expert assessment was determined using Receiver Operating Characteristic (ROC) curve analysis.

Results: The incidence of ED was 22.8%. All parameters examined in this study showed $p < 0.05$. Watcha's scoring correlates with the PAED scoring and shows the highest discrimination ability with AUC 0.741 and $p < 0.05$.

Conclusion: The incidence of ED in paediatrics is relatively high. Compared to others, Watcha score are more reliable for ED prediction. However, some demographic and perioperative factors are not the risk factor of ED.

KEYWORDS:
Emergence delirium, general anaesthesia, paediatric, risk factor, scoring system

INTRODUCTION

Emergence delirium (ED) is a mental disturbance during recovery from general anaesthesia, which consists of hallucination, delusion and confusion that manifests with moaning, anxiety, involuntary physical activity, and thrashing in bed. ED is a term often used to describe changes in behaviour after anaesthesia. Nevertheless, until now, there is no clear consensus for ED.[1] The incidence of ED is still unclear, ranging from 10 to 80%.[2,3] In some studies, it is mentioned that in conditions where pain and other confounding factors can be controlled, the incidence of ED may drop from 2 to 80% to 20 to 30%. Although ED can occur in adults, the highest incidence of ED is in children aged 2 to 7 years.[4]

It is a self-limited disorder (lasting 5 to 25 minutes after cessation of anaesthesia). It can repeatedly occur for up to 2 days and can be dangerous to the patient self. It may cause physical damage by removing intravenous lines, drainage tubes, patient monitoring devices, dressings or wound protectors.[1] A large prospective cohort study states that morbidity and mortality of postoperative delirium is around 7.2 to 8.7%.[5]

Controlling ED in children is a challenge. It requires more time, a longer length of stay in post anaesthesia care unit (PACU), and the addition of staff to treat patients after anesthesia.[3] During this decade, ED became one of the concerns whether it happened after surgery or not. Children with ED have a 1.43 times greater risk of experiencing maladaptive behaviour with long-term effects.[6] In different studies reported in patients who are preoperatively experiencing anxiety, the incidence of ED increases and even persists for up to 14 days.[7]

There are many risk factors for ED, but the exact cause and underlying mechanism have not been determined because the definition of ED is still unclear in consensus. Some of the factors that are considered to cause ED are age (children around 74%), previous ED (65%), mental condition of the patient (severe anxiety around 57%), untreated postoperative pain (60%), aesthetic method (with gas anaesthesia, rapid emergence in about 55%), and surgical procedures (surgery of the ear, eye or tooth in about 50%).[8,9]

Some limitations of existing studies on ED are that the numbers of samples are relatively small, done in a limited scope, and do not get much attention from the world of medicine, especially in the field of anaesthesia. In addition, There are many multifactorial aetiologies of ED and no gold standard for establishing ED diagnosis.[4]

This article was accepted: 22 February 2024
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Many scores for assessing ED are available, usually having three to five categories. Three most widely used scales are the Pediatric Anesthesia Emergence Delirium Scale (PAEDs), Watcha and Cravero. Each diagnostic tool available has advantages, disadvantages and methods.[1,2,10] However, scoring with PAEDs also has some limitations; some items have objective criteria, the responses are not well defined, and there is a possibility of false-positive values, even though each item has been validated from previous studies. Some items in PAED are not specific to ED, and there is no consensus on whether cut-off values should be included for ED.[1]

The existing problems, such as limited ED diagnosis and scoring, a large number of cases, variety of complications, can affect the safety and quality of surgery/anaesthesia services. Meanwhile, ED treatment and prevention can be done without difficulty by recognising risk factors, diagnosing ED, and providing the right drugs. Therefore, it is necessary to conduct a study to determine the incidence of ED, identify the risk factors, and external validation of the ED scoring system such as PAED, Watcha, and Cravero score systems as predictors of ED.

MATERIALS AND METHODS

This research was approved by the Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada research ethics commission. The approval number is KE/KF/0024/EC.

Research Design

This study uses a prospective cohort study design. The aim is to carry out external validation of PAED, Watcha and Cravero as predictors of ED in patients at Dr. Sardjito General Hospital. Sampling data is carried out using a non-probability sampling method in a consecutive manner where all subjects who meet the criteria are recruited into the study sequentially.[11] The inclusion criteria are: (1) Patients undergoing elective surgery, (2) paediatric age between 2 to 10 years and (3) ASA I-II. Exclusion criteria in this study are: (1) Diffable/communication interference, (2) history of neurological disorders and (3) history of cardiovascular disorders. Samples were taken prospectively and sequentially for two months after receiving ethical approval. With a data collection period of 2 months, the number of samples obtained is about 79 subjects.

Variable Dependent and Independent

The dependent variable in this study is the incidence of ED, assessed by experienced paediatric anaesthesiologists. There were two paediatric anaesthesiologists involved in the study. There were different thresholds for ED. The PAED score was >12, the Watcha score was 3-4 and the Cravero score was 4-5. The output variable in this study on the categorical scale is ED (yes or no). The independent variable is the variable that exists on the PAED, Watcha and Cravero scores (Supplementary material 1, 2 and 3).[1,4]

Procedure

Patients' age, body weight, gender, premedication, type of surgery and intraoperative anaesthesia and postoperative analgesia were also recorded. All children were observed by two experienced paediatric anaesthesiologists in a video recording. Observations are recorded at three-time points: (1) at the patient's initial arrival at the PACU, (2) the worst score for the initial 10 minutes, and (3) the worst score for the next 10 minutes by another researcher. At the same time, paediatric anaesthesiologists will observe whether an ED happened to the patient and decide on the therapy administration according to the protocol.

Data Analysis

To assess the inter-observer agreement, we used the kappa test. The kappa score between 0.81 to 0.99 shows almost perfect agreement, 0.61 to 0.80 shows good agreement, 0.41 to 0.60 shows moderate agreement, 0.21 to 0.40 shows fair agreement, and 0.01 to 0.20 shows slight agreement.12 Data analysis in this study focuses on the ability of discrimination and calibration. Discrimination ability was evaluated with a receiver operating characteristic (ROC) and the area under the curve (AUC).11 AUC values ranged from 0 to 1. The wider the AUC, the better the scoring ability to detect ED events. When an AUC area is found between 0.9 to 1, the scoring ability to detect ED could be interpreted as remarkable. Meanwhile, the scoring ability is good when the AUC area is found between 0.8 to 0.9. A mediocre ability is when an AUC is found between 0.7-0.8, and a poor ability is when the area found is between 0.6 to 0.7. While if the area is between 0.5 to 0.6, then the scoring is considered failed to detect ED.[11] The univariate were determined using independent t-test (if numerical) or chi-square (if categorical). After that, if $p < 0.05$, we continue to multivariate analysis to determine the risk factor ($p < 0.05$).

RESULTS

Before conducting the ED assessment, socialisation and training were done. The assessment is done through video recording and is assessed separately. The inter-observer agreement test shows a result of 0.76, which means that the agreement between the assessors is good. During the data collection period, 79 data were obtained. Demographic baseline data and those associated with ED incidence assessed using PAED can be seen in Table I and Table II. The mean age of the subjects in this study was 5.19 ± 2.6 years, body mass index (BMI) 15.7 ± 3.9 and surgery duration 113.4 ± 84.8 minutes. In general, research subjects were primarily male, ASA 2, underwent non-major surgery type, calm when separated from their parents, general anaesthesia techniques with endotracheal intubation, premedication with more than one drug, induction with a non-inhalant agent (intravenous) anaesthesia, maintenance via inhalation, without using muscle relaxants, without regional anaesthesia, use of analgesics during and post-surgery other than fentanyl.

According to the PAED score, the mean age was 5.05 ± 2.9 years for the subjects with ED, slightly younger than those without ED. In addition, the average BMI was 15.8 ± 4.8, and the operating time was 123.5 ± 97.7 minutes. In subjects who experienced ED, it was more common in female, ASA 2 physical status, non-major surgery, calm when separated from their parent, general anaesthesia intubation techniques, given more than one drug of premedication,

Table I: Baseline demographic data

Variables	Total
Age (years), mean±SD	5.19 ± 2.6
Body mass index (BMI), mean±SD	15.7 ± 3.9
Gender	
• Male, n (%)	46 (58.2%)
• Female, n (%)	33 (41.8%)
American Society of Anesthesiologists (ASA)	
• I, n (%)	38 (48.1%)
• II, n (%)	41 (51.9%)
Type of operation	
• Major, n (%)	15 (19.5%)
• Non-Major, n (%)	62 (80.5%)
Operation duration, mean±SD	113.4 ± 84.8
Child's behaviour on parental separation	
• Calm, n (%)	58 (74.4%)
• Restless, n (%)	20 (25.6%)
Anaesthesia technique	
• Total intravenous anaesthesia (TIVA), n (%)	14 (17.7%)
• Laryngeal mask airway (LMA), n (%)	26 (32.9%)
• Intubation, n (%)	39 (49.4%)
Premedication:	
• One drug, n (%)	22 (27.8%)
• More than one drug, n (%)	57 (72.2%)
Induction:	
• Inhalation, n (%)	19 (24.1%)
• Non-inhalation, n (%)	60 (75.9%)
Use of muscle relaxants	
• Yes, n (%)	37 (46.8%)
• No, n (%)	42 (53.2%)
Maintenance:	
• Inhalation, n (%)	77 (97.5%)
• Non-inhalation, n (%)	2 (2.5%)
Use of regional anaesthesia	
• Yes, n (%)	7 (8.9%)
• No, n (%)	72 (91.1%)
Analgesic uses during surgery:	
• Fentanyl, n (%)	9 (11.4%)
• Non-fentanyl, n (%)	70 (88.6%)
Postoperative analgesic usage:	
• Fentanyl, n (%)	5 (8.8%)
• Non-fentanyl, n (%)	52 (91.2%)

induced with non-inhalation, without using muscle relaxant, maintenance anaesthesia with inhalation, without using regional anaesthesia techniques, using non-fentanyl analgesics during and postoperatively.

In this study, none of the patients had communication, neurological, cardiological and eye contact disorders, nor were there any patients with decreased consciousness. All operations are elective operations. All variables studied did not make a significant difference to the incidence of ED.

The number of subjects who experienced ED as measured by PAED, Watcha, Cravero score, and expert assessment can be seen in Table III. From Table III, the highest number of patients diagnosed with ED were based on the Watcha score with 63.3%, and the lowest was based on expert's assessment with 10.1%. Details of the number of patients diagnosed with ED (based on PAED >12) either by Watcha, Cravero scoring or expert assessment can be seen in Figure 1. Only two patients (11.1%) agreed positively on ED incidence using Watcha, Cravero scores and expert assessments.

A correlation test was carried out between the PAED score and Watcha, Cravero score and expert assessment before the ROC analysis. From Table III, only Watcha's scoring correlates with PAED scoring ($p < 0.05$).

The three scores analysed by the ROC curve, only Watcha and Cravero scores showed discrimination in the incidence of ED (Figure 2). The ROC curve from the expert assessment did not show discrimination incidence of ED ($p = 0.935$).

The size of the AUC area shows how much the accuracy of a test is. In this study, the accuracy of scoring and assessments made by experts (can be seen in Table IV). From Table IV, both Cravero and expert assessment's have AUC between 0.5 to 0.6, which means that only Watcha's score shows the highest discrimination ability compared to Cravero's and expert assessment, although only classified as mediocre.

From the data that have been collected, there were no variables with p-value <0.05, so we stopped at the univariate analysis.

Table II: The incidence of emergence delirium with Pediatric Anesthesia Emergence Delirium

Variables	With emergence delirium	Without emergence delirium	*p*-value
Age (years), mean±SD	5.05 ±2.9	5.6 ± 2.8	0.795
BMI, mean±SD	15.8 ± 4.8	15.4 ± 3.8	0.919
Gender			
• Male, n (%)	7 (38.9%)	39 (63.9%)	0.101
• Female, n (%)	11 (61.1%)	22 (36.1%)	
ASA			
• I, n (%)	6 (33.3%)	32 (52.5%)	0.186#
• II, n (%)	12 (66.7%)	29 (47.5%)	
Type of operation			
• Major, n (%)	4 (22.2%)	11 (18.6%)	0.741#
• Non-major, n (%)	14 (77.8%)	48 (81.4%)	
Operation duration, mean±SD	123.5 ± 97.7	110.8 ± 84.5	0.837#
Child's behaviour on parental separation			
• Calm, n (%)	11 (61.1%)	47 (78.3%)	0.216#
• Restless, n (%)	7 (38.9%)	13 (21.7%)	
Anaesthesia technique			
• TIVA, n (%)	2 (11.1%)	12 (19.7%)	0.493#
• LMA, n (%)	5 (27.8%)	21 (34.4%)	
• Intubation, n (%)	11 (61.1%)	28 (45.9%)	
Premedication:			
• One drug, n (%)	6 (33.3%)	16 (26.2%)	0.561#
• More than one drug, n (%)	12 (66.7%)	45 (73.8%)	
Induction:			
• Inhalation, n (%)	2 (11.1%)	17 (27.9%)	0.212#
• Non-inhalation, n (%)	16 (88.9%)	44 (72.1%)	
Use of muscle relaxants			
• Yes, n (%)	8 (44.4%)	29 (47.5%)	0.999#
• No, n (%)	10 (55.6%)	32 (52.5%)	
Maintenance:			
• Inhalation, n (%)	17 (94.4%)	60 (98.4%)	0.406#
• Non-inhalation, n (%)	1 (5.6%)	1 (1.6%)	
Use of regional anaesthesia			
• Yes, n (%)	2 (11.1%)	5 (8.2%)	0.655#
• No, n (%)	16 (88.9%)	56 (91.8%)	
Analgesic uses during surgery:			
• Fentanyl, n (%)	3 (16.7%)	6 (9.8%)	0.999#
• Non-fentanyl, n (%)	15 (83.3%)	55 (90.2%)	
Postoperative analgesic usage:			
• Fentanyl, n (%)	1 (11.1%)	4 (8.3%)	0.418#
• Non-fentanyl, n (%)	8 (88.9%)	44 (91.7%)	

Statistical analysis with t-test and chi-square#.

Table III: The correlation between Pediatric Anesthesia Emergence Delirium cores and Watcha, Cravero and expert assessment score

Scoring	Number of patients with ED (N total=79)	*p*-value
PAED >12, n (%)	18 (22.8%)	ref
Cravero >3, n (%)	32 (40.5%)	0.057
Watcha >2, n (%)	50 (63.3%)	0.002*
Expert assessment, n (%)	8 (10.1%)	0.99

*$p < 0.05$.

Table IV: Area under curve on all three scores in diagnosing ED (based on PAED >12)

Scoring	AUC	95% CI	*p*-value
Cravero >3	0.630	0.476-0.784	0.104
Watcha >2	0.741	0.615-0.867	0.002*
Expert assessment	0.503	0.353-0.660	0.935

*$p < 0.05$

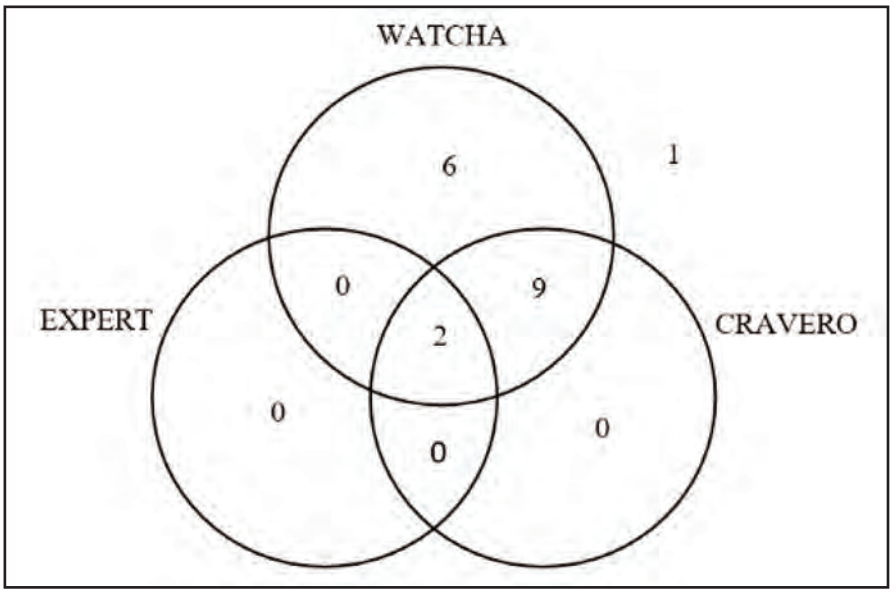

Fig. 1: Venn diagram between Cravero score, Watcha score and expert assessment in diagnosing emergence delirium (based on Pediatric Anesthesia Emergence Delirium >12)

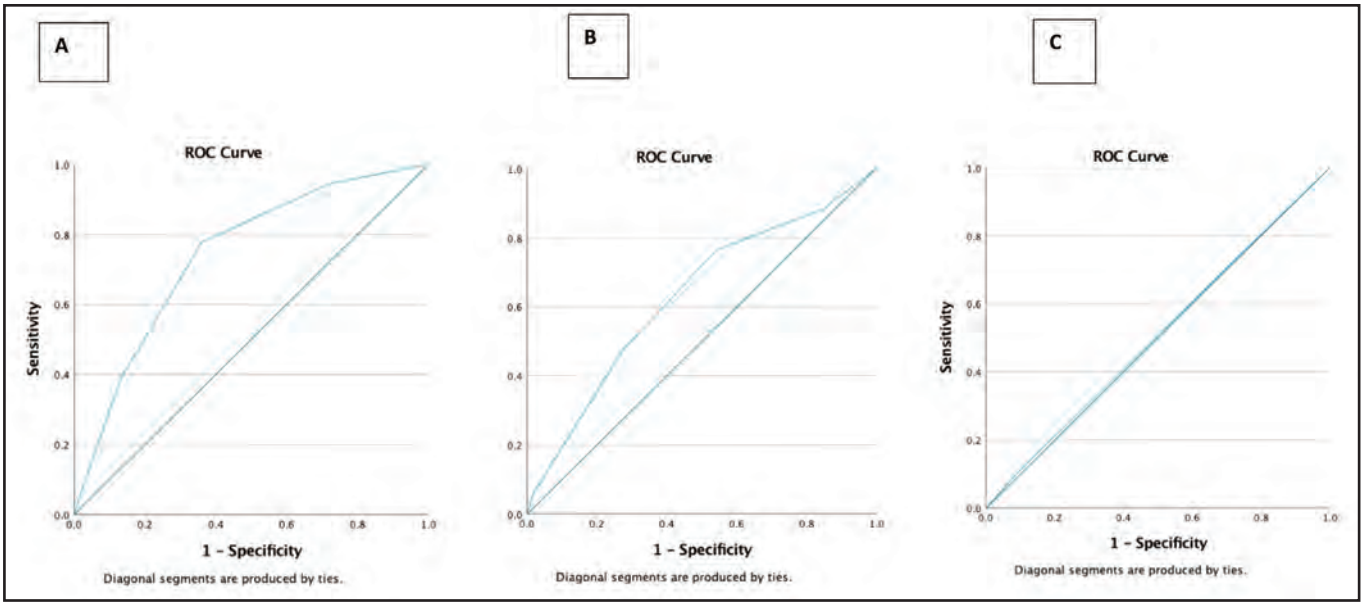

Fig. 2: Graph of receiver operating characteristic (ROC) on all three scores in diagnosing emergence delirium (based on PAED >12). A. Watcha, B. Cravero and C. Expert assessment

DISCUSSION

Post general anaesthesia ED is still considered a clinical problem for anaesthesiologists. Although there is no explicit agreement on the definition and measurement tool of ED, it is recognised by the patient's period of restlessness, agitation, inconsolable crying, disorientation, delusions, hallucinations, impaired cognitive function and memory.[13] In addition, there is no clear definition of ED and ED assessment instruments have various performance.

This study, which compares three scoring system, differs from the investigation conducted by Bajwa et al.[1] This study was focused on children aged 2 to 10 years, in contrast to previous studies involving children up to 18 years old. Additionally, the incorporation of expert assessment from two paediatric anaesthesiologist, rather than a single anaesthesiologist (as in the previous research) is expected to increase the validity of these findings.[1]

In assessing ED, PAED, Watcha and Cravero scores are widely used.[1] Based on existing knowledge and experience, the assessment carried out by paediatric anaesthesiologists is one way of detecting and measuring the incidence of ED and has been widely applied in diagnosing ED at Dr. Sardjito General Hospital. This study used PAED scoring as a standard. PAED score has been widely used because it has high sensitivity and specificity to detect ED incidence.[1] The PAED score with a cut-off >12 has a sensitivity of 100% and a specificity of 94.5%,[1,4]

so in this study, the PAED score is used as the standard to detect ED. Despite the high sensitivity and specificity, PAED scoring is not practical and fast to use.

The data obtained during this study were 79. One data was dropped out because the video recording did not exist. The data was taken by researchers who had been trained to use three ED assessment scores (PAED, Watcha and Cravero). An inter-observer agreement assessment was also carried out with good results. The evaluator assessed ED in the PACU room by all three scores without knowing the case.

As assessed by the PAED score, the incidence of ED is 22.8%, still within the range of ED incidence reported from various publications, around 20 to 80%.[1,2] In addition, the ED and non-ED groups were not significantly different, meaning that the two groups could be compared (Table II).

The incidence of ED was most diagnosed by Watcha scoring. The highest scoring able to detect for ED was Watcha scoring, followed by Cravero scoring, and lastly by expert assessment. Only two patients (11.1%) agreed positively on ED incidence using Watcha, Cravero scores and expert assessments. By looking at the numbers, this study illustrates that the agreement on ED assessment is still relatively low. However, the Watcha score being the only scoring correlated with the PAED score, has the highest discrimination compared to other scoring or expert assessments, even though the ability to detect ED incidents is classified as mediocre. From a previous study that compares PAED and Watcha, PAED has high sensitivity and specificity compared to Watcha. However, Watcha is easier to use in PACU.[1]

Many factors influence the incidence of ED, which makes the results of each study vary and differ from the results of this study. From previous studies, several risk factors that possibly can increase the incidence of ED are rapid emergence for anaesthesia, use of short-acting volatile aesthetic agents, postoperative pain, type of operation, age, preoperative anxiety, and child temperament.[14] However, we found that the variables we studied were unrelated to the incidence of ED.

Variations in the identification of risk factors between this study and previous studies could occur due to several reasons. One potential reason is the homogeneity of the subject ages, ranging from 2 to 10 years, which likely resulted in the age variable not demonstrating significant differences in this investigation. One of a study in Indonesia that studied ED in children aged 1 to 12 years showed that preoperative anxiety and pain were risk factors for ED.[15] In our study, preoperative anxiety as represented by child behaviour on parental separation was not associated with the incidence of ED. This may be because behavioural variables are assessed subjectively so this shows different results. Despite these differences, this study showed the same results that age, ASA physical status, type of surgery, and induction score were not the risk factors of ED.[15]

There were some limitations in our study. The scoring system used as gold standard for ED incidence in this study is the PAED scoring, with a cut-off value of more than 12. This is because there are study that reported the cut-off value of 12 have the highest sensitivity and specificity compared to another cut-off. But, one meta-analysis showed that the cut-off 10 or 12 was not significantly different.[16] In addition, one of the variables that examines preoperative anxiety was subjective, so we recommend to using scoring that has been proven to be valid and reliable. This study does not rule out other variables that may be significant but have not been studied as risk factors for ED.

CONCLUSION

All the parameters studied are not risk factors of emergence delirium (ED) incidence in paediatric patients. Only Watcha's score correlates with the Pediatric Anesthesia Emergence Delirium (PAED) score and shows the highest discrimination ability compared to Cravero's score and expert assessment, although the ability to discriminate is relatively good.

CONFLICT OF INTEREST

There is no conflict of interest.

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Effects of Malaysian thermal spring water as adjunct therapy for mild to moderate acne vulgaris – a prospective, randomised, controlled, split face study

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ABSTRACT

Introduction: Acne is a common skin disease with a high psychosocial burden, affecting mostly adolescents and youth worldwide. Management of acne is often challenged by cutaneous side effects that leads to therapeutic intolerance, poor compliance and impaired efficacy.

Materials and Methods: This was a single-centre, evaluator-blinded, split-face, randomised study investigating the effects of thermal spring water (TSW) in improving efficacy and tolerability of standard acne therapy. Total of 31 participants with mild-to-moderate acne were recruited and subjected to TSW spray to one side of the face 4 times daily for 6 weeks in addition to standard therapy. The other side received standard therapy only.

Results: Six (19.4%) males and 25 (80.6%) female with mean age 25.1±6.13 participated, 15 (48.4%) had mild acne while 16 (51.6%) had moderate acne. Seven (22.6%) were on oral antibiotics, 25 (80.6%) used adapalene, 6 (19.4%) tretinoin and 21 (67.7%) benzoyl peroxide. Skin hydration improved and better on spring water treated side with mean difference12.41±30.31, p = 0.04 at the forehead, 39.52±65.14, p < 0.01 at the cheek and 42.172±71.71, p < 0.01 at the jaw at week 6. Participants also report significant reduction in dryness at the treated side at week 6, mean difference 0.93±0.10, p < 0.001. TEWL, sebum and pH were comparable on both sides with no significant differences. Tolerability towards standard therapy improved as early week 2 with reduction of stinging following application of topical therapy (mean difference 0.62±1.43, p = 0.03), increase in skin feeling good (-1.79±1.70, p < 0.001) and skin suppleness (0.62±1.43, p < 0.001). These improvements were significantly maintained till week 6. Cardiff acne disability index significantly improved at week 6 (p<0.001) despite no significant changes in Comprehensive Acne Severity Scale score before and after treatment.

Conclusion: TSW may have a role as an adjunct to standard acne therapy by improving hydration, acne disability index and tolerability towards standard topical treatment.

KEYWORDS:
Acne, thermal spring water, trans-epidermal water loss, hydration

INTRODUCTION

Acne vulgaris is a common dermatologic disorder and was ranked as the 8th most prevalent disease worldwide by The Global Burden of Disease Project with a prevalence rate of 9·4%.[1] Approximately 85% of all individuals experience acne to some degree in their adolescence. Acne is a multifactorial chronic inflammatory disease of the pilo-sebaceous unit with four main pathogenetic mechanisms. Abnormal keratinocyte proliferation leads to ductal obstruction. An increase in sebum production creates a condition conducive for *Cutibacterium acnes* colonisation which cause production of inflammatory and chemotactic mediators that drive the inflammatory process leading to formation of comedones, papules pustules and sometimes nodules.[2] Acne has profound psychosocial effects that may undermine self-confidence and self-esteem at a vulnerable time in life.[3]

Patients with acne vulgaris exhibited markedly higher sebum secretion, greater transepidermal water loss (TEWL) and reduced stratum corneum (SC) hydration compared to age and gender matched controls.[4] The degree of SC barrier permeability impairment correlates directly with acne severity.[5] Current treatment for acne is effective and well established, however irritant dermatitis and side effects associated with local inflammation like dryness, irritability and redness are common and may lead to poor compliance. Restoring SC hydration and barrier function is an important factor in acne management to improve tolerability, compliance and ultimately efficacy.

Thermal spring water has been used for years in both spa and aerosol forms in patients suffering from multitude of skin diseases especially those associated with inflammation such as psoriasis and eczema. Their beneficial effect has been recognised for centuries especially in alleviating symptoms of inflammation.[6–10] Thermal spring water (TSW) use for burn scars, pruritus, rosacea-like dermatosis and ichthyosis have also been widely described.[9,11,12]

Our study objectives were to investigate the effect of a local thermal spring water on skin biophysical parameters including SC hydration, TEWL, sebum and pH in patients on treatment for acne vulgaris. Effect of the thermal spring water on local inflammatory symptoms associated with acne and tolerability to the standard acne topical therapy were determined.

This article was accepted: 08 March 2024
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MATERIALS AND METHODS

Study Design

This was an investigator-blinded, randomised split-face standard therapy-controlled trial conducted at the Department of Dermatology, Hospital Canselor Tuanku Muhriz in Kuala Lumpur, Malaysia. The sample size was determined using G*Power software (version 3.1.9.4). By comparing experiment and control groups with an effect size of 0.8, power of 80% and a 5% type 1 error and accounting for a 20% of drop-out rate, the final required sample size is approximately 31 patients for each treatment and control group.

Patients aged 14 to 45 years old with diagnosis of mild to moderate acne vulgaris on topical therapy (topical retinoids: adapalene 0.1% gel or tretinoin 0.05% cream) with or without oral antibiotics (doxycycline) were included. Diagnosis and severity of acne was confirmed by a dermatologist. Exclusion criteria was known hypersensitivity to thermal spring water or mineral bath, any generalised dermatitis, current or recent (within 1 month from initiation of study) local inflammation or infection on the face, and patients on isotretinoin or ≤ 8 weeks of discontinuation of isotretinoin therapy.

Participant's face was split with an imaginary midline and block randomisation was used to determine the side for thermal water therapy. One side received thermal spring water with standard therapy while the other side received standard therapy alone. Split face study design is used to reduce risk of other cofounding factors such as the skin type, spray technique, compliance and other environmental factors. Throughout the whole study period, the investigator assessing the clinical outcome was blinded to the side of treatment.

Clinical outcome assessment includes TEWL, SC hydration, sebum and surface pH were measured using Tewameter TM300, DermaLab Combo and Hanna Instrument pH meter respectively. Measurement was performed at the forehead, maxillary and mandibular areas on both sides of the face. Inflammatory (papules and pustules) and non-inflammatory lesion (comedones) of each side were counted by the same investigator and the severity of acne was assessed using Comprehensive Acne Severity Scale (CASS). All parameters were assessed at baseline, week 2 and week 6. All participants were acclimatised in dermatology laboratory for 20 to 30 minutes at temperature of 18○C prior to measurement so that the skin parameters were measured under the same conditions throughout the study.

Participants self-assessment include tolerability to topical therapy, local inflammatory symptoms stinging, itching, erythema and dryness was assessed using a visual analogue score (VAS) at three time points: before treatment (baseline), during treatment (week 4 and week 6). The impact of acne on quality of life and the participants' perception of their acne was scored using Cardiff Acne Disability Index (CADI) at baseline and week 6. CADI is a validated short five-item participants self-administered questionnaire derived from the longer version of acne disability index.[13]

Thermal Spring Water Collection and Storage.

The source of the thermal mineral spring water is from Sg Lalang located in Hulu Langat, Selangor, Malaysia. Spring water from this area is known to have low mineral composition with almost absence of sulphur component due to its non-volcanic nature. Sungai Lalang Hot Spring Water is a neutral spring water with pH 7.3 and low mineral content with Na 30.137 mg/L, K 1.64 mg/L, Silicates 27.96 mg/L, Fe 0.057 mg/L, Zn 0.009 mg/L, Mg 0.0425 mg/L, Ca 1.373 mg/L and Cu 0.0004 mg/L. The water also contains bicarbonates.[14] Thermal mineral spring water was obtained from the main well in Sg Lalang using a high-density polyethylene (HDPE) aspirator bottle. The water is left to cool to room temperature before filtered with filter paper No.54 via a glass funnel into the smaller 100 ml aluminium cylinder bottle and immediately sealed with mist spray nozzle. HDPE bottle is heat resistant with a low risk of leaching which may change the mineral composition of the studied water. Aluminium cylinder bottle was chosen due to its non-toxic and excellent corrosion resistance and act as a highly reflective coating for both light and heat and this is important to avoid thermal spring water composition alterations. Filtered water sample was cultured to ensure there was no bacteria contamination. All cultures showed no growth, similar to the autoclaved water sample which was used as control.

Patient Enrollment and Study Procedure

Thermal mineral spring water was supplied to the participants during their first visit (baseline) and second visit (week 2). Participants were instructed to spray one side of the face at a rate of five sprays in 1 minute, four times per day (7.00 to 8.00 am, 12.00 to 1.00 noon, 4.00 to 5.00 pm, 8.00 to 9.00 pm) for 6 weeks. A rigid plastic sheet was placed at the centre of the face to ensure the water mist did not reach the other side. The water was then left to air dried. The spray bottle was weighed weekly to monitor compliance.

Participants were required to continue their prescribed acne treatment on both sides of face. If the time of topical treatment coincided with the time for thermal water spray, thermal water was used first and let it air dried before application of topical medication. Participants were not allowed to change their usual skin care regime or use any acne treatment during the study period. Moisturisers or serum use were not allowed. Cosmetics use were allowed but adding new products was prohibited.

Written informed consent was obtained from all participants before participation in the study. The study was approved by University Kebangsaan Malaysia Research Ethic Committee, research code FF-2022-038.

Statistical Analysis

Data analysis was performed using SPSS version 24. Descriptive analyses determined sociodemographic characteristics of the study population. Categorical variables were presented as frequency with percentages. Continuous variables are presented as mean with standard deviation, median and inter-quartile range represent skewed data.

Bivariate analyses determined the effect of thermal spring water on TEWL, hydration, sebum, pH, tolerability to acne

Table I: Participants baseline sociodemographic characteristics (n = 31)

Characteristics	Mean(SD)	n	%
Age	25.1(6.13)		
Age of onset	17.2(4.95)		
Duration (months)			
Gender	24.1(14.2)		
Male		6	19.4
Female		25	80.6
Recurrence of Acne			
Yes		24	77.4
No		7	22.6
CASS			
Almost clear		5	16.1
Mild		10	32.3
Moderate		16	51.6
Current Treatment			
Tretinon		6	19.4
BPO		21	67.7
Adapalene		25	80.6
Antibiotic		7	22.6

Abbreviations: CASS, Comprehensive Acne Severity Score

Table II: Effects of TSW in skin barrier function, hydration, sebum and pH (n = 29) in both arms

Parameters	Mean Difference	Standard Deviation	*p*-value
TEWL			
Week 2			
Forehead	-0.27	3.88	0.711
Maxillary	0.07	4.44	0.932
Mandibular	0.13	2.79	0.8
Week 6			
Forehead	-0.53	3.98	0.48
Maxillary	-1.68	4.6	0.06
Mandibular	-0.77	3.57	0.26
Hydration			
Week 2			
Forehead	3.53	35.89	0.59
Maxillary	-8.1	47.12	0.35
Mandibular	5.7	78.37	0.69
Week 6			
Forehead	12.41	30.31	0.04
Maxillary	39.52	65.14	0.003
Mandibular	42.17	71.71	0.004
Sebum			
Week 2			
Forehead	0.83	11.74	0.7
Maxillary	-0.37	7.45	0.79
Mandibular	-2.03	6.79	0.11
Week 6			
Forehead	-0.31	9.67	0.86
Maxillary	-1.55	7.73	0.29
Mandibular	-2.14	10.12	0.27
PH			
Week 2			
Forehead	0.05	0.19	0.14
Maxillary	0.06	0.27	0.24
Mandibular	0.03	0.33	0.66
Week 6			
Forehead	0.01	0.19	0.74
Maxillary	0.10	0.29	0.06
Mandibular	0.02	0.19	0.56

Note: Results presented as a mean difference of skin biophysical parameters between side treated with standard topical acne therapy combined with TSW and standard topical acne therapy alone at week 2 and week 6.
Abbreviations: TSW, Thermal Spring Water; TEWL, Trans-epidermal Water Loss.

Table III: Comparison of effects of TSW on TEWL, hydration, sebum and pH between week 0 and week 6 (n = 29)

Parameters	Mean		Mean Difference	SD	*p*-value
	Week 0	Week 6			
TEWL					
Forehead	14.819	10.949	3.869	3.768	<0.001
Maxillary	12.645	11.406	1.24	4.96	0.19
Mandibular	11.118	9.493	1.62	4.63	0.07
Hydration					
Forehead	154.48	167.93	-13.45	59.85	0.24
Maxillary	224.79	266.28	-41.48	83.39	0.01
Mandibular	202.83	271.76	-68.93	82.71	<0.001
Sebum					
Forehead	13.38	12.38	1	15.81	0.74
Maxillary	10.3	9.07	0.97	11.33	0.65
Mandibular	7.41	9.93	-2.52	8.79	0.13
PH					
Forehead	5.49	5.38	0.11	0.45	0.22
Maxillary	5.71	5.69	0.02	0.43	0.79
Mandibular	5.72	5.65	0.07	0.42	0.39

Note: Results presented as a mean difference of skin biophysical parameters between baseline and 6 weeks (end of study period) over the side treated with TSW
Abbreviations: TSW, Thermal Spring Water; TEWL, Trans-epidermal Water Loss.

Table IV: Assessment on the effect of TSW on local inflammatory symptoms associated with acne and topical acne treatment (n = 29)

Symptoms	Mean Difference	Standard Deviation	*p*-value
Pruritus			
Week 2	0.03	1.49	0.90
Week 6	0.10	1.15	0.63
Dryness			
Week 2	0.3	1.37	0.24
Week 6	0.93	0.99	<0.001
Redness (Erythema)			
Week 2	0.33	1.27	0.16
Week 6	-0.17	1.23	0.46
Stinging			
Week 2	0.1	1.45	0.70
Week 6	0	1.07	1

Note: The mean difference of inflammatory symptoms associated with acne and the topical therapy between the treated side with TSW versus the untreated side.
Abbreviations: TSW, Thermal Spring Water.

Table V: Assessment of clinical effect of the TSW on immediate skin sensation post acne topical treatment

Sensation	Mean difference	Standard deviation	*p*-value
Skin Suppleness			
Week 2	-1.29	1.61	<0.001
Week 6	-1.82	1.36	<0.001
Skin tightness			
Week 2	0	2.39	1
Week 6	0	2.61	1
Skin feeling good			
Week 2	-1.79	1.7	<0.001
Week 6	-2.14	1.43	<0.001
Stinging			
Week 2	0.62	1.43	0.026
Week 6	0.79	1.95	0.037

Note: The mean difference of skin sensation between the treated side with TSW versus the untreated side.
Abbreviations: TSW, Thermal Spring Water.

Table VI: Effects of TSW on acne severity and acne associated disability

	Mean	Mean difference	Standard deviation	*p*-value
CADI				
Week 0	7	2.774	3.074	<0.001
Week 6	4.23			
CASS				
Week 0		0	0.72	1
Week 6		0	0.76	1

Abbreviations: TSW, Thermal Spring Water; CASS, Comprehensive Acne Severity Score; CADI, Cardiff Acne Disability Index.

treatment, quality of life and local inflammatory symptoms. Level of significance was pre-set at 0.05.

RESULTS

A total of 31 participants were enrolled, 29 completed the study and were included in the statistical analysis. One patient withdrew secondary to treatment related adverse event and another one was lost to follow up. Baseline sociodemographic characteristics were summarised in Table I.

Clinical Outcome Assessment

Evaluation of effect of TSW in Skin Biophysical parameters

TSW treated side demonstrated better hydration compared to the untreated side with $p < 0.05$ at week 6. Mean difference in hydration between the treated side and the control side was 12.41 ($p = 0.036$) at forehead, 39.52 ($p = 0.003$) over maxillary area and 42.17 ($p = 0.004$) over the mandibular area. Sebum, TEWL and pH showed no significant difference between the treated side and the control side at each visit as shown in Table II. On the side treated with TSW, there was improvement in TEWL and hydration at week 6 in comparison to baseline. All areas namely forehead, maxillary and mandibular showed reduced TEWL and increased hydration numerically but the results were statistically significant over forehead area for TEWL and maxillary and mandibular area for hydration as shown in Table III.

Evaluation of effect of TSW in acne severity

There were no significant CASS score changes between the treatment arm and the control arm at baseline and at the end of the study. Some patients had improvement in acne severity which were not statistically significant.

Patient's Subjective Assessment

The effect of improved stratum corneum hydration of the skin was reflected by patients' self-assessment of symptoms. A significant number of patients reported improvement in skin dryness at treated side compared to the untreated side at week 6 with a mean difference of 0.931 ($p < 0.001$). Other inflammatory symptoms such as pruritus, erythema and stinging sensation showed no significant difference as shown in Table IV.

The side treated with thermal spring water significantly improved tolerability towards standard topical therapy as a significant number of participants reported reduced stinging sensation over the treated side of the face immediately after application of the topical treatment compared to the control side of the face and the difference can be felt as early as week 2 ($p = 0.026$). There was also improvement of the skin feeling good sensation and skin suppleness over the treated side compared to the non-treated side with ($p < 0.001$). However, there were no significant changes in the skin tightness sensation as per shown in Table V. These show that the TSW has a calming effect on the skin irritation induced by the topical acne treatment, and this would likely to improve participants adherence to therapy.

Majority of patients had reduction in CADI score at week 6 with mean difference of 2.774 ($p < 0.001$) as depicted in Table VI. At baseline, most participants had a mean score of 7, indicating moderate quality of life impairment. However, by the end of the 6-week study period, the mean CADI score had decreased to 4.23, indicating mild quality of life impairment. Participants' self-perceived improvement in quality of life impacted by acne measured by CADI score did not translate to improvement in their acne severity measured by CASS. There was no significant difference between the CASS score of the treated side of the face and the non-treated side of the face.

Safety

One participant developed adverse reaction to the studied water. She had facial erythema and itchiness on the treated side of the face after using the thermal spring water for 1 day (total of four spray). She was withdrawn from the study, symptoms resolved after stopping TSW. A few participants experienced mild tingling sensation over the treated side of the face, immediately after spraying which is transient self-limiting and did not warrant any intervention.

DISCUSSION

Emerging scientific data supports the beneficial effects of thermal spring water balneotherapy as an alternative or adjunctive treatment of skin diseases.[9,10,15–29] Hulu Langat thermal spring water has low mineral concentration compared to other hot springs worldwide.[14] Renowned thermal spring water with low mineral concentration include Avène (ASW) and La Roche-Posay (LRP) in France.[9,21,27] The beneficial effects of these waters were attributed to its low mineral content with some specific characteristic like presence of unique microflora which is *Aquaphilus dolomiae* found in Avène and *Vitreoscilla filiformis* found in La Roche Posay, an ideal calcium magnesium ratio, high silicates content for ASW and high selenium content for LRP. Low mineral water has been shown to produce better hydration and skin comfort compared to high mineral content. Water with low salt concentration stay in contact with the skin longer as high surface tension caused the water to spread less over the skin surface and evaporated slower leading to a

better hydration.[28] Scanning electron microscopy showed application of low mineral concentration spring water on human skin explants resulted in homogeneous deposits of small crystals composed of only sodium and chlorine, whereas application of mineral rich spring water resulted in the formation of needle-like crystals composed of calcium and small sulphur grains which were heterogeneously spread across the skin surface.[30]

The mineral content of thermal spring water affects the physical sensations experienced upon application to the skin and regular use. Freshness, suppleness, softness and comfort were perceived greater with lower mineral concentration thermal spring waters.[28] Thermal spring water also possess anti-inflammatory properties and exhibit antioxidant qualities which has been clearly documented in multiple *in vitro* studies. Lymphocytes cultured in Avène water had increased lymphoproliferative response to some mitogens, increased IL-2 and IFN-γ productions and decreased production of IL-4.[31] La Roche Posay and Avène waters showed clear inhibitory effect on IL-6 and attenuated the formation of reactive oxygen species in human keratinocytes after UVB stimulation.[15] The reduction of IL-6 levels was similar to betamethasone-17-valerate treatment.[15] Avène water was able to inhibit histamine release and it was postulated that calcium and bicarbonate ions play a major role in its anti-allergic properties.[32] It also reduced the inflammatory effect in a model of human skin explants stimulated by a neurotransmitter (vasoactive intestinal peptide).[33] High silicates content in Hulu Langat thermal spring water is advantageous as silica rich water like Monfortinho thermal spring water in Portugal has been shown to reduce cell metabolism and proliferation of keratinocytes and macrophages[34] and improve skin hydration in clinical study.[35] These findings suggest that silicate-rich spring water may hold promise in managing abnormal follicular keratinisation and inflammation in acne as well as alleviating irritation and barrier dysfunction associated with acne therapy.

Hulu Langat thermal spring water was an effective adjunct therapy for mild to moderate acne vulgaris in our study. Local symptom of dryness significantly improved, accompanied by objective increase in stratum corneum hydration and reduction in TEWL. Improvement of the skin barrier function might be one of the reasons thermal spring water reduce the irritant effect of topical retinoids and giving a better skin comfort sensation post topical retinoids application. Multiple studies have shown the beneficial effect of thermal spring water on skin hydration and barrier. Study using Sao Pedro of Sul thermal water in Portugal was able to improved skin barrier disruption in 82.4% of volunteers with skin irritation induced by sodium lauryl sulphate compared to sites treated with purified water.[36] Daily 20-minute baths in saline groundwater in South Korea for 2 weeks resulted with significant improvement in SCORAD index, skin hydration, TEWL, and pruritus in patients with atopic dermatitis.[26] A gel formulation containing Cró thermal water from Portugal which is rich in sodium, silica, potassium, and calcium resulted in improvement of skin textural parameters with significant improvements in hydration, TEWL, and skin relief.[37] The benefit on the skin barrier repair is likely due to the combination of magnesium and calcium salts.[38] This beneficial effect of TSW in barrier function of the skin has also been demonstrated in other studies involving an atopic dermatitis patient where skin barrier defect is one of the underlying pathology with positive results.[17–20,26,27]

Acne therapy especially topical retinoids contribute to inflammatory symptoms perceived by patients. This hinders adherence to therapy which leads to poor control of acne. Regular use of thermal spring water is beneficial in combating local inflammatory symptoms induced by acne and standard topical acne therapy. Significant reduction in desquamation was observed with retinoic acid combined with thermal spring water sprays compared to retinoic acid alone after 4 weeks in a randomised study.[22] A significant number of our study participants reported enhanced suppleness and skin feeling good with thermal spring water post topical retinoid application as early as 2 weeks of therapy. Similar study using Leopoldine spa water showed a reduction in erythema measured by chromometer post sodium lauryl sulphate application which support an inhibitory effect of irritation.[39] Ave`ne thermal spring water use after fractional photo thermolysis has demonstrated a calming effect by minimising short-term adverse effects namely pain, dryness and redness in patients with dermal melasma treated with fractional resurfacing.[23] The use of low mineral thermal spring water following various dermatology procedures has been shown to effectively relieved pain and pruritus hence restoring patient comfort.[21,24,25,29]

We did not observe significant changes in acne severity measured by CASS score likely due to the short study duration. A longer treatment duration would probably improve the efficacy as better hydration promotes better absorption of the medications. Improvement in acne treatment tolerability equal to a better adherence to therapy and the combined effect of these two would lead to a clinical improvement in acne. This study found that addition of thermal spring water to standard acne therapy resulted in a mean improvement on 2.7 points in CADI score reflecting the enhancement of stratum corneum hydration, reduction of local inflammatory symptoms and positive sensation did translate into better patient's quality of life (QoL). Acne is a dermatological condition with substantial psychosocial impact. The CADI is a questionnaire commonly used in clinical practice and therapeutic research to evaluates the impact of acne on patient quality of life. It has been identified as the simplest QoL scale to employ in dermatology practice.[39] A recent review revealed the widespread use of CADI questionnaire in therapeutic research globally.[36] Acne is a dermatological condition with substantial psychosocial impact. Although we did not demonstrate an improvement in CASS score, it established the relevance of CADI as a valuable addition to standard topical acne therapy in enhancing quality of life.

Numerous studies conducted on TSW from various regions around the world have demonstrated their positive impact on skin health both in vivo and in vitro studies and this also translated into their observed beneficial role in clinical studies. Although TSW from different sources may have distinct mineral compositions, each appears to offer skin

health benefits. The findings of this study offer further scientific support for the therapeutic application of spa waters in the management of chronic inflammatory skin diseases.

Treatment with thermal spring water is generally safe and the occurrence of adverse effect is almost negligible. Previous study in Thailand to evaluate acute cutaneous tolerance with thermal spring water with patch test found to be non-irritating under occlusion.[18] However, one of our patients developed a reaction which necessitate withdrawal from the study. Although rare, hypersensitivity or irritation reaction to thermal spring water is possible and need to be further explored.

CONCLUSION

Hulu Langat thermal spring water was safe, well tolerated and beneficial as an adjunct treatment in mild to moderate acne vulgaris. Stratum corneum hydration improved associated improvement in symptoms of dryness. Adjuvant treatment with thermal spring water improve tolerability towards standard topical acne therapy such as benzoyl peroxide and retinoids by mitigating the irritation caused by these therapies. This led to lower patient-based rating of their acne impact on life.

LIMITATION

This study is limited by the small sample size and the lack of placebo control to determine if improved hydration and tolerability towards standard acne treatment is purely due the effect of thermal spring water or just water itself.

The optimal duration and frequency of thermal spring water treatment has yet to be determined. A longer follow up would also give more information on its effect on the acne severity.

ACKNOWLEDGEMENT

The authors would like to thank Mr. Mohammad Noorakmal Anuar for his assistance with the thermal spring water collection and Puan Juliana Ramli and Puan Nor Afifah for their kind assistance with the participant assignment according to the block randomisation.

CONFLICT OF INTEREST

This is an investigator initiated study, none of the authors have relevant conflicts of interest.

DISCLOSURE

This research is partially funded by Ministry of Higher Education Malaysia as part of UKM SULAM programme initiatives. The author report no other conflicts of interest.

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A retrospective study of breathlessness supportive therapy on chronic refractory breathlessness in a palliative care unit

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ABSTRACT

Introduction: Chronic refractory breathlessness is a debilitating symptom which negatively affects quality of life with profound impact on physical and psychosocial functioning of patients and/or carers. Multidisciplinary based interventions which focus on non-pharmacological approach have shown to be effective. We developed a breathlessness intervention service called breathlessness supportive therapy (BST) in a palliative care unit with limited resources. The aim is to evaluate the feasibility of developing a BST service and to study the characteristics and outcome of patients with chronic refractory breathlessness.

Materials and Methods: This is a retrospective study of patients with chronic refractory breathlessness and Modified Medical Research Council (mMRC) dyspnoea scale grade ≥ 2 who attended the BST clinic over 1 year period. BST consists of two clinic sessions 2 weeks apart. Data was retrieved from patients' medical notes and analysis done using Microsoft Excel.

Results: A total of 21 patients were identified. Median age was 69 years with 52% of females. 72% had non-malignant diagnoses. Median Charlson's Comorbidity Index score was 6.5. Median mMRC dyspnoea scale was 3. 47.6% had long term oxygen usage. Median Australian Karnofsky Performance Scale (AKPS) was 65 and the median baseline breathlessness visual analogue scale (VAS) was 2. 62% completed two sessions, the remaining 38% completed only one session. Mean time from BST intervention to death was 18.26 weeks, median was 22 weeks. 72% died at home, whilst 28% died in the hospital. All the patients scored 4 (somewhat agree) and 5 (strongly agree) on the overall feedback score.

Conclusions: Development of a breathlessness intervention service is feasible in a resource limited setting and generally accepted by most patients. More research and prospective studies are needed to evaluate the effectiveness of BST in the future.

KEYWORDS:
Chronic refractory breathlessness, palliative care, breathlessness intervention service, breathlessness supportive therapy, nonpharmacological intervention

INTRODUCTION

Chronic refractory breathlessness is defined as breathlessness at rest or on minimal exertion that persists despite optimal treatment of underlying causes.[1] Breathlessness is a debilitating symptom that leads to suffering and negatively affects quality of life with profound impact on physical and psychosocial functioning of patients and/or carers.[2] Two large whole-of-population surveys done suggest that the prevalence of chronic breathlessness in the community is 9 to 11%.[3,4] Prevalent aetiologies include chronic obstructive pulmonary disease (up to 95%), advanced cancer (up to 90%), heart failure (up to 88%) and end stage renal failure.[5,6]

The breathing, thinking and functioning model proposed by Spathis et al postulates that the problems arising from one or more of these domains contribute to the generation of breathlessness. For example, a person with chronic breathlessness may has an ineffective breathing pattern with increased work of breathing (breathing domain) which can lead to anxiety and/or fear (thinking domain), perpetuating the symptom of breathlessness. Patient may become socially isolated with reduced physical activity, leading to cardiovascular and muscle deconditioning, further worsening breathlessness (functioning domain).[7] These domains may co-exist and interconnect. Hence, identification of the domain which predominantly causes breathlessness helps clinicians focus on the management strategies to break the vicious cycle.

Oral or parenteral opioids can improve refractory breathlessness however the quality of evidence is low.8 Nonpharmacological approaches such as handheld fans, breath training, pulmonary rehabilitation, cognitive behavioural therapy, mindfulness therapy, exercise and self-management strategies have been shown to improve breathlessness.[7-10] There is emerging evidence of multidisciplinary based interventions shown to improve breathlessness. The Cambridge breathlessness intervention service is effective in reducing patients' distress and fear/worry due to breathlessness, as well as demonstrating cost effectiveness in the management of breathlessness.[11] An integrated service including palliative care, respiratory medicine, physiotherapy and occupational therapy showed that patients with chronic refractory breathlessness report improved breathlessness in both cancer and non-cancer groups.[12]

This article was accepted: 05 March 2024
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Table I: Patient characteristics

Patient characteristics	
Variables	
Age, median (IQR)	69 (57.5 – 74.25)
Gender	
Male, n (%)	10 (47.6%)
Female, n (%)	11 (52.4%)
Diagnosis	
Malignancy, n (%)	6 (28.6%)
COPD, n (%)	6 (28.6%)
Heart failure, n (%)	6 (28.6%)
ESRD, n (%)	1 (4.76%)
Pulmonary hypertension, n (%)	1 (4.8%)
Pulmonary fibrosis	1 (4.8%)
CCI, median (IQR)	6.5 (4.25-8)
0-3, n (%)	1 (4.8%)
4-6, n (%)	7 (33.3%)
7-9, n (%)	6 (28.8%)
≥10, n (%)	1 (4.8%)
Missing data, n (%)	6 (28.6%)
mMRC dyspnoea scale, median (IQR)	3 (2-3.75)
2, n (%)	5 (23.8%)
3, n (%)	5 (23.8%)
4, n (%)	5 (23.8%)
Missing data, n (%)	6 (28.6%)
Oxygen use	
Yes, n (%)	10 (47.6%)
No, n (%)	5 (23.8%)
Missing data, n (%)	6 (28.6%)
AKPS, median (IQR)	65 (60-70)
40, n (%)	1 (4.8%)
50, n (%)	2 (9.5%)
60, n (%)	6 (28.6%)
70, n (%)	4 (19%)
80, n (%)	2 (9.5%)
Missing data, n (%)	6 (28.6%)
Baseline VAS score, median (IQR)	2 (2-4.5)
1, n (%)	2 (8.3%)
2, n (%)	3 (14.3%)
3, n (%)	1 (4.8%)
4, n (%)	1 (4.8%)
5, n (%)	2 (9.5%)
6, n (%)	1 (4.8%)
Missing data, n (%)	11 (52.4%)

IQR: Interquartile Range; COPD: Chronic Obstructive Pulmonary Disease; ESRD: End Stage Renal Disease; CCI: Charlson Comorbidity Index; mMRC: Modified Medical Research Council; AKPS: Australia-modified Karnofsky Performance Scale; VAS: Visual Analogue Score

To our knowledge, there is no dedicated multidisciplinary breathlessness intervention service in Malaysia. The exact prevalence of chronic refractory breathlessness in Malaysia is unknown. Based on an Asia-based population survey amongst individuals above 40 years of age, the estimated prevalence of chronic obstructive pulmonary disease (COPD) is 4.7%, and 12.5% has severe symptomatic phenotype.[13] In addition, with increasing cancer incidence annually and increasing percentage (89.5 to 93%) of late-stage lung cancer on diagnosis, patients with refractory breathlessness is expected to rise.[14,15]

The Palliative Care Unit in Hospital Raja Permaisuri Bainun has developed a breathlessness supportive therapy (BST) outpatient service which incorporates non-pharmacological interventions and provides an individualised breathlessness action plan. The aims of this study are to assess the feasibility and acceptability of the BST to patients and evaluate outcomes of the service. This can help guide us to develop better services in the future to manage patients with chronic refractory breathlessness.

MATERIALS AND METHODS

Study Design

We conducted a retrospective cohort analysis of patients with chronic refractory breathlessness who attended the BST clinic in a single Palliative Care Unit at Hospital Raja Raja Permaisuri Bainun, Ipoh, Malaysia. This is a descriptive study. We obtained ethics approval from the Medical Ethics and Research Committee, Ministry of Malaysia (NMRR ID-23-01300-PLD).

Study Population

All adult patients ≥ 18 years with chronic refractory breathlessness and mMRC dyspnoea scale grade ≥ 2 who attended the BST from 1st January 2022 to 31st December 2022 were included in the study.

Table II: Outcomes of BST intervention.

Outcomes	n (%)
Number of patients, n (%)	21 (100%)
Completed 2ndsessions, n (%)	13 (61.9%)
Only completed 1st session, n (%)	8 (38.1%)
Clinical outcome (n = 21)	
Died, n (%)	18 (85.7%)
Alive, n (%)	3 (14.3%)
Reason for not completing 2nd session (n = 8)	
Too unwell, n (%)	5 (62.5%)
Not interested, n (%)	1 (12.5%)
Died, n (%)	1 (12.5%)
Logistics, n (%)	1 (12.5%)
Hospital admission post BST (n = 21)	
Yes, n (%)	7 (33.3%)
No, n (%)	13 (61.9%)
Missing data, n (%)	1 (4.8%)
Time from BST intervention to death (weeks)	
Median, weeks (IQR)	22 (8.5-26)
Place of death (n = 18)	
Home, n (%)	13 (72%)
Hospital, n (%)	5 (28%)

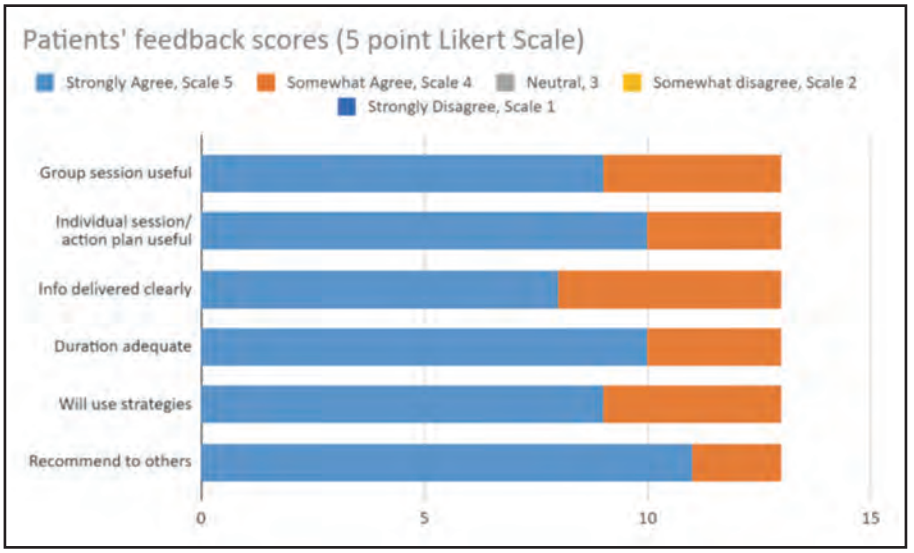

Fig. 1: Patients' feedback score for BST.

Data Collection

Data was retrieved from the patients' medical records which are stored in the medical records department. As medical records were kept in a physical folder, data from the medical records were transcribed into a password protected computer. Baseline data collected from the first BST clinic visit included demographics (age and gender); diagnosis, comorbidities; Australia-modified Karnofsky performance scale (AKPS); mMRC dyspnoea scale, oxygen use, and baseline breathlessness visual analogue score (VAS). Charlson comorbidity index (CCI) is used to categorise comorbidities of patients by the sum of all the individual scores for every comorbidity score assigned.

Outcome data extracted include BST clinic completion rates, clinical outcome, post BST intervention breathlessness VAS scores, reasons for not completing two sessions, feedback scores, number of hospital admission post BST intervention. Feedback scores are recorded using a 5-point Likert scale of 1 to 5.

Data Analysis

We used Microsoft Excel to perform summary statistics in the format of mean and standard deviation (SD), median and interquartile range (IQR). As the number of patients is too small and with significant missing data, further statistical analysis is not carried out as it is likely to be insignificant.

RESULTS

A total of 21 patients attended BST with chronic refractory breathlessness and mMRC grade ≥ 2 from 1st January 2022 to 31 December 2022. 52% were females. The median age was 69 years (IQR: 57 to 74). Malignancy accounts for 28.6% of primary diagnosis. Non-malignant diagnoses such as COPD, heart failure end stage renal disease, pulmonary fibrosis and pulmonary hypertension account for the remaining 71.4%. The median CCI score was 6.5 (IQR: 4.25 to 8). Median mMRC dyspnoea scale was 3 (IQR: 2 to 3.75). 47.6% have long term oxygen usage. Median AKPS score was 65 (IQR: 60 to 70) and the median baseline breathlessness VAS score was

2 (IQR: 2 to 4.5). Baseline patient characteristics are shown in Table I.

Outcomes

A total of 62% of patients completed two sessions, the remaining 38% completed only the first session. For the eight patients who did not complete the 2nd session, five (62%) were too unwell to participate, one (12%) was not interested, one (12%) died and one (12%) was unable to attend due to logistic reasons. 18 (86%) patients died and three (14.3%) remained alive during the time of writing.

After BST intervention, 13 patients (62%) did not require hospital admission. Of the seven (33%) patients who had hospital admission, one (14%) had only one admission, five (72%) had two admissions and one (14%) had five admissions. Only one remains alive at the time of data collection, amongst those who had no hospital admission post BST intervention. The mean time from BST intervention to death was 18.26 weeks (SD: 11.99), median time was 22 weeks (IQR: 8.5 to 26). 13 (72%) died at home, whilst five (28%) died in the hospital.

We were only able to extract data on post BST intervention breathlessness VAS score for seven patients (33%). Two patients showed improvement with change of VAS -2 where both had baseline VAS score of 5 and 6 respectively. Three had no change in VAS score, although they had baseline VAS score of less than 2. One had a worsening VAS score from 3 to 4 post intervention. No adverse events were recorded during BST clinic.

All the participants responded with scores of 4 (somewhat agree) and 5 (strongly agree) to the feedback scores on BST intervention. Among questions asked on feedback form include: 1) group sessions useful 2) Individual session/action plan useful; 3) info delivered clearly; 4) Duration adequate; 5) will use strategies and 6) recommend to others. None of the participants scored 3 or less on any of the category.

DISCUSSION

Our study showed that it is feasible to initiate a breathlessness intervention service in a resource limited setting. By adopting a multi-disciplinary approach and focusing on non-pharmacological interventions to manage breathlessness, most patients find that BST clinic to be helpful. Majority of patients (62%) were able to complete two sessions. To our knowledge, the BST clinic is the first breathlessness intervention service in the country, especially in a locality with limited resources.

Each BST clinic session is run by a dedicated palliative care medical officer and an occupational therapist. The role of the medical officer is to perform clinical assessment during BST clinic, while the occupational therapist provides education and training on non-pharmacological strategies in managing breathlessness. No additional staff members were recruited, or extra funds required to run the BST clinic. The BST clinic is conducted in an existing PCU outpatient building, hence no new infrastructure is required. Inpatient referrals come from the palliative care ward and other departments where the specialist palliative care team provides consultative service. Outpatient referrals are from the palliative care clinic. Patients with chronic refractory breathlessness with mMRC dyspnoea scale grade ≥ 2 are considered for referral to the BST clinic, regardless of diagnosis. In the first BST clinic session, patients undergo initial clinical assessment followed by a group session on non-pharmacological interventions. An information booklet containing information on interventions such as breathing techniques, breathing positions, energy conserving strategies and thought management strategies is given to patients who are advised to practise twice daily for 10 minutes based on a practice schedule. Patient is then reassessed individually 2 weeks later, and a personalised breathlessness action plan is created.

As this is a newly developed service, all referrals are received upon assessment and deemed appropriate by the specialist palliative care team. A total of 32 referrals were recorded in 2022. There were 11 patients (34%) who were not able to attend BST clinic upon referral. Nine of them were either too ill to attend or have died prior to BST clinic appointment. This highlights the need to triage patients and improve patient selection for BST clinic in the future.

Our cohort of patients with chronic refractory breathlessness have better functional status (70% with AKPS ≥ 40) and with predominantly cardiorespiratory diagnoses (71.4%). However, due to small sample size, we were not able to adequately assess symptom burden or intensity in our study. It is postulated that breathlessness intensity in people with better functional status (AKPS ≥ 40) and with cardiorespiratory diseases in the last weeks of life.[16] This indicates that our group of patients may have a more significant symptom burden and highlight the need to improve breathlessness management strategies.

Interestingly, our study shows that there is lesser hospital admission (62% not hospitalized) post BST intervention. In addition, majority of the patients died at home (72%) compared to 28% in the hospital. This may suggest that BST intervention is useful in managing breathlessness and subsequently reduce the need for acute hospital services utilisation and inpatient end of life care.

There are several limitations to our study. Firstly, this is a retrospective study and is subjected to biases associated with this study design. The sample size of the study is small and unlikely to contribute to statistically significant data. As previously mentioned, there are significant gaps in the baseline data collected especially with pre and post BST intervention breathlessness score. Hence, we are not able to measure the effectiveness of the BST intervention and study associated factors. Although we manage to show lower hospital admission and increased home deaths post BST intervention, there could be many other confounding factors that could contribute to this observation and are not included in the analysis of this study.

CONCLUSION

Multidisciplinary non-pharmacological approach to manage chronic refractory breathlessness is helpful. We have demonstrated that developing a breathlessness intervention

service is feasible in a resource limited setting. However, further prospective studies are required to measure its effectiveness.

ACKNOWLEDGMENT

We would like to thank the Hospital Director of Hospital Raja Permaisuri Bainun, Ipoh for the support given to initiate the BST clinic. A special mention of Intan Sofia Bt Mohamed Daud who has contributed to the initiation and delivery of BST clinic services and has recently retired.

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ORIGINAL ARTICLE

Clinical characteristic and management of haemophilia patients in Malaysia: A single centre experience

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ABSTRACT

Introduction: Haemophilia is one of the commonest inherited bleeding disorders which may lead to long term disabilities if not treated properly. Our aim of study is to understand the clinical characteristic, treatment and complications of adult haemophilia patients in our centre.

Materials and Methods: A retrospective cross-sectional review of all adult haemophilia A (HA) or haemophilia B (HB) patients who received treatment in Hospital Pulau Pinang from January 2021 to December 2022 was conducted. Data was retrieved from patients' medical records.

Results: A total of 75 haemophilia patients (64 HA and 11 HB) were included in this study with median age of 37 years (range 19 70). 42 of them had severe haemophilia (50% of HA, 91% of HB). All HB and 93.8% of severe HA patients were on prophylaxis. Six severe and one mild HA patients developed inhibitor with four of them currently on non-factor prophylaxis. 24 patients (32%) had prior hepatitis C infection and all of them have been successfully treated. The mean annual bleeding rate for severe haemophilia patients were 1.77 (SD ±3.6). Target joints were observed in 9.3% of patients with ankle joint (71.4%) being the most affected joint. More than one quarter (26.7%) of our patients have comorbidities with majority of them having hypertension (17/20), followed by diabetes mellitus (5/20) and ischemic heart disease (5/20).

Conclusion: Our study showed that a significant number of adult patients with haemophilia have comorbidities. Apart from optimising factor replacement therapy, future planning should include improvement in screening, risk modification and prevention of cardiovascular disease.

KEYWORDS:
Haemophilia, Malaysia, comorbidities

INTRODUCTION

Haemophilia is a group of inherited bleeding disorders caused by deficiency or dysfunction of the coagulation proteins factor VIII and factor IX which lead to haemophilia A (HA) and haemophilia B (HB) respectively. Haemophilia is a X-linked recessive disorder, affecting mainly males. Both, factors VIII and IX genes are located on the X chromosome in which factor VIII gene is large and more complex (26 exons) as compared to factor IX gene (eight exons).[1] Since the discovery of factor VIII gene sequencing, a large number of mutations that cause HA, have been identified. The most common genetic defect in severe HA is intron 22 inversion and intron one inversion which occurred 45% and 4% of patients, respectively.[2] HB is also genetically heterogenous and predominantly due to missense mutation in contrast to inversions in the factor VIII gene. The prevalence is around 17.1 and 3.8 per 100,000 male births for HA and HB globally.[3] Based on the report of the Annual Global Survey 2022 by World Federation of Haemophilia, the prevalence of people with haemophilia in Malaysia is 1048, with 899 (85.8%) haemophilia A and 149 (14.2%) haemophilia B.

Patients with moderate to severe haemophilia are prone to spontaneous bleeding, mainly into joints and muscles. Historically, the bleeding episodes of haemophilia were treated with fresh frozen plasma and cryoprecipitate in the 1960's to 1970's and replacement therapy with plasma derived clotting factors in the 1980's onwards. However, multiple transfusion of blood products has been linked to higher risk of transfusion-transmitted infections due to lack of strict screening of blood and its components in the past.

With the advances in clotting factor concentrates, development of specialised haemophilia treatment centres and usage of factor prophylaxis, the number of severe haemorrhages has decreased. Advances in management of haemophilia have also led to significant improvements in life expectancy. Haemophilia patients are experiencing higher numbers of medical conditions associated with aging such as cardiovascular disease. The health burden of the current generation of adult haemophilia patients are due to both the haemophilia-related complications and increasing age-related comorbidities.

Our aim of study is to understand the demographic, comorbidities, treatment and complications of haemophilia patients in our centre. We hope this study will help to improve our understanding about adult haemophilia patients and help in future planning and management of this group of patients.

MATERIALS AND METHODS

This is a single centre, retrospective cross-sectional study of all adult patients with HA and HB who received treatment in Hospital Pulau Pinang, Malaysia from January 2021 to December 2022. Demographic data, clinical characteristics, comorbidities, treatment history, complications and factor consumption were retrieved from patients' medical records

This article was accepted: 06 March 2024
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and data were collected using a standardised form. Transfusion-transmitted infections (hepatitis B, hepatitis C, human immunodeficiency virus infection) and comorbidities (hypertension, diabetes mellitus, dyslipidaemia, cardiovascular disease, chronic kidney disease, liver cirrhosis and malignancy) were obtained.

Severity of haemophilia was defined as: a) Mild: clotting factor level between 5 to 40% of normal factor activity, b) Moderate: clotting factor level between 1 to 5% of normal factor activity and c) Severe: clotting factor level less than 1% of normal factor activity. Target joint is defined as the joint with 3 or more spontaneous bleeds that have occurred within a consecutive 6-month period. Annual bleeding rate was defined as the total number of reported bleeding events for each patient for 1 year.

Data were analysed using Statistical Package for Social Sciences software (version 21.0). Categorical data were expressed as frequencies and percentages. Wilcoxon signed rank test were used to compare dependent variables and p value <0.05 was considered as statistically significant.

RESULTS

Patient Characteristics

A total of 75 haemophilia patients were included in this study with median age of 37 years (range 19 to 70). Majority of them were Chinese (50.7%) followed by Malay (36%) and Indian (13.3%). There were 64 patients diagnosed with HA (50% of them had severe haemophilia) and 11 patients were diagnosed with HB (91% with severe haemophilia B) (Table I). All severe HB patients and 93.8% of severe HA patients were on prophylactic factor replacement therapy, respectively (Table II). Besides, there were eight mild and moderate HA patients on prophylaxis therapy due to recurrent bleeding episodes and antiplatelet therapy for various underlying comorbidities.

Comorbidities

More than one quarter (26.7%) of our patients have comorbidities with majority of them having hypertension (17/20). They were diagnosed with hypertension at median age of 42 years (range 29 to 61). Five patients (6.7%) have ischemic heart disease and diabetes mellitus respectively (Table III). Two patients died during the study period due to cardiovascular event and hepatocellular carcinoma respectively.

Clinical Characteristics

Plasma-derived factor concentrate is the main treatment for our haemophilia patients without inhibitor, except for one patient who is receiving recombinant factor concentrate due to allergic reaction towards plasma-derived factor concentrate. The mean prophylaxis dose for haemophilia A and B was 59.8 ± 28.1 IU/kg/week and 48.5 ± 16.2 IU/kg/week, respectively.

The mean annual bleeding rate for severe haemophilia patients were 1.77 (SD ±3.6). Target joints were observed in 9.3% of patients with ankle joint (71.4%) being the most affected joint. There was a significant number of patients (41.3%) who developed haemophilic arthropathy. Among those with haemophilic arthropathy, 58.1% had single-joint involvement and knee joints were the most commonly affected (Table IV).

Hepatitis C infection (32%) was the commonest blood-borne infection among our study population. All of them successfully cleared the virus either with treatment (13/24) or spontaneous seroconversion (11/24). None of our study population had hepatitis B or human immunodeficiency virus (HIV) infection.

Seven patients (9.3%) developed inhibitor and six of them were severe HA and one was a mild HA. The patient with mild HA was exposed to intensive treatment with factor VIII concentrate for haemothorax requiring cardiothoracic surgery. The incidence of inhibitor among HA patients who were on demand and prophylaxis factor replacement therapy were 4.2% (1/24) and 15% (6/40), respectively (Table V). This was not statistically significant (p = 0.241). Among the patients with inhibitor, four of them are currently on non-factor prophylaxis therapy. Four of the patients with inhibitor have factor VIII gene mutation (intron 22 inversion and large deletion) that are commonly associated with inhibitor development. Besides, two of these patients are siblings.

DISCUSSION

With the advancement in haemophilia care, life expectancy of people with haemophilia (PWH) is now approaching that of the general population. There are a number of complications of haemophilia such as inhibitor development, joint disease and cardiovascular disease (CVD) which are increasing with aging.[4-6]

Transfusion-transmitted infection is one of the serious complications of haemophilia patients. Older haemophilia patients who were exposed to fresh frozen plasma and cryoprecipitate prior to availability of viral inactivation techniques were infected with hepatitis C and HIV.[7] These infections occurred more often before 1985. Majority of the infected patients do not suffer any acute symptoms and cleared the infection spontaneously, the remaining patients become chronic carriers. These older haemophilia population have higher risk of liver cirrhosis and hepatocellular carcinoma.[8] In our study, hepatitis C infection was the commonest transfusion-transmitted infection and was found in 32% of our haemophilia patient. Another study on haemophilia patients in Malaysia by Boo YL et al, reported almost similar rate of hepatitis C infection (30%) among their study cohort.[9] Almost half of our haemophilia patients with hepatitis C infection had cleared the virus spontaneously and the remaining were started on anti-viral treatment and all of them were cured from hepatitis C infection.

Musculoskeletal bleeding is the most common haemorrhagic manifestation among haemophilia patients. Haemarthrosis mainly affects large joints such as knees, elbows, ankles and more frequently involve the dominant side of weight-bearing joints as child begins to walk. Repeated haemarthrosis will lead to synovial hyperplasia and angiogenesis with further

Table I: Demographic and clinical characteristics of patient with haemophilia

	Mild	Moderate	Severe	Total
Haemophilia A				
Severity, n (%)	16	16	32	64
Age distribution, n (%)				
15-24	1	1	3	5
25-34	3	4	11	18
35-44	4	3	11	18
45-54	3	6	6	15
55-64	4	1	0	5
65-75	1	1	1	3
Ethnicity, n (%)				
Malay	5	2	16	23
Chinese	11	10	12	33
Indian	0	4	4	8
Haemophilia B				
Severity, n (%)	0	1	10	11
Age distribution, n (%)				
15-24	0	0	1	1
25-34	0	1	5	6
35-44	0	0	3	3
45-54	0	0	1	1
55-64	0	0	0	0
65-75	0	0	0	0
Ethnicity, n (%)				
Malay	0	0	4	4
Chinese	0	0	5	5
Indian	0	1	1	2

Table II: Treatment characteristic of patients with haemophilia

	Mild	Moderate	Severe	Total
Haemophilia A				
On demand, n (%)	15	9	2	26
Prophylaxis, n (%)	1	7	30	38
Inhibitors				
Yes, n (%)	1	0	6	7
No, n (%)	15	16	26	57
Haemophilia B				
On demand, n (%)	0	1	0	1
Prophylaxis, n (%)	0	0	10	10
Inhibitors				
Yes, n (%)	0	0	0	0
No, n (%)	0	1	10	11
Mean prophylaxis dose (IU/kg/week)				
Haemophilia A	59.7 ± 28.1			
Haemophilia B	48.5 ± 16.2			

Table III: Comorbidity of patients with haemophilia

Comorbidity	n = 20 (26.7%)
Diabetes mellitus	5
Hypertension	17
Dyslipidaemia	4
Ischemic heart disease	5
Chronic kidney disease	3
Chronic liver disease	3
Stroke	2

Table IV: Complications of patients with haemophilia

Complications	Value
Inhibitor	
Yes, n (%)	7 (9.3)
No, n (%)	68 (90.7)
Blood-borne infections	
Hepatitis B	
Yes, n (%)	0 (0)
No, n (%)	75 (100)
HIV	
Yes, n (%)	0 (0)
No, n (%)	75 (100)
Hepatitis C	
Yes, n (%)	24 (32)
Treated	13
Not treated	11
No, n (%)	51 (68)
Musculoskeletal	
Haemophilic arthropathy	
Yes, n (%)	31 (41.3)
Single joint	18 (58.1)
Multiple joints	13 (41.9)
No, n (%)	44 (58.7)
Chronic synovitis	
Yes, n (%)	4 (5.3)
No, n (%)	71 (94.7)
Target joint	7 (9.3)
Yes, n (%)	
Knee, n	1
Ankle, n	5
Elbow, n	1
No, n (%)	68 (90.7)
Annual bleeding rate (Severe haemophilia)	1.77 ± 3.6
Surgery	
Yes, n	6
Major	3
Minor	3

Table V: Characteristics of haemophilia patients with inhibitor

	Presence of inhibitor		P value
	Yes	No	
Factor replacement therapy			
On demand	1	23	0.241
Prophylaxis	6	40	

bleeding occurring in the friable and thickened synovium.[10] Eventually, these will result in chronic synovitis and progressive chronic haemophilic arthropathy. The gold standard in prevention of bleeding and its complication is the prophylaxis with clotting factor replacement. Almost all our severe haemophilia patients were on prophylactic factor replacement therapy currently. However, there is still a significant number of our patients (41.3%) who developed haemophilic arthropathy. This was mainly due to lack of access or non-compliance to prophylaxis factor replacement therapy previously. There are other factors contribute to the development and progression of arthropathy in haemophilia patients, such as genetic susceptibility and environmental factors.[11] Gene polymorphisms associated with an increased expression of pro-inflammatory cytokines such as tumour necrosis factor (TNF)-α and thus lead to more rapid joint damage progression. Overweight and obesity is associated with increased joint weight loading, decreased range in motion of joints, accelerated loss of joint mobility and involved in progression of haemophilic arthropathy in patients with haemophilia.[12] According to the World Health Organisation, the prevalence of obesity has tripled since the 1975 and the concerns this trend raises for managing the health of all patients. Several epidemiological data in United States and Europe suggest that the prevalence of overweight and obesity in haemophilia patients is comparable with the general population.[13] A study in Taiwan showed that obesity had a positive correlation with annual joint bleeding rate and thus leads to higher rate of haemophilic arthropathy.[14]

The development of inhibitors remains one of the most serious challenges in haemophilia patient care. This has been associated with significant morbidity and results in deterioration in quality of life (QoL) as well as with increased healthcare cost.[15] A European multicentre study evaluated the orthopaedic complications and QoL in severe haemophilia patients with or without inhibitors, they reported that higher number of patients with inhibitors suffered joint pain, reduced mobility, orthopaedic

complications and poor QoL as compared to those without inhibitors.[16] In addition, severe studies show the similar results and haemophilia patients with inhibitors experienced more bleeding complications and haemophilic arthropathy.[17-8]

Besides, there are emergence of age-related comorbidities, and these poses additional challenges in providing optimal care for this aging population of patients. Previously, there is little attention on cardiovascular disease (CVD) prevention in PWH. Several studies reported lower risk of CVD among PWH as compared with general male population due to perception that they are protected from thrombus formation by their hypocoagulability.[19-21] However, CVD in particular are increasingly being reported among PWH recently. A study by Pocoski et al. showed that cardiovascular comorbidities are more prevalent among PWH and they appear earlier in life in comparison to the general male population in United States.[22] Another study by Wang JD et al, reported prevalence of CVD among PWH was comparable to that of general population but appeared at earlier age among PWH.[23] In our study, there were five patients (6.7%) with ischemic heart disease and two patients (2.7%) had developed non haemorrhagic stroke. Hypertension is the commonest comorbidities among our study cohort. These results are consistent with ARCHER study, which included the largest Canadian cohort of PWH, in which 31.3% of them has hypertension and 10.5% has diabetes mellitus.[24] Besides, the prevalence of hypertension in PWH were also reported to be higher compared to the general population in several studies.[25-26] It was also highlighted that hypertension starts at younger age among PWH as compared to the general population, therefore blood pressure monitoring should be part of standard care in haemophilia patients.

There were several limitations in the present study which include being a single centre study and small sample size. Due to the small sample size, it is difficult to made a significant comparison of prevalence of comorbidities between our haemophilia patient with the general male population.

CONCLUSION

With the increasing age of adult haemophilia patients, management of this population will become more complex. Our study showed that a significant number of adult patients with haemophilia have comorbidities, in which majority of them have hypertension. Management of these age-related comorbidities in haemophilia patients remains a challenge due to its complexity and lack of evidence-based guidelines on usage of antithrombotic and antiplatelet agents in this condition. Therefore, future planning should include implementation of strategies on improvement in screening, risk modification and prevention of cardiovascular disease.

ACKNOWLEDGEMENTS

We thank the Director General of Health Malaysia for the permission to publish these findings.

FUNDING

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

DECLARATION OF CONFLICTING INTEREST

The authors declare that there is no conflict of interest.

APPROVAL

Ethical approval of this study was obtained from Malaysia Medical Research & Ethics Committee (NMRR ID-23-01195-HTS).

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ORIGINAL ARTICLE

Improving routine health data in Indonesia: Utilising the WHO data quality tool for *Aplikasi Satu Data Kesehatan*

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ABSTRACT

Introduction: Assessment of data quality in the era of big data is crucial for effective data management and use. However, there are gaps in data quality assessment for routine health data to ensure accountability. Therefore, this research aims to improve the routine health data quality that have been collected and integrated into *Aplikasi Satu Data Kesehatan* (ASDK) as the primary health data system in Indonesia.

Materials and Methods: This descriptive study utilises a desk review approach and employs the WHO Data Quality Assurance (DQA) Tool to assess data quality of ASDK. The analysis involves measuring eight health indicators from ASDK and *Survei Status Gizi Indonesia* (SSGI) conducted in 2022. The assessment focuses on various dimensions of data quality, including completeness of variables, consistency over time, consistency between indicators, outliers and external consistency.

Results: Current study shows that routine health data in Indonesia performs high-quality data in terms of completeness and internal consistency. The dimension of data completeness demonstrates high levels of variable completeness with most variables achieving 100% of the completeness.

Conclusion: Based on the analysis of eight routine health data variables using five dimensions of data quality namely completeness of variables, consistency over time, consistency between indicators, outliers. and external consistency. It shows that completeness and internal consistency of data in ASDK has demonstrated a high data quality.

KEYWORDS:
Data quality, Completeness, consistency

INTRODUCTION

Big data is important to monitor population health status to evaluate population-based health service quality, and to conduct research for innovative solutions which bring great promise for public health.[1] However, poor data quality has resulted in several consequences, including misallocation of health resources, misguided decisions and plans, missed opportunities, incorrect reports and follow-up actions and the indirect impact to the future direction of health plans.[2,3] To avoid the poor data quality, the assessment of data quality of health programs is conducted to review activities during the implementation period of the health program that must be carried out on a routine basis and using a standardised data quality assessment tool.[4–6] WHO has released a data quality tools (DQA) as a method for determining data quality criteria through routine data analysis by using the data quality dimensions such as completeness, consistency and timeliness.[7]

The utilisation of the data quality tool plays a crucial role in monitoring population health status, assessing the quality of population-based health services and supporting evidence-based research for innovative public health solutions.[8–10] Previous research shows that the quality of routine data remains poor in the primary health care facility as the main source of the health data.[11,12] Based on the study, a health management information system is not an effective tool for monitoring health-care performance and as a source of data for planning and decision-making. The similar condition happened in Indonesia where in 2012, the Ministry of Health had issued a data quality assessment tool called *Penilaian Mandiri Kualitas Data Rutin* (PMKDR) (Independent Routine Data Quality Assessment).[13,14] However, several barriers had been raised during the data quality assessment using the PMKDR tool i.e. limited data entered into the system, limited operating system and manual input using excel template which may cause the data inaccuracy.[15]

To streamline the diverse range of data from multiple health information systems in healthcare facilities across Indonesia, the Ministry of Health has introduced a unified system called ASDK, short for Aplikasi Satu Data Kesehatan (ASDK) or Single Health Data Application.[16] ASDK leverages District Health Information System (DHIS2), an open-source platform that enables data analysis, reporting and visualisation of various health program data. The integrated information system ensures that all data entered adhere to a standardised data quality assessment system, specifically employing the dimensions of aggregate data quality, given that reporting primarily relies on aggregate data.[17] Conducting a comprehensive review of data quality dimensions is crucial at

This article was accepted: 10 March 2024
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all levels, starting from the local health care facilities up to the national level.[16,17] The data collected from health facilities, most are individual data being reported to the higher levels with multiple purposes including reporting, program review, planning and monitoring activities to enhance the program quality as the aggregate data.

The assessment of aggregate data involves three processes: data review by using the aggregate data quality dimension approach, data verification by comparing reported data with field data and monitoring and evaluation systems that identify unqualified data. On the other hand, individual data undergoes assessment during the data collection on the early stage using the dimensions of individual data quality. Thus. the research is aimed to analyse the routine data quality using the WHO DQA which is integrated to the ASDK platform as the main health data resource in Indonesia.

MATERIALS AND METHODS

A cross-sectional study was carried out from January to February 2023 which involves 34 provinces in Indonesia. Convenient sampling technique was used to select the region from west to east of Indonesia. The study involved reviews of documents from ASDK and *Survei Status Gizi Indonesia* (SSGI) in the year 2022. The source of data was transferred from the monthly summary report in electronic form. Eight variables were selected namely number of births in health facilities, number of antenatal visits, number of maternal deaths, number of neonatal visits, number of stunting cases, number of tuberculosis cases treated, prevalence of stunting from SSGI (variable number 7) and ASDK (variable number 8). The detail of variables is as follow:

All the variables considered are key indicators of the health program and are required to be regularly collected on a monthly basis. The analysis of these variables was conducted using the desk review method. employing the WHO DQA on the ASDK platform. Initially, patient data is recorded in a healthcare information management system or register book and these records are compiled and submitted at the end of the month to the District Health Office as aggregate data. The report is then transferred to an electronic system known as the DHIS2. Additionally, the report for each program is submitted to the ASDK platform for further analysis, such as data quality assessment using the WHO DQA tool.

The authors monitored the reporting data of selected variables on the ASDK platform throughout January to December 2022, aiming to analyse the dimensions of data quality including completeness, consistency over time, internal consistency between indicators and external consistency. The WHO DQA tool was employed to analyse the five dimensions of data quality, namely completeness, consistency over time, consistency between indicators, outliers and external consistency.[19]

RESULTS

Completeness

Completeness refers to the availability of data, calculated as a percentage of the reports submitted to the system. A total of eight variables from 34 provinces were evaluated using the ASDK platform. However, only one variable was chosen for assessment and this assessment included eight provinces: Aceh, Sumatera Utara, Sumatera Barat, Riau, Jambi, Sumatera Selatan, Lampung and DKI Jakarta. The findings reveal that all provinces successfully submitted their annual reports for the year 2022 and no records were missing for the variable representing the number of pregnant women giving birth in a health facility (Figure 1).

Internal Consistency

Internal consistency over time

Internal consistency over time is analysed by comparing the data for the year to be analysed with the average data for the previous three years.[19] In this activity, the primary data was taken from the year 2022 and compared to previous 2 years from 2019 to 2021. The position of the dot on the vertical axis on this chart represents the numerator value for the month selected. The dot on the horizontal axis represents the average value in the same district over the previous 11 months. A difference of more than ± 33% would indicate inconsistency.

Based on the result as seen in Figure 2, it shows that most of the data is located between the lines which means that most of the data have consistency over time.

Consistency between indicators

Consistency between indicators is analysed by comparing two related variables.[19] In this study, two variables were being compared such as the number of pregnant women giving birth in a health facility and the number of antenatal visits. Comparison ratio between these two variables in each region is then compared to the national ratio. A difference of more than ± 33% would indicate inconsistency in the observed year. Internal consistency over time can be analysed using the consistency analysis menu with the type of analysis between indicators. Each dot on the scatter plot represents the total values for one district over the last 12 months. A diamond shape represents provinces with values that fall

Table I: List of variables

No	Variables	Metadata	Source
1	Number of pregnant women giving birth in a health facility	Data element	ASDK
2	Number of antenatal visits	Data element	ASDK
3	Number of maternal deaths	Data element	ASDK
4	Number of neonatal visits	Data element	ASDK
5	Number of stunting children	Data element	ASDK
6	Number of tuberculosis cases treated	Data element	ASDK
7	Prevalence of stunting	Data element	SSGI 2022
8	Prevalence of stunting (ASDK)	Indicator	ASDK

Table II: Data quality analysis using WHO data quality tools in ASDK

Province	1			2			3			4			5			6			1 and 2 (Internal consistency)	7 and 8 (External consistency)
	Dimensions																			
	1	2	4	1	2	4	1	2	4	1	2	4	1	2	4	1	2	4	3	5
Aceh	100	-0.29	33.33	100	-0.95	33.33	58.3	-0.34	0.00	100	-0.17	33.33	100	1.61	N/A	100	-0.12	8.33	-0.05	0.73
North Sumatra	100	0.03	25.00	100	0.61	25.00	58.3	-0.36	0.00	100	0.37	41.67	100	-0.14	16.67	100	0.00	N/A	-0.02	0.74
West Sumatra	100	0.05	33.33	100	0.70	33.33	50	0.17	0.00	100	0.40	25.00	100	-0.17	16.67	100	-0.03	N/A	0.00	0.53
Riau	100	0.01	25.00	100	0.64	25.00	58.3	0.12	0.00	100	0.26	25.00	100	0.25	16.67	100	-0.11	N/A	-0.09	0.79
Jambi	100	-0.03	41.67	100	0.66	41.67	58.3	0.71	0.00	100	0.39	41.67	100	0.02	16.67	100	-0.10	N/A	-0.08	0.76
South Sumatra	100	0.13	25.00	100	0.92	25.00	58.3	0.07	0.00	100	0.52	41.67	100	0.49	N/A	100	-0.14	N/A	-0.03	0.88
Bengkulu	100	0.03	N/A	100	0.67	N/A	50	0.68	0.00	100	0.39	N/A	100	-0.53	16.67	100	-0.02	N/A	-0.05	0.78
Lampung	100	0.09	33.33	100	0.75	33.33	50	-0.04	0.00	100	0.53	33.33	100	-0.07	16.67	100	-0.09	N/A	-0.03	0.65
Bangka Belitung	100	-0.01	N/A	100	0.57	N/A	58.3	0.72	0.00	100	0.38	N/A	100	-0.49	8.33	100	0.07	N/A	0.02	0.66
Riau islands	100	0.07	N/A	100	0.74	8.33	50	-0.24	0.00	100	0.55	0.00	100	0.37	16.67	100	-0.14	N/A	-0.11	0.51
DKI Jakarta	100	-0.13	8.33	100	0.40	8.33	58.3	-0.33	0.00	100	0.30	N/A	100	0.71	N/A	0	0.11	N/A	-0.05	0.78
West Java	100	0.06	33.33	100	0.65	25.00	58.3	0.23	8.33	100	0.44	33.33	100	0.18	16.67	100	0.02	N/A	-0.02	0.59
Central Java	100	0.02	8.33	100	0.60	8.33	50	-0.41	0.00	100	0.58	8.33	100	5.00	8.33	100	0.07	8.33	0.01	0.43
In Yogyakarta	100	-0.01	N/A	100	0.63	8.33	50	0.14	8.33	100	0.30	N/A	100	0.28	8.33	100	0.02	N/A	0.00	0.36
East Java	100	-0.12	N/A	100	0.20	8.33	58.3	-0.25	8.33	100	0.19	8.33	100	0.27	16.67	100	-0.01	8.33	0.18	0.56
Banten	100	-0.02	8.33	100	0.47	8.33	58.3	0.18	16.67	100	0.50	8.33	100	0.27	16.67	100	-0.12	8.33	-0.05	0.73
Bali	100	-0.14	25.00	100	0.39	33.33	50	0.11	0.00	100	0.22	25.00	100	0.31	N/A	100	-0.06	N/A	0.00	0.51
West Nusa Tenggara	100	-0.08	33.33	100	0.33	33.33	50	0.27	0.00	100	0.26	33.33	100	1.85	16.67	100	-0.07	N/A	0.01	0.40
East Nusa Tenggara	100	0.01	8.33	100	0.09	8.33	50	0.48	8.33	100	0.38	8.33	100	-0.79	8.33	100	-0.03	N/A	0.08	0.28
West Kalimantan	100	0.03	8.33	100	0.66	8.33	50	0.27	0.00	100	0.56	25.00	100	0.12	16.67	100	-0.08	N/A	-0.13	0.45
Central Kalimantan	100	0.00	33.33	100	0.62	41.67	50	0.22	8.33	100	0.45	41.67	100	0.22	N/A	100	0.13	N/A	-0.18	0.51
South Kalimantan	100	-0.07	8.33	100	0.51	8.33	58.3	0.16	0.00	100	0.26	33.33	100	0.02	8.33	100	-0.05	8.33	-0.01	0.55
East Kalimantan	100	-0.06	8.33	100	0.51	8.33	50	-0.26	0.00	100	0.66	16.67	100	0.84	16.67	100	-0.02	8.33	0.03	0.35
North Kalimantan	100	0.07	25.00	100	0.71	16.67	50	0.80	0.00	100	0.49	16.67	100	0.78	16.67	100	-0.15	8.33	0.01	0.31
North Sulawesi	100	-0.17	N/A	100	0.47	N/A	50	-0.53	8.33	100	0.30	41.67	100	0.62	8.33	100	-0.06	N/A	0.00	0.81
Central Sulawesi	100	0.08	8.33	100	0.61	8.33	58.3	0.05	0.00	100	0.44	33.33	100	0.22	16.67	100	-0.11	N/A	0.04	0.44
South Sulawesi	100	0.11	N/A	100	0.79	41.67	58.3	0.34	0.00	100	-0.87	N/A	100	-0.22	16.67	100	-0.14	N/A	0.01	0.55
Southeast Sulawesi	100	0.02	41.67	100	0.62	N/A	58.3	0.33	0.00	100	0.31	41.67	100	1.08	16.67	100	-0.20	N/A	0.07	0.57
Gorontalo	100	0.47	8.33	100	1.29	N/A	50	0.07	0.00	100	0.97	8.33	100	1.94	8.33	100	-0.20	N/A	0.14	0.56
West Sulawesi	100	0.23	16.67	100	0.90	25.00	58.3	0.50	0.00	100	0.77	N/A	100	0.07	16.67	100	-0.13	8.33	0.09	0.23
Maluku	100	-0.17	41.67	100	0.27	41.67	58.3	-0.29	8.33	100	0.12	33.33	100	1.03	N/A	100	-0.09	N/A	-0.11	0.64
North Maluku	100	0.03	33.33	100	0.58	33.33	58.3	0.60	0.00	100	0.49	41.67	100	0.80	8.33	100	-0.06	N/A	-0.01	0.58
Papua	100	0.02	N/A	100	0.70	N/A	50	1.34	16.67	100	0.70	N/A	100	1.09	8.33	100	-0.08	N/A	0.19	0.39
Papua Barat	100	0.85	N/A	100	0.67	N/A	50	-0.77	0.00	100	2.37	N/A	0	-1.00	0.00	100		N/A	-0.19	N/A

*The red result value indicates that the value exceeds the threshold on the analysis of data quality dimensions.

Variables:
1. Number of mothers giving birth at health facilities
2. Number of antenatal visits
3. Number of maternal deaths
4. Number of neonatal visits
5. Number of stunting children
6. Number of tuberculosis cases treated
7. The prevalence of stunting from SSGI
8. The prevalence of stunting data from ASDK

Quality dimensions:
1. Variable completeness
2. Consistency over time
3. Consistency between indicators
4. Outlier
5. External consistency

Unit	Data	Jan 22	Feb 22	Mar 22	Apr 22	May 22	Jun 22	Jul 22	Aug 22	Sep 22	Oct 22	Nov 22	Dec 22	Weight / Missing	
11 - ACEH	dqa_num_Jumlah Ibu melahirkan di faskes	6708.0	12157.0	18068.0	24327.0	25245.0	26144.0	26115.0	26128.0	26156.0	26151.0	26124.0	32945.0	0	
12 - SUMATERA UTARA	dqa_num_Jumlah Ibu melahirkan di faskes	16574.0	32195.0	51846.0	71982.0	92523.0	111628.0	111628.0	111628.0	111628.0	111628.0	111628.0	133681.0	0	
13 - SUMATERA BARAT	dqa_num_Jumlah Ibu melahirkan di faskes	6617.0	12946.0	19113.0	25261.0	31973.0	41019.0	41019.0	41019.0	41019.0	41019.0	41019.0	44859.0	0	
14 - RIAU	dqa_num_Jumlah Ibu melahirkan di faskes	8536.0	15861.0	23764.0	31800.0	39243.0	41786.0	41786.0	42810.0	43089.0	43748.0	43748.0	48910.0	0	
15 - JAMBI	dqa_num_Jumlah Ibu melahirkan di faskes	4596.0	9178.0	12664.0	17115.0	22562.0	26605.0	26712.0	26803.0	26885.0	27023.0	27171.0	27328.0	0	
16 - SUMATERA SELATAN	dqa_num_Jumlah Ibu melahirkan di faskes	11512.0	22671.0	33721.0	45060.0	55351.0	68559.0	68733.0	69054.0	69227.0	69451.0	69684.0	77203.0	0	
18 - LAMPUNG	dqa_num_Jumlah Ibu melahirkan di faskes	10611.0	21224.0	32535.0	44002.0	56013.0	67404.0	67404.0	67404.0	67404.0	67404.0	67404.0	72465.0	0	
31 - DKI JAKARTA	dqa_num_Jumlah Ibu melahirkan di faskes	25077.0	30072.0	44417.0	53628.0	62387.0	68361.0	68361.0	68361.0	68361.0	68361.0	68361.0	68361.0	0	

Fig. 1: Missing data analysis.

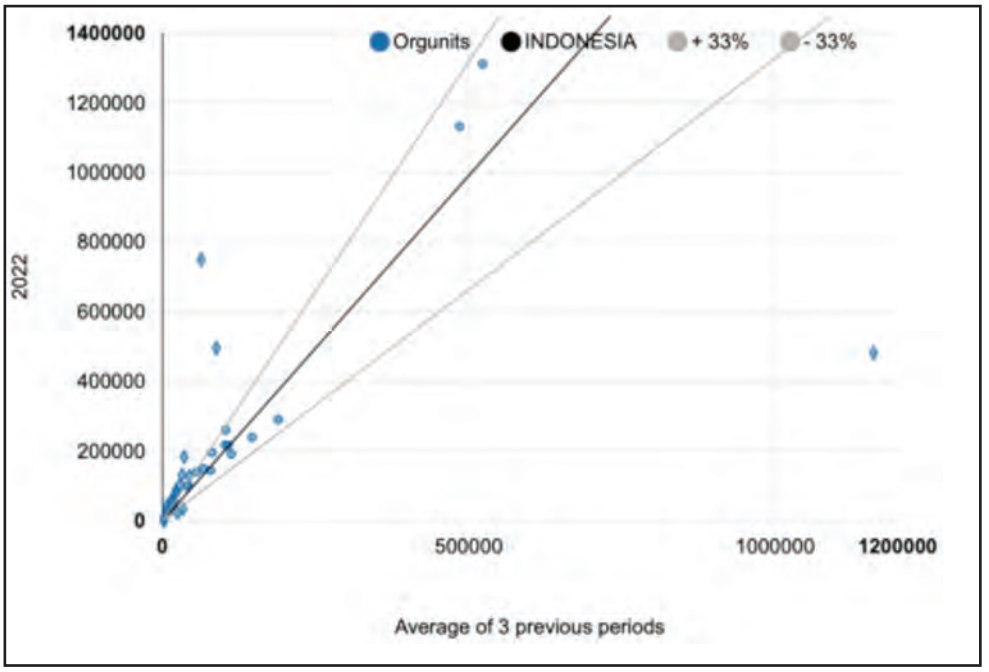

Fig. 2: Internal consistency analysis over time.

outside of the grey threshold lines. This result shows there was no diamond shape outside the lines which means a good internal consistency (Figure 3) and this variable is increasing over time.

Outlier

In this study, outliers are determined automatically by the WHO data quality tool that was identified by comparing monthly values to the mean of values for the year for the same unit. Data is classified as an 'extreme' outlier if it is more than three standard deviations and 'moderate' outliers for those between two and three standard deviations. The shaded values are indicative of data quality problems. This study shows that several data from 12 provinces in the earlier 2022 (January to April) was classified as outliers by the system (Figure 4). Based on DQA tool, grey shading is for moderate outliers while pink shading is for extreme outliers.[19]

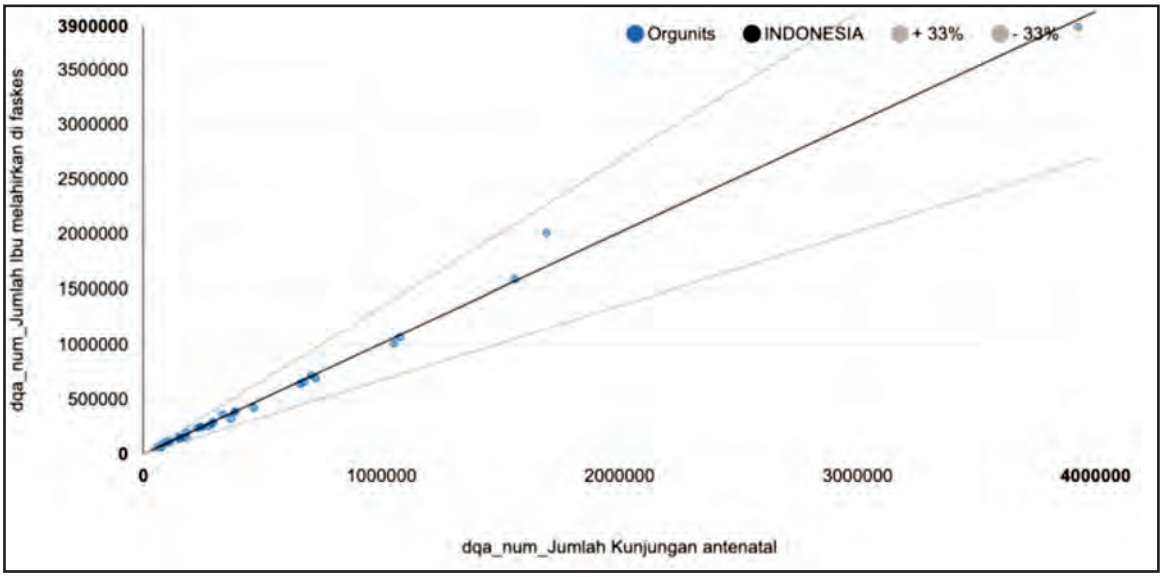

Fig. 3: Internal consistency analysis between indicators.

Unit	Data	Jan 22	Feb 22	Mar 22	Apr 22	May 22	Jun 22	Jul 22	Aug 22	Sep 22	Oct 22	Nov 22	Dec 22
11 - ACEH	dqa_num_Jumlah Ibu melahirkan di faskes	6708.0	12157.0	18068.0	24327.0	25245.0	26144.0	26115.0	26128.0	26156.0	26151.0	26124.0	32945.0
12 - SUMATERA UTARA	dqa_num_Jumlah Ibu melahirkan di faskes	16574.0	32195.0	51846.0	71982.0	92523.0	111628.0	111628.0	111628.0	111628.0	111628.0	111628.0	133681.0
13 - SUMATERA BARAT	dqa_num_Jumlah Ibu melahirkan di faskes	6617.0	12946.0	19113.0	25261.0	31973.0	41019.0	41019.0	41019.0	41019.0	41019.0	41019.0	44859.0
14 - RIAU	dqa_num_Jumlah Ibu melahirkan di faskes	8536.0	15861.0	23764.0	31800.0	39243.0	41786.0	41786.0	42810.0	43089.0	43748.0	43748.0	48910.0
15 - JAMBI	dqa_num_Jumlah Ibu melahirkan di faskes	4596.0	9178.0	12664.0	17115.0	22562.0	26605.0	26712.0	26803.0	26885.0	27023.0	27171.0	27328.0
16 - SUMATERA SELATAN	dqa_num_Jumlah Ibu melahirkan di faskes	11512.0	22671.0	33721.0	45060.0	55351.0	68559.0	68733.0	69054.0	69227.0	69451.0	69684.0	77203.0
18 - LAMPUNG	dqa_num_Jumlah Ibu melahirkan di faskes	10611.0	21224.0	32535.0	44002.0	56013.0	67404.0	67404.0	67404.0	67404.0	67404.0	67404.0	72465.0
31 - DKI JAKARTA	dqa_num_Jumlah Ibu melahirkan di faskes	25077.0	30072.0	44417.0	53628.0	62387.0	68361.0	68361.0	68361.0	68361.0	68361.0	68361.0	68361.0
32 - JAWA BARAT	dqa_num_Jumlah Ibu melahirkan di faskes	76834.0	129392.0	198496.0	263541.0	338285.0	400335.0	403994.0	407749.0	411572.0	411572.0	419050.0	434068.0
33 - JAWA TENGAH	dqa_num_Jumlah Ibu melahirkan di faskes	35005.0	66106.0	104465.0	134205.0	142171.0	158301.0	158301.0	158301.0	158301.0	158301.0	158301.0	158301.0
36 - BANTEN	dqa_num_Jumlah Ibu melahirkan di faskes	20040.0	37090.0	53820.0	71037.0	91938.0	104721.0	104721.0	104721.0	104721.0	104721.0	104721.0	104721.0
51 - BALI	dqa_num_Jumlah Ibu melahirkan di faskes	5010.0	9524.0	14813.0	16570.0	20027.0	23734.0	23734.0	23734.0	23734.0	23734.0	23734.0	38906.0

Fig. 4: Outlier analysis.

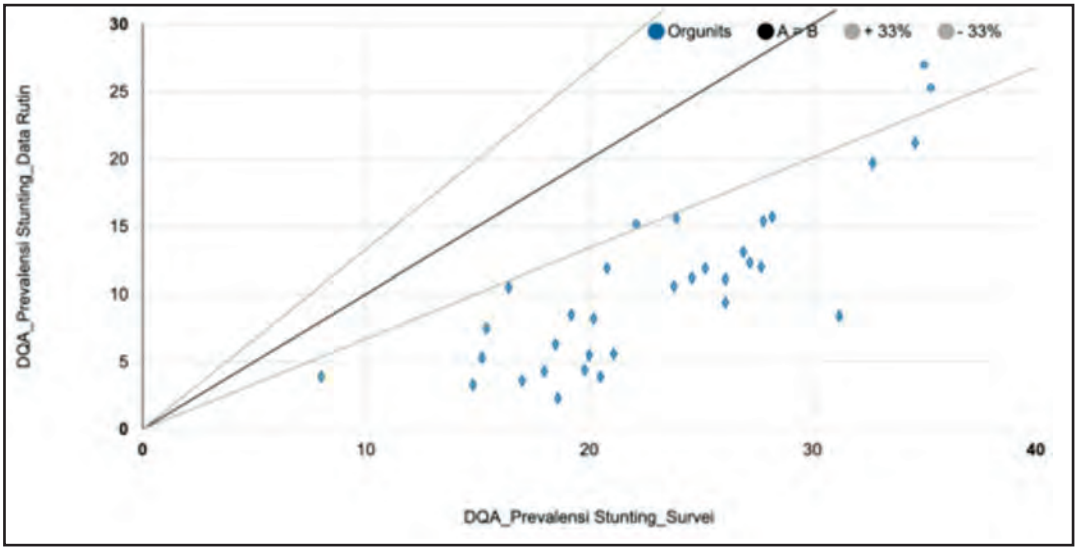

Fig. 5: External consistency analysis.

External consistency

External consistency is analysed by comparing the routine data in ASDK with other survey data sources. The two data sources being compared must have the same variables. In this study, we used the prevalence of stunting variables from two data sources, ASDK and SSGI in the year 2022. The ratio of the routine value to the survey value is then calculated. If the result is more than 0.33, it is said to be inconsistent. The output of the outlier analysis is a scatterplot with the national-level ratio of data source 1 compared to data source 2 depicted by the dark grey line. Subnational unit values that fall above or below the thresholds are potential data quality problems (Figure 5).

The study shows that most of the values fall below the thresholds for quality which represent differences from the national-level ratio that are greater than standard and are therefore potential data quality problems. In general, data quality analysis of the ASDK platform for the year 2022 is represented Table II.

DISCUSSION

ASDK is an integrated data platform which collects information from several *electronic registers such as Komunikasi Data platform* or *Komdat elektronik-Pencatatan dan Pelaporan Gizi Berbasis Masyarakat* or ePPGBM, *Sistem Informasi Tuberkulosis* or SITB and eKohort.[16] The system integration is a potential solution for improving data quality and data collection in developing countries.[20–22] However, some literature conclude that barriers and challenges in low resource settings might impact the quality of the data.[23,24] These studies suggest that the data integration must be followed by a routine data quality assessment. Thus, our study was conducted to assess the data quality using WHO DQA tool which integrates to the ASDK platform using the data quality dimensions such as completeness, Consistency over time, consistency between indicators, outlier and external consistency.

The recent study shows that most variables have improved the completeness of data such as number of mothers giving birth at health facilities. number of antenatal visits. number of neonatal visits. number of stunting in under five children. and number of treated tuberculosis cases. There is only one variable namely the number of maternal deaths which have insufficient data in all provinces. Many instances of incompleteness in this variable seem to arise due to lack of integration system or lack of infrastructure to record relevant data. Thus. the data for this variable is only available from January to May 2022.

The current research shows that the data have good consistency over time in several variables such as the number of mothers giving birth at health facilities. number of stunting children. and number of treated tuberculosis cases. There are no significant data fluctuations in the year 2022 compared to previous years. However. the other variables such as the number of antenatal and neonatal visits have poor consistency over time. These results indicate that the data quality is different in several periods which might be caused by several barriers during the data collection or data report such as the significant decrease number of visits amongst pregnant women to health facilities during pandemic[25] or other technical errors and barriers such as lack of infrastructure. and limited health care resources which brings impact to the technology adoption.[26]

In this study. we conducted a comparison of data between related indicators. specifically examining two variables: the number of pregnant women giving birth in a health facility and the number of antenatal visits. The findings reveal that there were no instances of a diamond shape outside the lines. indicating a satisfactory consistency between related indicators and an overall upward trend in the variables over time. According to the results. most provinces demonstrate good consistency between related indicators (Table II). Despite these positive findings confirmation through other data sources, known as external consistency. is essential. Many indicators in this study exhibit data classified as outliers. However, some areas do not present outliers in their data. The presence of outliers may result from various issues, such as errors in the data entry process in the information system used. The DQA tool can offer insights into the extreme values, explaining where and why a value deviates significantly from others around it by drilling down the data and displaying values by districts within the province.

External consistency was analysed by comparing the consistency of routine data from ASDK with data from other data sources. In this study, we used a variable of prevalence of stunting from ASDK and compared with the prevalence of stunting from SSGI 2022. The results show that the data from the two sources are inconsistent. There are significant differences between routine data and survey data in most provinces in Indonesia. Data consistency between routine data and survey data was only found in three provinces such as East Nusa Tenggara, North Kalimantan and West Sulawesi. This difference might occur due to several barriers including: 1) competency of data collectors, 2) differences in the selection of the respondents that were collected, 3) different data collectors where ASDK was taken by governance health workers while SSGI data was taken by surveyor, 4) data collection periods where routine data are collected in consistently every month while the survey data collection period is carried out only once a year.

This study provides an account of the data quality analysis using the WHO DQA tool, encompassing five data quality dimensions: completeness, consistency over time, consistency between related indicators, outliers and external consistency. The results reveal that the majority of provinces in Indonesia have adopted integrated data collection using the ASDK platform and consistently submit reports. Leading to high percentages of data completeness. However, limitation of this study is the absence of guidelines recommending the minimum acceptable percentage of data incompleteness in routine health data collection. Additionally, the study was unable to directly verify issues related to data quality dimensions at the data sources as it did not scrutinise the data collection process at the health facility level. Instead it relied on secondary data available in the ASDK, collected through an integration mechanism. Regarding data completeness, it is also influenced by the data integration

process from the information system of each variable's data source. It is possible that a health facility or health office has entered and sent data to a higher level but due to delayed data integration, the information is not yet accessible in the ASDK application. Nonetheless, further follow-up is necessary to confirm with the data source by conducting field assessments.

CONCLUSION

The current study shows that routine data quality in Indonesia performs high-quality data in terms of completeness and internal consistency. The dimension of data completeness demonstrates high levels of variable completeness with most variables achieving 100% of the completeness. Regarding the dimension of internal consistency over time, all variables except variables related to maternal and neonatal health show good consistency. Therefore, it indicates the need for improvement in these areas. Furthermore, the analysis reveals that the majority of provinces demonstrate good consistency between indicators due to the limited number of interrelated variables in *Aplikasi Satu Data Kesehatan* (ASDK). In terms of external consistency, the analysis shows inconsistent results between the prevalence of stunting from ASDK and prevalence of stunting from the SSGI 2022 survey. It might be caused by the data collection process in the field.

Based on the aforementioned results, the utilisation of WHO Data Quality Tools (DQA) on ASDK proves to be a selected tool for assessing the quality of routine data in Indonesia. While there are areas that require improvement such as to provide further training and guidance of the health information managers regarding the assessment methods. Furthermore, monitoring of the data quality on a routine basis using ASDK should be carried out at all levels through the desk review at the local health office. The limitation of this study is that this research solely relies on the secondary data recorded in the ASDK system and does not examine the data collection process from the lowest level nor the data transfer from lower levels to the central system.

CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest related to the research.

ACKNOWLEDGEMENT

We are grateful to all informants from national and sub-national level who took part in the study and the World Health Organisation Indonesia. for providing research funding.

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ORIGINAL ARTICLE

The effect of hypoxic ischemic encephalopathy towards multi-organ complications and its early outcome at a Malaysian district hospital

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ABSTRACT

Introduction: Hypoxic ischemic encephalopathy (HIE) is a clinically defined syndrome of disturbed neurologic function in the newborn with evidence of perinatal asphyxia. Stages of HIE are categorised into mild, moderate or severe based on the Sarnat classification. Neurological dysfunction constitutes a part of the wide spectrum of hypoxic ischemic insult as affected infants can have co-existing multi-organ dysfunction which further contributes to morbidities and mortality. This study aims to determine the relationship between the severity of HIE with multi-organ complications and early clinical outcomes.

Materials and Methods: All neonates who were admitted to the NICU at Hospital Sultan Abdul Halim between January 2018 to December 2022, who fulfilled the inclusion criteria were included. Demographic data, clinical course and investigation results were retrospectively obtained from the medical records.

Results: From a total of 90 infants (n = 90) who fulfilled our inclusion criteria, 31 (34%) were mild, 31 (34%) were moderate and 28 (31%) were severe HIE. The mean maternal age was 27 years. Common antenatal issues include diabetes mellitus (37.8%) and anaemia (22.2%). The Apgar scores at 1 and 5 minutes, initial resuscitation requiring intubation, chest compression and adrenaline were associated with higher severity of HIE (p < 0.05). Coagulation dysfunction was the most common complication (79.7%), followed by respiratory dysfunction (33.3%), cardiac dysfunction (28.9%), renal dysfunction (16.1%), haematological dysfunction (15.6%) and hepatic dysfunction (12%). Respiratory and haematological dysfunctions were significantly associated with higher mortality (p < 0.05). There was a significant longer hospital stay (p = 0.023), longer duration of ventilation (p < 0.001) and increase in frequency of seizures (p < 0.001) when comparing moderate and severe HIE patients to mild HIE patients. With increasing severity of HIE, there was also statistically significant higher mortality (p < 0.001).

Conclusions: There is a significant relationship between multiorgan dysfunction, the severity of HIE and mortality. Early anticipation of multi-organ injury is crucial for optimal early management which would reduce the mortality and improve the neurological outcome of the patients.

KEYWORDS:
Hypoxic ischemic encephalopathy, term newborn, multiorgan dysfunction, early outcome, mortality

INTRODUCTION

Neonatal encephalopathy is a clinically defined syndrome of disturbed neurologic function in the earliest days of life in an infant born at or beyond 35 weeks of gestation.[1] The most prominent cause of neonatal encephalopathy is perinatal asphyxia, more appropriately called hypoxic ischemic encephalopathy (HIE). There is no gold standard test for the diagnosis of HIE and it is a diagnosis made based on the clinical evidence and markers of acute hypoxia-ischemia.[2]

The incidence of neonatal encephalopathy in the developed world is estimated at 2 to 6 per 1000 live term births, with HIE occurring in approximately 1.5 per 1000 live term births.[2] It is also very common in Malaysia and the incidence of HIE in Malaysia in 2012 was 2.59 per 1,000 live births.[3]

HIE is classified as mild, moderate or severe based on Sarnat criteria and infants with moderate to severe encephalopathy are more likely to develop the long-term neurologic morbidity.[4] An alternative scoring system for identifying HIE in Malaysia NICUs is the Thompson score. Thompson score is based on features of HIE and it can have a maximum (worst) score of 22.[5] It allows a very precise clinical description of infants by assigning a numeric score rather than 'mild', 'moderate' or 'severe'. Day 1 Thompson score showed statistically significant correlation with morbidity and mortality of HIE babies, p-values 0.024 and 0.001 respectively.[6]

Neurological dysfunction is only part of the spectrum of hypoxic ischemic insult, infants can have co-existing multi-organ dysfunction which further contributes to subsequent morbidities and mortality.[7] The underlying cause of cell damage in each organ is likely to be secondary to a mixture of reperfusion, direct reactive oxidative stress, and cytokine injury.[8]

This article was accepted: 08 March 2024
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There are several studies evaluating organ(s) dysfunction in newborns with HIE. The prevalence of each organ involvement varies in previous literatures, with pulmonary involvement (26 to 86%), cardiac involvement (29 to 78%), renal involvement (15 to 72%), liver involvement (73.7 to 85%) and coagulopathy (41 to 50.9%).[9-12] A study by Michniewicz et al. (N = 57) comparing the incidence of end organ complications between stage II and stage III HIE patients showed that the latter had experienced significantly higher incidence of kidney and liver dysfunction, with thrombocytopaenia.[12] Sweetman et al. created a simple multi-organ dysfunction in neonatal encephalopathy scoring (MODE) system which include the cardiovascular, respiratory, gastrointestinal, haematological and neurological systems and found that neonates with higher MODE scores were significantly more likely to have moderate/severe NE (grade II/III) p-value ($p < 0.001$).[13]

The understanding of the relationship between organ dysfunction and HIE is lacking and there is currently no data available in the Malaysian population. The emergence of new biomarkers such as urinary cystatin C (CysC), kidney injury molecule-1, troponin T and brain natriuretic peptide showed good ability to predict early organ dysfunction involvement in neonatal encephalopathy.14,15 However, these biomarkers are not readily available in a developing country like Malaysia. Therefore, a good understanding of the co-existing and prevalence of organ dysfunction in newborns with HIE in Malaysia is important. The anticipation and early detection of cardiac, respiratory, hepatic, renal, haematological and coagulation dysfunction will assist the acute management and hopefully improve outcomes of these patients.

MATERIALS AND METHODS

We performed a retrospective study of 90 neonatal patients diagnosed with HIE in the neonatal intensive care unit (NICU), Hospital Sultan Abdul Halim between 2018 and 2022. Newborns with presumed HIE who fulfilled our eligibility criteria were included and we retrieved the relevant data from our hospital medical records.

Inclusion Criteria

We included late preterm and term infants born at or beyond 35 weeks of gestation who met all the diagnostic criteria for HIE:

(a) Any three features of encephalopathy within 72 hours of birth, such as abnormal level of consciousness (e.g. hyperalert state, lethargy, stupor or coma), abnormal muscle tone, abnormal deep tendon reflexes, seizure, abnormal Moro reflex, abnormal sucking reflex, abnormal respiratory pattern and oculomotor or pupillary abnormalities.
(b) Three or more findings of acute perinatal events, such as arterial cord pH < 7.00, Apgar score < 5 at 5 minutes of life, evidence of multi-organ system dysfunction within 72 hours of birth, evidence of foetal distress on antepartum monitoring, abnormal electroencephalogram and abnormal imaging of the brain showing ischaemia or oedema within seven days of birth.[16]

We further classify the severity of HIE newborns as mild, moderate or severe according to modified Sarnat's criteria[17,18] and Thompson score.[5] The highest Thompson score obtained for the infant was used as classification. Infants with score 1 to 10 were considered to have mild HIE, 11 to 14 have moderate HIE and 15 to 22 were considered to have severe HIE.[6] If the classification of the severity between the Sarnat staging and Thompson score is different, the more severe one would be chosen to classify the patient.

Exclusion Criteria

Patients with underlying congenital cerebral infections/abnormalities or inborn errors of metabolism that could account for the encephalopathy are excluded.

Criteria for Organ Dysfunction and Outcome

Although multi-organ dysfunction is well described and included in the criteria of HIE there are no standardised consensus definitions of individual organ dysfunction. We defined the criteria for involvement of each organ as follows based on previous literature.

Early outcomes are measured based on length of hospital stay, presence of clinical or subclinical neonatal seizures, in-hospital mortality and presence of MRI abnormalities done in 10 to 14 days of life.

Statistical Analysis

The data was analysed using SPSS version 29. Continuous data is presented as mean/SD or median/IQR while categorical data is presented as frequency/percentage. Categorical data was analysed using Chi-square or Fisher's exact test. The relationship between the three severities of HIE was analysed using one way ANOVA for normally distributed data or Kruskal Wallis test for non-normally distributed data. Post hoc Dunn-Bonferroni test was performed for two groups comparison. Independent T test was used to measure the differences between the survivor and non-survivor groups (normally distributed) or Mann-Whitney test for non-normally distributed data. A value of $p < 0.05$ is considered statistically significant.

RESULTS

A total of 98 newborns were identified with the diagnosis of neonatal encephalopathy. Two patients were excluded in view of prematurity at 33 weeks, five were excluded as they failed to meet the diagnosis criteria for HIE and one was excluded as he was diagnosed with Edward syndrome. The remaining 90 patients were eligible and subjected to this study.

Table II shows the maternal characteristics of the affected newborn. The mothers of the affected babies had a mean age of 27 (8) years, and the majority were of Malay ethnicity (77, 85.6%). 47 (52.2%) of them were primigravida. Diabetes mellitus (34, 37.8%) and anaemia (20, 22.2%) were the two most common maternal illnesses and none of them were affected by eclampsia, chorioamnionitis and placenta praevia. There was no significant difference in maternal age, ethnicity, primigravida, diabetes mellitus, hypertension, eclampsia, anaemia, abruptio placenta and obesity among the mothers of newborns with HIE.

Table I: Criteria for organ dysfunction

Cardiac dysfunction	Measured qualitatively by evaluating the heart haemodynamics and contractility using echocardiography.[19] Hypotension requiring inotropic support beyond 2 hours post birth was also included as having cardiac dysfunction.[10]
Respiratory dysfunction	Needed respiratory support with 40% oxygen for at least the first 4 hours after birth.[9]
Hepatic dysfunction	Liver enzymes aspartate aminotransferase >100 IU/l or alanine aminotransferase > 100 IU/l at any time during the first week after birth.[9]
Renal dysfunction*	Serum creatinine greater than 100 mm/L (1.5 mg/dL).[13] An increased of serum creatinine of at least 17 to 27 mm/L (0.2 to 0.3 mg/dL) per day from a previous lower value.[20]
Haematological dysfunction	Thrombocytopenia (platelet count (PLT) <100,000/mm3.[10] International normalized ratio (INR) >1.5, activated partial thromboplastin time (aPTT) >50 seconds or features of haemorrhagic diathesis.[12]
Multiorgan dysfunction	Involvement of two or more organ dysfunctions (cardiac, respiratory, hepatic, renal, haematological). Central nervous system dysfunction is excluded since it is considered a baseline characteristic for HIE.

*Blood for renal profile must be taken at least after 24 hours of life

Table II: Maternal characteristics of newborns with hypoxic ischaemic encephalopathy (n = 90)

Variable	No. (%)				
	Total (n = 90)	Mild HIE (n = 31)	Moderate HIE (n =31)	Severe HIE (n = 28)	*p*-value
Age*	27 (8)	26 (5)	27 (7)	29.5 (11)	0.667
Ethnicity					0.548
Malay	77 (85.6)	26 (83.9)	29 (93.5)	22 (78.6)	
Chinese	2 (2.2)	1 (3.2)	0 (0)	1 (3.6)	
Indian	6 (6.7)	2 (6.5)	2 (6.5)	2 (7.1)	
Others	5 (5.6)	2 (6.5)	0 (0)	3 (10.7)	
Primigravida	47 (52.2)	21 (67.7)	15 (48.4)	11 (39.3)	0.080
Diabetes mellitus	34 (37.8)	15 (48.4)	9 (29)	10 (35.7)	0.280
Hypertension	2 (2.2)	1 (3.2)	0 (0)	1 (3.6)	0.760
Eclampsia	0 (0)	0 (0)	0 (0)	0 (0)	NA
Chorioamnionitis	0 (0)	0 (0)	0 (0)	0 (0)	NA
Anaemia	20 (22.2)	6 (19.4)	7 (22.6)	7 (25.0)	0.872
Abruptio placentae	1 (1.1)	0 (0)	1 (3.2)	0 (0)	1.000
Placenta previa	0 (0)	0 (0)	0 (0)	0 (0)	NA
Obesity	14 (15.6)	4 (12.9)	5 (16.1)	5 (17.9)	0.935

*Data presented as median (interquartile range).

Table III shows that most babies affected were from the 37 weeks to 40 weeks gestation group (60, 66.7%) and they had a good weight of more than 2.5 kg (80, 88.9%). Statistically, there were no significant differences in terms of birth weight, gestational age, growth status, gender, mode of delivery or being inborn in the different HIE categories. The mean APGAR score at 1 and 5 minutes were 3.6 (2.2) and 5.6 (2.7) respectively. APGAR score was significantly lower as the severity of HIE increased ($p < 0.001$). The mean pH from cord blood gas or blood gas taken in 1 hour of life was 6.99 (SD 0.19). 89 (98.9%) of them required oxygen support at initial resuscitation and severe HIE neonates have significantly higher chance of ETT ventilation ($p = 0.038$), chest compression ($p < 0.001$) and adrenaline requirement ($p < 0.001$). There was also a higher proportion of them in increasing severity of HIE to receive cooling therapy ($p < 0.001$).

Table IV demonstrates that coagulation dysfunction was the most common complication (63, 79.7%), followed by respiratory dysfunction (30, 33.3%), cardiac dysfunction (26, 28.9%), renal dysfunction (14, 16.1%), haematological dysfunction (14, 15.6%) and hepatic dysfunction (9, 12%). Coagulation and haematological dysfunction showed a significant difference among the three groups with p-values of 0.006 and 0.019 respectively. Multi-organ dysfunction affected (41/90) 45.6% of the subjects and it showed significant differences among the three groups ($p = 0.011$). There was a significantly longer hospital stay ($p = 0.023$), longer duration of ventilation ($p < 0.001$) and increased in

Table III: Characteristics of newborns with hypoxic ischaemic encephalopathy (n = 90)

Variable	No. (%)				
	Total (n = 90)	Mild HIE (n = 31)	Moderate HIE (n = 31)	Severe HIE (n = 28)	*p*-value
Birth weight					0.766
≤1500 g	0 (0)	0 (0)	0 (0)	0 (0)	
1501 to 2500 g	10 (11.1)	4 (12.9)	4 (12.9)	2 (7.1)	
≥2501 g	80 (88.9)	27 (87.1)	27 (87.1)	26 (92.9)	
Gestational age					0.053
35 to 36weeks+ 6days	10 (11.1)	1 (3.2)	4 (12.9)	5 (17.9)	
37 to 40 weeks	60 (66.7)	26 (83.9)	16 (51.6)	18 (64.3)	
> 40 weeks	20 (22.2)	4 (12.9)	11 (35.5)	5 (17.9)	
Growth status					0.427
SGA	6 (6.7)	2 (6.5)	1 (3.2)	3 (10.7)	
AGA	81 (90)	29 (93.5)	29 (93.5)	23 (82.1)	
LGA	3 (3.3)	0 (0)	1 (3.2)	2 (7.1)	
Male	58 (64.4)	20 (64.5)	21 (67.7)	17 (60.7)	0.824
Singleton	90 (100)	31 (100)	31 (100)	28 (100)	NA
Mode of delivery					0.394
Vaginal	36 (40)	14 (45.2)	10 (32.3)	12 (42.9)	
Forceps	17 (18.9)	7 (22.6)	5 (16.1)	5 (17.9)	
Vacuum	7 (7.8)	1 (3.2)	4 (12.9)	2 (7.1)	
EMLSCS	28 (31.1)	9 (29.0)	10 (32.3)	9 (32.1)	
ELLSCS	2 (2.2)	0 (0)	2 (6.5)	0 (0)	
APGAR score					
at 1 min*	3.6 ± 2.2	4.4 ± 2.0	4.1 ± 1.9	2.1 ± 1.9	<0.001
at 5 min*†	5.6 ± 2.7	7.0 ± 2.5	6.4 ± 2.0	3.1 ± 2.0	<0.001
Blood gas pH*	6.99 ± 0.19	6.99 ± 0.18	7.03 ± 0.20	6.96 ± 0.18	0.313
Resuscitation at birth					
Oxygen	89 (98.9)	31 (100)	30 (96.8)	28 (100)	1.000
Bag-and-mask ventilation	85 (94.4)	28 (90.3)	29 (93.5)	28 (100)	0.365
Chest compression	27 (30)	5 (16.1)	4 (12.9)	18 (64.3)	<0.001
ETT ventilation	79 (87.8)	25 (80.6)	26 (83.9)	28 (100)	0.038
Adrenaline	19 (21.1)	3 (9.7)	3 (9.7)	13 (46.4)	<0.001
Inborn	76 (84.4)	30 (96.8)	24 (77.4)	22 (78.6)	0.051
Cooling therapy	68 (75.6)	12 (38.7)	28 (90.3)	28 (100)	<0.001

*Data presented as mean ± standard deviation. †n=76, after excluding missing data.
SGA: small for gestational age; AGA: appropriate for gestational age; LGA: large for gestational age; EMLSCS: emergency lower segment Caesarean section; ELLSCS: elective lower segment Caesarean section; ETT: endotracheal tube.

frequency of seizures ($p < 0.001$) when comparing moderate and severe HIE patients to mild HIE patients. However, post hoc analysis showed no statistically significant difference between moderate and severe HIE groups. With increasing severity of HIE, there was also statistically significance higher mortality ($p < 0.001$). 53 of the subjects underwent MRI at day 10 to 14 of life and 36/53 (67.9%) had evidence of HIE on the scan; however, no difference was found in the occurrence between the three groups.

Table V shows comparison of factors affecting survivors and non-survivors. Respiratory and haematological dysfunctions were significantly higher among non-survivor groups with the p-value of 0.018 and 0.019 respectively. All the non-survivors had multi-organ dysfunction and this was significantly higher ($p < 0.001$) compared to the survivors group. Lower APGAR scores at 1 and 5 minutes were observed among non-survivor group as well ($p < 0.001$). There were no statistically significant differences in seizure occurrence, cooling therapy requirement and being outborn among the two groups.

DISCUSSION

Antenatal, intrapartum and initial resuscitation affects the severity and outcome of newborns with HIE. Our study revealed diabetes mellitus, anaemia and obesity are the most common antenatal problems, and this finding is similar to our country's national data reported in 2012.[3] Gestational diabetes mellitus is common, with the recent meta-analysis in 2021 showing a prevalence of 21.5% among Malaysian women. Maternal hyperglycaemia significantly increases the risks of low Apgar scores and asphyxia-related neonatal complications in the infants.[21,22] A standardised screening for gestational diabetes mellitus and proper antenatal follow up are crucial to reduce the risk of HIE. Our current study did not reveal any maternal factor that significantly affected the severity of HIE. However, intrapartum factors including low APGAR, extensive initial resuscitation requiring intubation, CPR or adrenaline highly correlate with the severity of HIE; this is similar to observations in another study.[3]

In addition to CNS involvement, 81% of the subjects have at least 1 other organ involvement. Coagulation dysfunction was the most common complication (79.7%) and showed statistically significant differences among the different

Table IV: Clinical problems, organ(s) dysfunction and outcome of newborns with hypoxic ischaemic encephalopathy (n = 90)

Variable	No. (%)				
	Total (n = 90)	Mild HIE (n = 31)	Moderate HIE (n =31)	Severe HIE (n = 28)	*p*-value
Cardiac dysfunction	26 (28.9)	5 (16.1)	12 (38.7)	9 (32.1)	0.132
Respiratory dysfunction	30 (33.3)	7 (22.6)	12 (38.7)	11 (39.3)	0.292
Hepatic dysfunction*	9 (12)	3 (16.7)	3 (10.0)	3 (11.1)	0.816
Renal dysfunction†	14 (16.1)	2 (6.9)	5 (16.1)	7 (25.9)	0.163
Haematological dysfunction	14 (15.6)	2 (6.5)	3 (9.7)	9 (32.1)	0.019
Coagulopathy#	63 (79.7)	13 (59.1)	24 (80)	26 (96.3)	0.006
Multi-organ dysfunction	41 (45.6)	8 (25.8)	15 (48.4)	18 (64.3)	0.011
Number of organ(s) dysfunction≠	1 (2)	1 (2)	1 (2)	2 (2)	<0.001
Highest oxygen support					0.171
Nasal prong oxygen	1 (1.1)	1 (3.2)	0 (0)	0 (0)	
Non-invasive ventilation	3 (3.3)	3 (9.7)	0 (0)	0 (0)	
Conventional ventilation	80 (88.9)	24 (77.4)	30 (96.8)	26 (92.9)	
HFOV	6 (6.7)	3 (9.7)	1 (3.2)	2 (7.1)	
Length of hospital stay (day)≠	11 (10)	7 (9)	13 (13)	12 (13)	0.023
Ventilation duration (day)≠	4 (4)	1 (2)	4 (3)	5 (3)	<0.001
Seizures (clinical/subclinical)	36 (40)	4 (12.9)	16 (51.6)	16 (57.1)	<0.001
Positive MRI findings of HIEμ	36 (67.9)	6 (50)	20 (74.1)	10 (71.4)	0.343
Alive	78 (86.7)	31 (100)	30 (96.8)	17 (60.7)	<0.001

*n=75, after excluding missing data ; †n=87, after excluding missing data ; #n=79, after excluding missing data ;μ=53, after excluding missing data ; ≠Data presented as median (interquartile range). HFOV: high frequency oscillation ventilation ;MRI: magnetic resonance imaging.

Table V: Comparison of survivors and non-survivors of hypoxic ischaemic encephalopathy (n = 90)

Variable	No. (%)			
	Total (n = 90)	Survivor (n = 78)	Non-survivor (n = 12)	*p*-value
Cardiac dysfunction	26 (28.9)	20 (25.6)	6 (50)	0.097
Respiratory dysfunction	30 (33.3)	22 (28.2)	8 (66.7)	0.018
Hepatic dysfunction*	9 (12.0)	7 (10.9)	2 (18.2)	0.612
Renal dysfunction†	14 (16.1)	10 (13.2)	4 (36.4)	0.072
Haematological dysfunction	14 (15.6)	9 (11.5)	5 (41.7)	0.019
Coagulopathy#	63 (79.7)	51 (76.1)	12 (100)	0.112
Multi-organ dysfunction	41 (45.6)	29 (37.2)	12 (100)	<0.001
Number of organ(s) dysfunction≠	1 (2)	1 (1)	3 (1)	<0.001
Seizure	36 (40)	29 (37.2)	7 (58.3)	0.210
Cooling therapy				0.384
Completed active cooling	40 (44.4)	36 (46.2)	4 (33.3)	
Completed passive cooling	16 (17.8)	12 (15.4)	4 (33.3)	
No cooling/incomplete cooling	34 (37.8)	30 (38.5)	4 (33.3)	
APGAR score at 1 min≠	3 (3)	4 (2)	0.5 (2)	<0.001
APGAR score at 5 min≠&	6 (3)	6 (3)	2 (3)	<0.001
Outborn	14 (15.6)	10 (12.8)	4 (33.3)	0.088

*n = 75, after excluding missing data; †n = 87, after excluding missing data; #n = 79, after excluding missing data; and n = 76, after excluding missing data; ≠Data presented as median (interquartile range)

severities of HIE (p = 0.006), this result is comparable to a study by Michniewicz et al, which also showed highest incidence of coagulation dysfunction in their subjects.[12] Haematological dysfunction and thrombocytopenia, which are closely related to coagulopathy, also showed significant differences between different stages of HIE and between survivors and non-survivor groups (p = 0.019). The disturbance in haemostasis is due to various factors after birth asphyxia. Oxygen deprivation to the liver and bone marrow may suppress the coagulation factors and platelet production while disseminated intravascular coagulopathy may follow a severe asphyxial event.[23] In addition, hypothermia therapy, which was initiated in 75.6% of newborns in this current study may impair haemostasis by slowing enzymatic function of the coagulation cascade, impairing thrombin generation and further triggering DIC.[24]

Respiratory and cardiac dysfunctions were the next commonest complications following coagulopathy with involvement of 33.3% and 28.9% of the newborns. This was similar to other studies with reported incidences of between 20 to 30%.[11,12] 87.8% of the newborns in this study required intubation at birth but most of them were ventilated with low ventilation setting. However, some of them developed respiratory failure and this may be directly related to hypoxia induced persistent pulmonary hypertension (PPHN) or be indirectly associated with meconium aspiration syndrome or perinatal sepsis/pneumonia.[25]

Cardiovascular dysfunctions include myocardial damage, right ventricular (RV) dysfunction and altered transitional circulation, all of which will further lead to greater risk of adverse cerebral injury.[26] Giesinger et al,[27] suggested that a

complete haemodynamically assessment (including clinical evidence, biochemical evaluation and echocardiography) should not only be performed early in all infants with HIE treated with a cardiovascular agent, but also in infants with moderate to severe HIE before or at 24 hours after initiation of therapeutic hypothermia (TH) to identify myocardial dysfunction that may not be clinically apparent. Our incidence might underestimate the actual incidence as many of our subjects involved did not have a biochemical evaluation or echocardiography done in view of lack of resources and expertise.

Renal dysfunction affected 16.1% of HIE newborns in this study. This is lower compared to other studies, which varied from 22 to 70%.[28] This study also did not show significant differences of renal involvement in different stages of HIE. Urine output and serum creatinine were used to identify patients with renal injury in our study. However, creatinine is not an ideal biomarker of neonatal AKI as it peaks late (often lags 48 to 72 hours behind the onset of injury) and may reflect maternal creatinine level.[29] Cystatin C and Neutrophil gelatinase-associated lipocalin (NGAL) are better biomarkers to reflect renal injury but are not readily available in our center.[14,30]

Hepatic dysfunction is the least affected organ, with only 9/75 (12%) of newborns affected and it showed no significant differences among the different HIE severity. This is in contrast with previous studies which showed the incidence to be high at 80 to 85%.[9,10] This could be due to improvement in HIE management in terms of hypothermia therapy as both previous studies were done prior to the hypothermia era. The pathogenesis of liver injury is related to the hypoxic ischemic insult causing formation of blebs and ruptures of plasma membrane in the liver resulting in the release of intracellular enzymes (AST, ALT, ALP).[31]

This study also showed statistically significant relationship between the number of organ dysfunction, severity of HIE and infant death, which were also demonstrated in other studies.[11,23] With increasing severity of HIE, there was also statistically significant higher mortality. Moderate and severe HIE babies also had significantly longer hospital stay, longer duration of ventilation and higher rate of seizure activity when compared to mild HIE babies. However, there were no differences between moderate and severe HIE babies. This may be in part due to shorter durations of ventilation in severe HIE infants because of higher mortality.

MRI brain abnormality did not show a significant difference among the groups as there was much missing data, especially from the mild and severe HIE groups. We did not proceed with the MRI brain in some mild HIE babies due to cost limitations; whereas for the severe HIE babies, 11 babies passed away prior to the MRI brain, which was usually done at second week of life for better prognostication value.[32]

Several limitations were identified in this study. Our scales and criteria for organ dysfunction were selected based on previous studies and there were no standardized criteria for them. This may explain the inconsistent findings of the incidences in organ dysfunction among the studies. This was an observational study among HIE cohorts without having a normal control. The strength of this study was the use of readily available biomarkers and clinical criteria that could be applied to most hospitals with limited resources.

CONCLUSION

In conclusion, this study shows the relationship of multiorgan dysfunction with hypoxic ischemic encephalopathy (HIE) severity and outcome. Early anticipation of multi-organ injury is crucial for optimal early management which will reduce the mortality and improve the neurological outcome of the patients. In the absence of multiorgan dysfunction, the origin of neonatal encephalopathy should be carefully investigated as perinatal asphyxia might not be the underlying aetiology.

CONFLICT OF INTEREST

The authors have no conflict of interest to declare.

ETHICAL APPROVAL

The study had been registered under National Medical Research Register (NMRR) and ethical approval by the Medical Research and Ethics Committee (MREC). Research ID: RSCH ID-23-02012-TYG.

ACKNOWLEDGEMENTS

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

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The current state of understanding of oncology expanded access programs in Malaysia

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ABSTRACT

Introduction: An expanded access program (EAP) is a regulatory mechanism that provides access to an investigational drug, which is not approved for use, in treating life-threatening conditions when all the standard-of-care treatments are exhausted.

Materials and Methods: An online, anonymous, voluntary survey was conducted to assess the level of knowledge and understanding about EAPs among Malaysian oncologists using SurveyMonkey® between April 2020 and June 2020. Oncologists who had enquired about EAP in the past, were invited at random to participate in the survey. Participants who did not provide consent or failed to complete the survey were excluded.

Results: A total of 15 oncologists participated in the survey, from both public (46.6%) and private (46.6%) practices. Most respondents (80%) had filed between 1 to 10 EAP applications in the past 12 months. For 73.3% respondents, resources or training were not provided for EAPs from institutions. Around 53% of the respondents reported that their knowledge of EAPs and application processes including country regulations is 'good'. The majority of respondents (73.3%) reported that the educational modules on an overview of EAPs, country regulations and the EAP application process will be beneficial. Most participants received information about the existing EAPs either by reaching out to a pharmaceutical sponsor or through another health care provider and some received information about the existing EAPs through their institutions or patients/caregivers. Most of the respondents recommended that pharmaceutical companies should have readily available information related to the availability and application of EAPs for all pipeline products on their websites.

Discussion: EAPs are crucial treatment access pathways to provide investigational drugs to patients who have exhausted their treatment options and are not eligible for participation in clinical trials. Malaysian oncologists have a fair understanding about the EAPs and the application processes.

Conclusion: Additional training and awareness are needed for Malaysian oncologists to upscale the utilisation of EAPs.

KEYWORDS:
Expanded access program, oncology, investigational drug, life-threatening conditions

INTRODUCTION

Expanded access program (EAP) is one of the treatment access pathways that provides the use of investigational medicinal products (IMP), which is otherwise not approved for use, at a defined conditions to patients.[1] Depending on the country or region of the world, these programs are known by different terms such as 'Expanded access', 'Compassionate use', 'Compassionate drug use', 'Preapproval access', 'Special access', 'access' and 'Treatment use'.[2] These programs are made available to patients who are not eligible for a clinical trial and have exhausted all standard of care treatments for a life-threatening or serious diseases.[1] Compared to clinical trials, the eligibility criteria for EAPs are usually less rigorous and are more in line with the indication of the drug for which the approval is sought.[3-7]

In Malaysia, EAPs are available for the treatment of patients with life-threatening diseases with high unmet medical needs.[3] There is a guideline in place for importing/manufacturing products which are not registered with the Ministry of Health (MOH) Malaysia Drug Control Authority (DCA) for treating life-threatening diseases. Unregistered products may be brought to Malaysia via approved import license issued by DCA. Any serious or unexpected adverse drug reactions of the treatment is required to be reported to the Centre for Investigational New Products.[3]

In this study, we report result of a survey that primarily focuses on assessing the level of understanding of Malaysian oncologists for EAPs based on the different parameters including educational needs, perceptions and perspectives.

MATERIALS AND METHODS

An online survey that was anonymous, voluntary, structured and self-administered was conducted using SurveyMonkey® online questionnaire tool between 29 April 2020 and 17 June 2020. Randomly invited oncologists took part in the survey and were required to answer all the survey questions. The oncologists who had contacted Pfizer previously for oncology related EAPs were eligible to be a part of the survey. The exclusion criteria of the survey involved participants who could not furnish informed consent (e. g., language barriers and unavailability of an interpreter)8 or failed to complete the survey (exclusion was confirmed at the discretion of the principal investigator). The participants were excluded from the study, if they were not comfortable with the language of the interview that was taken.

This article was accepted: 15 February 2024
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The survey questionnaire consisted of 13 questions and qualitative data was extracted based on the questionnaire. The questionnaire comprised of three subscales: i) 'demographics and experience in practice with EAPs applications' (four items), (ii) 'educational needs' (three items) and (iii) 'perception and perspectives' (six items).

The study met the tenets of the 18th World Medical Assembly, Helsinki, 1964, and its subsequent revisions. Potential participants were notified about the study objective and the scope of the participants involvement. The survey participants did not receive any financial incentives and no approval was required from the ethics committee (EC).

A literature search was carried out using PubMed and Google Scholar databases to identify articles published on EAPs in Malaysia. Studies published between 1st January 2011 and 31st December 2021 were screened for information related to EAPs in Malaysia, the current regulation, the procedure, the Health Care Providers (HCPs) experiences, and other associated challenges.

RESULTS

A total of 15 oncologists from Malaysia answered the survey questions. Most of the respondents either practiced in a public or government hospital/clinic (7 (46.6%)) or a private hospital/clinic (7 (46.6%)). One of the respondents worked in both public and private hospital/clinic (Figure 1a). Among the participants, eight respondents (53.3%) reported having an oncology practice experience between 10 to 20 years (Figure1b). A total of 12 (80%) respondents reported having filed between 1 to 10 applications for EAPs in the past 12 months when the survey was undertaken (Figure 1c).

According to 11 (73.3%) of the respondents, their institutions did not provide the resources/training for EAPs applications whereas only four (26.6%) of the respondents reported having the resources/training for EAPs at their institution (Figure 2a). The total number of respondents that reported having 'good' knowledge of EAPs and application processes including country regulations was eight (53.3%) (Figure 2b). In addition, among other respondents, one (6.6%) participant rated their adequacy of knowledge as 'very good', one (6.6%) rated it as 'excellent', two (13.3%) rated their knowledge to be 'poor' and three (20%) rated it as 'Fair' (Figure 2b). Majority of the respondents (10 (66.6%)) reported being 'mostly clear' about the application process set in place by pharmaceutical sponsors for applying for EAPs while the rest of participants reported that they were either 'very clear' (2 (13.3%)) or 'somewhat unclear' (2 (13.3%)) regarding the application process set in for applying for EAPs (Figure 3b). Additionally, most respondents 10 (66.6%) stated being 'mostly clear' about their country's regulations and processes set in place by the regulatory authorities for applying for EAPs, other respondents were 'somewhat unclear' or 'totally unclear' (4 (26.6%) and (1 (6.6%)) (Figure 2d). Furthermore, most of the participants got to know about an existing EAPs either by reaching out to a pharmaceutical sponsor or through another health care provider (Figure 2c). Few other respondents stated that they were informed about an existing EAPs either through their institutions or through patients or caregivers. In addition, most respondents (12 (80%)) reported that global pharmaceutical sponsors provide more options for EAPs related to their practice (Figure 2e).

According to majority of the respondents (10 (66.6%)), it was not very challenging to educate the eligible patients about EAPs (Figure 3a). Most of the respondents (11 (73.3%)) stated that the educational model on 'Overview of compassionate use programs', 'Country EAPs regulations and overview', and 'EAPs application process' would be a beneficial educational initiative (Figure 3c). Two of the respondents stated that there is no major difference between the global and domestic sponsors, whereas one respondent reported that domestic sponsors provide more options for EAPs related to their practice. Many respondents recommended that pharmaceutical companies should have information related to the availability and application of EAPs for all pipeline products that are readily available on their websites (Figure 3d).

Among the 29 articles screened, no articles were found related to EAPs in Malaysia. A similar search was conducted on Google Scholar with the same search strings which resulted in 16,11,900 hits. Out of the total hits only two articles were relevant and had some information related to EAPs in Malaysia.

DISCUSSION

This study summarises the results of a survey that was conducted with a focus to understand the current standing of EAPs and its associated challenges pertaining to the regulations, resources/training available, and overall knowledge of its application process among Malaysian oncologists. In this survey, an equal number of oncologists took part from both public and private practices. Most of the participants involved had experience of about 10 to 20 years of oncology practice. Furthermore, most of the oncologists reported that no resources/training was provided by their institutions related to the EAPs applications. Overall, more than half of the respondents reported having a good knowledge of EAPs and application processes including country's regulations. Most respondents stated that they were very clear about the application process and the local regulations that have been set in place by the pharmaceutical sponsors and the regulatory authorities for applying for EAPs. However, most respondents think an educational model on different topics such as overview of EAPs, country EAPs regulations and overview, and EAPs application process can be a beneficial educational initiative. Information related to EAPs is mostly obtained from pharmaceutical sponsors or through other health care providers. Moreover, the global pharmaceutical sponsors are considered to provide more options for EAPs related to their practice. In terms of patient education, most respondents did not feel it to be very challenging to educate the eligible patients about EAPs. Even though more than half (53.3%) of the oncologists participated represented having a good understanding of EAPs, there is still a need to have clearer regulations and processes in place.[6] This can help address issues and create further awareness among physicians regarding EAPs application process which can lead to better

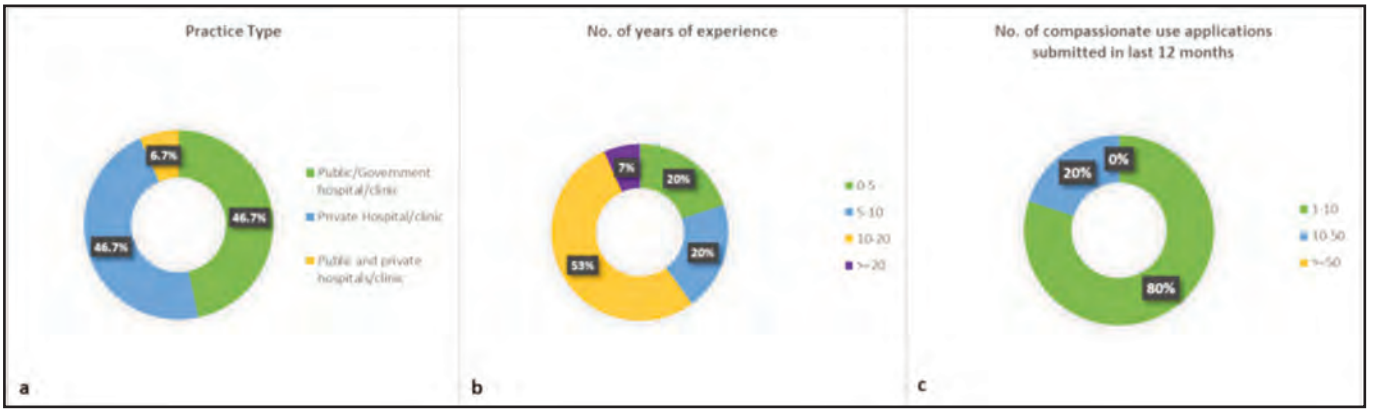

Fig. 1: Demographics of the survey participants.

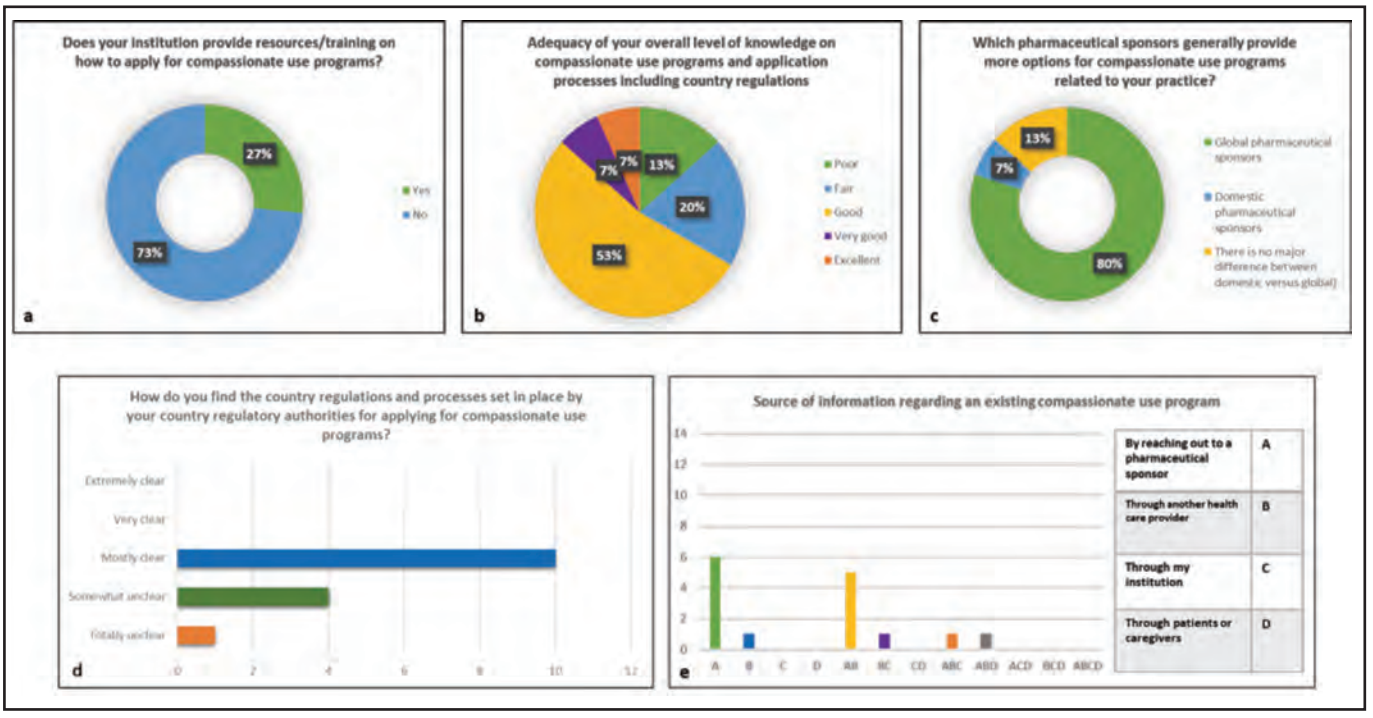

Fig. 2: Survey participants knowledge on compassionate use program in Malaysia.

outreach of the programs, patient access and ultimately patient outcomes.[6]

Our study results were found to be in line with the results of the overall study conducted by Singh et al., 2021, which included oncologists from various parts of Asia and has shown that majority of the respondents were clear about the EAPs application processes including the country regulations (88.23%). It was also shown that physicians had clarity regarding the EAPs application process through a pharmaceutical sponsor (71.56%), and EAPs regulations and processes set by country's regulatory authorities (53.92%).[6] Most respondents stated that their institutions did not provide any resources/training for EAPs application and felt that educational model on 'Country EAPs regulations and overview' would be beneficial for such application processes. In Malaysia, according to the Regulation 15(6) of the Regulations Drug and Cosmetic Control 1984, medical experts from private hospital or institutes or from organisation that are not under the Ministry of Health Malaysia are required to apply for import/manufacture of products that are not registered with the MOH Drug Control Authority.[3] Such application for unregistered drugs through EAPs are only indicated for patients with life-threatening disease.(3) The ongoing scenario with respect EAPs in Malaysia indicates that apart from government institutes, private physicians can also apply for EAPs and get access to life saving drugs. The results witnessed in this study could be due to lack of clarity related to countries regulation and paucity of information related to EAPs in Malaysia.

One of the other challenges of expanded access (EA) use is the time and effort needed to be invested by the treating physicians to this process. The physicians must be willing to

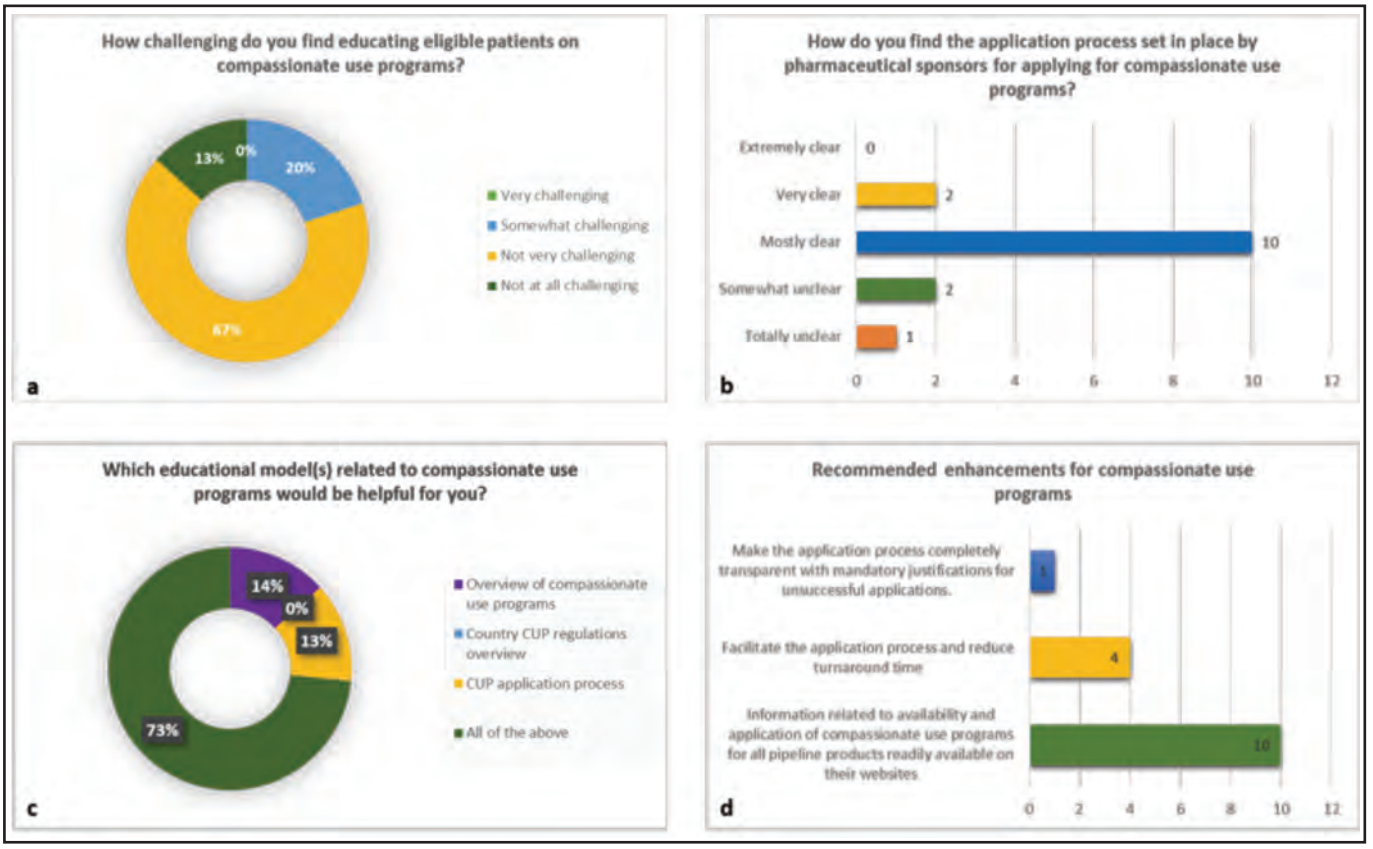

Fig. 3: Survey participant's educational needs.

be actively involved in the EA process and must be familiar with the investigational drug.[9] In general, the request of EA use of a treatment by a physician is infrequent due to complexity of the process. Physicians often face the pressure of helping the patients to decide whether to receive an investigational treatment, frequently without having adequate data. Such processes are usually a time-consuming affair, and the physician is usually uncompensated for their work.[9] There are also concerns of legal issues, as there are no defined boundaries regarding whether the physician will be held responsible in the case of a fatal adverse event and whether the patient's informed consent will be considered adequate.[9]

In the USA, the fundamental public policy goal associated with the regulatory approval of drugs is to ensure only safe and effective drugs reaches the market. Such drugs are extensively tested in both animals and humans.[10,11] Yet, individuals who are critically ill are often in a state, where they are unable to wait for such new drugs that are yet to be approved.[10,11] In such context, for maximizing the chances of cure or remediation, patients seek investigational drugs regardless of the lack of information about their efficacy or safety through EAPs.[10,11] The U.S. Food and Drug Administration's (FDA) initiated EAPs, for critically ill patients, where an investigational product can be used as a last resort of cure or remedy when no other comparable or effective treatments are available,[7,11,12] to patients who are either ineligible or have already participated in a clinical trial.[13] Access to investigational drugs is completely supported by the FDA for patients that are in most need. Though, the most preferred option is to enrol patients in clinical trials, whenever possible, for those patients who wish to gain access to investigational drugs.[14]

In the case of individual patients, expanded access usually depends on the cooperation and expertise of many parties, that includes the physician (who applies on behalf of the patient), the drug company, the institutional review board (IRB), and the FDA. Each of these involved individuals have an important role and must work together for the expanded access process to succeed.[14]

According to the Code of Federal Regulation (CFR) of the Food and Drug Administration (FDA) EAPs, sometimes also known as Compassionate Use Programmes (CUPs).[13] The definition of EAP varies across the world. According to the European Medicines Agency (EMA) recommendation, which is meant for EU countries, suggests including EAP patients who were previously treated in a clinical trial and wished to continue the treatment further. Nevertheless, around the world, it is recognised that patients treated in a clinical trial could have the option of continuing treatment for an extended period in an Open-label Extension study to generate long-term data on the intervention efficacy, safety, tolerability, and administration of the drug. Furthermore, in contrast with the FDA, the meaning of CUPs and EAPs are different in Europe.[13] In Europe, the EMA permits companies that manufacture promising medicines to run CUPs to allow early access to their medicine and to extend its use to patients who can

benefit from it. In addition, the EMA also allows patients that have been treated with the medicine during a clinical trial and who wish to continue using it may be able to do so via an EAP.[13]

There are numerous healthcare decisions that are faced by patients diagnosed with life threatening cancerous diseases, which have various implications on their life expectancy and quality of life.[11] In scenarios when patients do not respond to the standard anti-cancer treatments, opting for medication by participating in clinical trial remains to be the last choice, especially when the preliminary result of the research is promising.[11,15] But, in such instances there might be some set of patients who might not be eligible to be a part of such trials and through EAPs access to such drugs can be obtained.[11,15] A study conducted by Moerdler et al. 2018 involved paediatric patients under 18 years of age where enrolling of such patients in critical clinical trials is often difficult.[15] In this study the primary focus was to evaluate the experiences of paediatric oncologists in terms of applying and obtaining access to EAPs.[15] During this study it was reported that about 37% of respondents considered themselves as either competent or very competent in seeking approval from pharmaceutical companies for the use of an investigational drug.[15] The study also reported that participation in EAPs is influenced by physician's experience in clinical practice, size of institution, and availability of educational resources and administrative support.[15] Besides, the most common challenges in terms of utilisation of the EAPs were reported to be the inability to identify a drug which has a potential efficacy and lack of understanding and knowledge about the application process.[15]

EAPs involves various strategies being assessed to simplify the processes and reduce the approval time. Many expanded access requests are being initiated based on the evidence that demonstrate treatment matched to a patient's tumour molecular/biologic aberrations that maybe associated with superior clinical outcomes compared to treatment not matched to patients' alterations.[9] Generating and using real-world evidence from expanded-access patients provides an opportunity to offer critical data on patient outcomes that can serve regulatory approval in conjunction with other observational datasets or clinical trials, and in limited circumstances may be the best data available for regulatory review.[16] In addition, it may also support and encourage patient-centred care and a personalised medicine approach towards drug development.[16]

In this survey some of the country-based limitations have been highlighted related to EAPs. Devising proper channels and strategies to increase awareness among physicians and patients is crucial. Availability of adequate information, resources and trainings can make the program to be more accessible to a larger population who are in dire need of some life-saving medicines. A well-defined landscape of EAPs can be a game changer for providing effective treatment to oncology patients that doesn't have any other medical alternatives in Malaysia.

ACKNOWLEDGEMENTS

The authors would like to acknowledge Ms. Vaidehi Wadhwa (Senior Scientific Communications Specialist, Medical Excellence, Pfizer), Ms. Shrestha Priyadarsini (Senior Scientific Communications Specialist, Medical Excellence, Pfizer) and Ms. Hoa Ly My (Senior Scientific Communications Specialist, Medical Excellence, Pfizer) for their medical writing and editorial support in preparing this manuscript.

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ORIGINAL ARTICLE

Salvage neck surgery in recurrent nodal NPC: Do all patients require a comprehensive neck dissection in the modern MRI era?

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ABSTRACT

Objective: The standard treatment for regional failure in nasopharyngeal carcinoma (NPC) is the radical neck dissection (RND). Our study sought to determine if magnetic resonance imaging (MRI) may accurately predict nodal involvement to allow selected levels of neck dissection to be preserved.

Study Design and Setting: We analysed retrospectively all NPC patients in our centre undergoing neck dissections as salvage therapy for nodal recurrence. Nodal involvement based on the preoperative MRI was assessed and compared with postoperative histopathology.

Methods: This is a retrospective study conducted on patients in our centre with recurrent NPC from February 2002 to February 2017. Patients were identified from the database of the otolaryngology oncology division at our institution. Of these, 28 patients met all our inclusion and exclusion criteria. We calculated sensitivity and specificity as well as average number of nodes per patient.

Results: In our study, we calculated the false negative and false positive rates of preoperative MRI neck by levels. Overall sensitivity of MRI picking up disease by level was 76% and specificity was 86%.

Conclusion: Based on our study, we will be missing a total of 10 (7.1%) diseased neck levels in eight (28.5%) patients. MRI alone, therefore, does not provide enough information to allow safe selective preservation of neck levels in surgical salvage of neck recurrences in NPC.

KEYWORDS:
Nasopharyngeal carcinoma, radical neck dissection, selective neck dissection, magnetic resonance imaging, neck recurrence

INTRODUCTION

Nasopharyngeal carcinoma (NPC) is a distinct type of head and neck cancer. It has a high incidence of nodal metastases, with up to 70% of patients presenting with cervical lymphadenopathy.[20] The mainstay of treatment for primary tumours and neck nodal metastases includes radiotherapy (RT) or a combination of RT and chemotherapy. Local recurrence has been reported to be between 10 to 20% of patients following primary curative treatment,[26] while locoregional recurrent nodal metastases has been reported to be 5.8 to 12.9% at 3 years in existing literature[21] Locoregional recurrences are typically salvaged with surgery if resectable. Re-irradiation or chemotherapy can be utilised in unresectable cases. Distant systemic metastases is treated with first line chemotherapy or second line chemotherapy or immunotherapy.[25] Patients who underwent chemotherapy in our centre received a combination of chemotherapy agents such as cisplatin, carboplatin, 5-FU and gemtricitabine.[9]

Locoregional recurrent nodal metastases following primary treatment requires salvage surgery, though the extent of salvage surgery is controversial. Various types of neck dissection are employed. In RND, levels I to V are addressed together with resection of sternocleidomastoid (SCM), internal jugular vein (IJV) as well as accessory nerve. In a modified RND (MRND), levels I to V are addressed with removal of one or more of the more structures (SCM, IJV or accessory nerve). In a selective neck dissection (SND), levels likely to have occult nodal metastases are preferentially dissected. In a super selective neck dissection (SSND), two or fewer contiguous neck levels are dissected as appropriate.[19]

Currently, the widely adopted standard-of-care for neck nodal management is the radical neck dissection (RND). This philosophy was a result of the landmark study by William Wei et al.[5] In this study, Wei examined the extent of nodal disease in 43 RND specimens following NPC recurrence and found that all levels of the neck had the potential to be involved, with level II being the most common (53%) while metastases at levels I or V occurred in only 4% of patients. More than 70% of specimens had a higher number of tumour-bearing lymph nodes than evident on clinical examination and/or preoperative computerised tomography (CT) scans and was frequently complicated by extracapsular spread involving the accessory nerve and the internal jugular vein.[5] Preoperative clinical examination and CT scans were gross underestimates of true nodal involvement. The authors hence concluded that RND is the treatment of choice.

Routine use of RND is, however, associated with significant acute and chronic morbidities.[9,11] As such, some centres have moved towards offering selective neck dissections (SND).

This article was accepted: 19 December 2023
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Several previous retrospective studies have reported that SND offers high overall survival and comparable 5-year disease free survival rates[7,32] and can be considered non-inferior to RND.

Additionally, Wei's study was based on clinical examination, with a CT scan performed in selected cases to form an overall clinical impression of the neck levels involvement. The advent, in recent years, of contrast enhanced magnetic resonance imaging (MRI) as the preferred imaging modality with superior soft tissue delineation has enabled more accurate determination of the location of recurrent cancers, relationship to adjacent vital structures and extent of nodal involvement.[13,16]

We therefore sought to determine if modern-day MRI may allow a better assessment of disease, and hence more targeted neck dissections, than clinical exam and/or CT scan alone. This would potentially allow the treating clinician to perform MRI imaged guided selective neck dissections.

MATERIALS AND METHODS

This is a retrospective study conducted on patients in our centre with recurrent NPC from February 2002 to February 2017.

The management of persistent or recurrent nodal disease from NPC at our institution involves preoperative cross-sectional imaging with MRI followed by RND or modified radical neck dissection (MRND). RT and chemotherapy are reserved for selected cases. Because the philosophy has been a comprehensive neck dissection for every patient, this allowed us to compare the final histology with the preoperative MRI, to determine the performance of the MRI scan in delineating the nodes.

Patients were identified from the database of the otolaryngology oncology division at our institution. Between February 2002 and February 2017, 55 patients had suspected nodal recurrence of NPC at our centre. Inclusion criteria were all NPC patients from our institution with (1) residual/recurrent nodal disease after completion of primary RT/CRT, (2) who received a RND or MRND as part of salvage treatment or electively in the presence of local recurrent disease and had a (3) preoperative MRI scan prior to salvage surgery. Of these, 34 patients were excluded for the following reasons (1) 15 had no preoperative MRI and (2) 12 records were not available in our database (Figure 1).

A total of 28 patients with histopathology-proven isolated regional recurrence met all our inclusion and exclusion criteria. This study was approved by our local institutional review board. (NHG DSRB reference: 2018/00184)

Management Protocol

Of the patients undergoing salvage surgery, 11 (39.3%) patients had received RT alone in their initial treatment; 17 (60.7%) patients received both chemotherapy and RT in their initial treatment. All patients in our series underwent only unilateral neck dissection and none received neoadjuvant chemotherapy prior to salvage surgery. As part of workup to evaluate disease extent, all patients with locoregional nodal recurrences included in our study had MRI performed preoperatively. These MRIs were performed at least 3 months following initial treatment to assess for recurrence and within a month prior to salvage surgery.

The MRI protocol consisted of the following sequences: axial T1 weighted, coronal T1 weighted, axial T2 weighted fat sequence spin echo and contrast enhanced axial and coronal spin echoes. Subsequently, the coronal contrast enhanced sequence and axial T2 weighted sequence were later replaced in our institution with an isotropic 3D gradient echo sequence and T2 weighted non-fat saturated sequence respectively. All cases were performed by experienced head and neck surgeons in our department.

Retrospective evaluation of the scans by levels were performed by two senior head and neck radiologists. Both radiologists evaluated all scans independently and any discordance was resolved by mutual discussion and consensus.

All the patients underwent neck dissection of all the five levels. 18 (64.3%) underwent RND while 10 (35.7%) underwent MRND. Lymph node specimens were excised, marked by level, and sent for postoperative histopathological examination.

Number of nodes involved with disease were reported by level and this data was collected retrospectively. Key patient demographics and disease characteristics are summarised in Table I. All patients were staged using the criteria of American Joint Committee on Cancer (AJCC) 8th Edition.

Radiological Criteria

All preoperative MRI scans were read by experienced clinical radiologists in our centre. Each level was analysed for the presence and number of radiologically suspicious nodes using evidence-based criteria. Our criteria to classify lymph nodes seen as suspicious was if the node had any one of the following:

(1) Short axis diameter (retropharyngeal lymph node > 5 mm, level I/II > 11 mm, all other levels >10 mm).[17]
(2) Shape (round or irregular - pathological | ovoid - not pathological).[14]
(3) Margins (irregular or ill-defined - pathological | well-defined - not pathological).[14]
(4) Any extranodal extension (grade 1 and 2) (0 – Tumour confined within the lymph node with no extranodal extension | 1 – Tumour invading beyond the capsule of lymph node, 2 – All tumour tissue with no residual nodal tissue).[22]
(5) Necrosis and clustered[10]

False negative (FN) was defined as a particular level with no suspicious lymph nodes seen on preoperative MRI but metastatic nodes were found on postoperative histopathological analyses. Conversely, false positive (FP) was defined as when suspicious nodes were seen on preoperative MRI but no metastatic nodes were found on histology postoperatively.

Table I: Summary of patient and disease characteristics

Characteristics	N = 28 (%)
Gender	
Female	4 (14.3%)
Male	24 (85.7%)
Age	
<60	15 (53.6%)
≥60	13 (46.4%)
Primary tumor AJCC VIII stage	
I	0 (0.0%)
II	8 (28.6%)
III	8 (28.6%)
IV	7 (25.0%)
Unknown	5 (17.8%)
Primary tumor treatment	
RT	11 (39.3%)
ChemoRT	17 (60.1%)
Recurrence AJCC VIII stage	
r0	2 (7.1%)
rI	1 (3.6%)
rII	23 (82.1%)
rIII	1 (3.6%)
rIV	1 (3.6%)
Type of surgery	
RND	18 (64.3%)
MRND	10 (35.7%)

Table II: Collective radiological and histopathological analyses of all included specimens

Characteristics	N = 28 (%)
Total number of suspicious lymph nodes on preoperative MRI	
Level I	3
Level II	24
Level III	9
Level IV	2
Level V	7
Total number of tumor-containing lymph nodes on histopathology	
Level I	3
Level II	18
Level III	10
Level IV	6
Level V	4
False negatives	
Level I	3
Level II	0
Level III	2
Level IV	4
Level V	0
False positives	
Level I	3
Level II	6
Level III	2
Level IV	1
Level V	3
Extracapsular spread	
Yes	8 (28.6%)
No	20 (71.4%)

Table III: Patient's with one or more false negative lymph node levels are summarized above with any corresponding extranodal extension noted on postoperative histopathology

Subject number	False negative levels	Extranodal extension
1	1	Yes
3	3	No
17	4	Yes
19	1	No
20	3, 4	Yes
25	4	Yes
27	3, 4	Yes
36	1	No

Table IV: Sensitivity and specificity of preoperative MRI in the detection of recurrent/residual nodal disease of NPC per neck level. Overall sensitivity and specificity were also calculated

N = 28	Sensitivity	Specificity
Level 1	25%	92%
Level 2	100%	40%
Level 3	70%	89%
Level 4	33%	95%
Level 5	100%	88%
Overall	76%	86%

Table V: Overall number of false negatives and positives on modern day preoperative MRI

Total number of levels dissected	140
Overall false negatives	10 (7.1%)
Overall false positives	14 (10%)

Table VI: Mean lymph nodes per patient found in our study with modern-day preoperative MRI compared to Wei et al's landmark study in 1992 using CT and clinical examination. In our study, there is a closer correlation between mean number of suspicious nodes found clinically and that found on histopathology

	Clinically suspicious lymph nodes on clinical exam/CT on histopathology or MRI	Range per patient	Mean per patient	Tumor-containing lymph nodes	Range per patient	Mean per patient	Ratio Difference in detection of nodal recurrence on preoperative scans and postoperative histopathology
Wei et al., 1992[5]	59	0 to 5	1.5	294	0 to 62	7.4	4.6
Current study	105	0 to 10	3.8	91	0 to 5	3.6	0.95

Pathological Analyses

All intraoperative lymph node specimens were sent for postoperative histopathological analyses in 10% neutral buffered formalin for histopathological analyses. These specimens were oriented by the surgeon using orientating sutures demarcating lymph node subgroups (level I to level V) and was sent en-bloc to our histopathology lab for further tissue processing. All the macroscopically negative or equivocal lymph nodes were submitted in totality. Limited representative sections of grossly apparent positive nodes or matted positive nodes were submitted for microscopic documentation of metastasis. Each tissue slice was cut to a thickness of 3 to 4 mm for processing and further paraffin block preparation. Standard 4-micron thick tissue sections were cut on glass slides and stained with haematoxylin and eosin for histology assessment.

Apart from the number of nodes involved by metastatic carcinoma, the greatest dimension of metastatic deposit and the presence or absence of extranodal extension was also documented.

RESULTS

Histopathological Findings

A total of 23 patients had metastatic carcinoma in at least one lymph node level, while five patients had no metastatic carcinoma found in all five levels following RND or MRND. Single level involvement was found in 11 patients, while other 12 patients had multilevel involvement. Nodal recurrences most frequently occurred in levels II and III (n = 8 (28.6%), n = 8 (28.6%) respectively). Eight patients (28.6%) had extracapsular spread in at least one lymph node seen on postoperative histopathology. Tumour infiltration was found in structures including the perinodal soft tissue, skeletal muscle and vasculature. Interestingly, all levels on preoperative MRI in our study were found to have false negatives, except for levels II and V. Exact distribution of nodal involvement for both preoperative MRI and postoperative histopathology is summarised in Table II.

Comparison Between MRI and Histology (Mean Positive Nodes Detected Per Patient)

In our study, for the 28 patients analysed, a total of 105 radiologically suspicious lymph nodes were detected by MRI with a range of 0 to 10 lymph nodes (mean, 3.8) per patient. In contrast, the number of positive nodes that actually contained tumour on histopathology were 91, with a range of 0 to 5 per patient (mean, 3.6).

False Positives by Level

There were two (6.0%) false positives in level I, six (18.2%) in level II, two (6.0%) in level III, one (3.0%) in level IV and three (9.1%) in level V.

False Negatives by Level

Eight (28.6%) patients had one or more false negatives in one or more neck levels. There were three (10.7%) false negatives in level I, zeo (0%) in level II, three (10.7%) in level III, four (14.3%) in level IV and zero (0%) in level V. Five of these patients also had extranodal extension (Table III).

These figures translate into sensitivities and specificities per level as documented in Table IV. Taking into account all

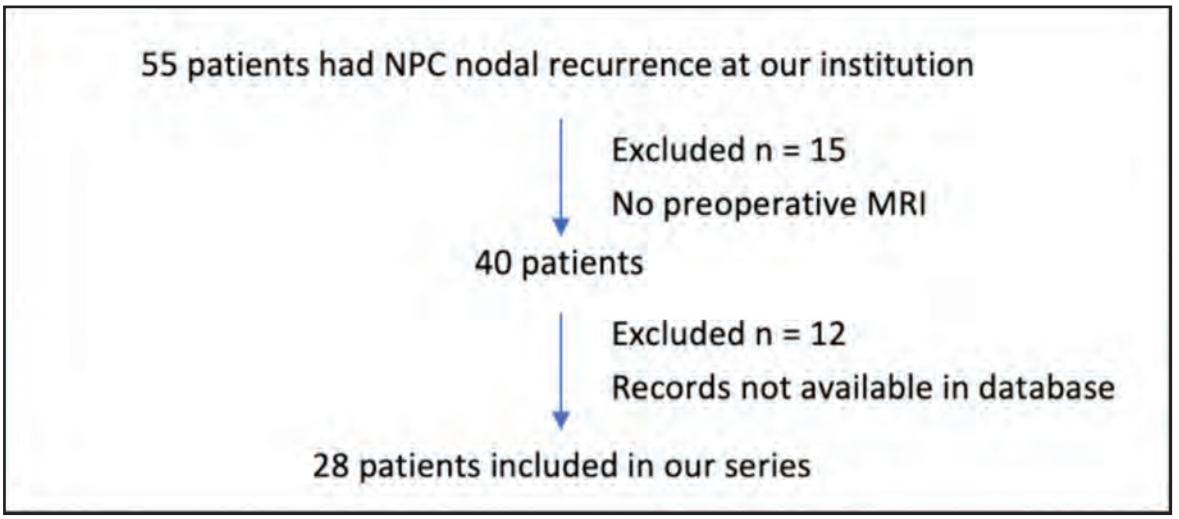

Fig. 1: Exclusion table.

levels, the overall sensitivity and specificity based on all lymph node levels in our series of patients were 76% and 86% respectively. Table V summarises the overall number of false negative and false positives levels out of the 140 levels dissected.

We would, in theory, conserve a total of 95 out of 140 neck levels in our 28 patients if we were to perform selective neck dissections based solely on suspicious lymph node levels on preoperative MRI. This would however result in 10 missed neck levels, affecting eight patients in total (28.6%).

Outcomes

All patients were followed up regularly until discharge or death. Two (7.1%) were lost to follow up. Of the 26 remaining patients, the follow-up interval ranged from 2 months to 14 years and 2 months with a median follow up of 1 year and 7 months. There were four (14.3%) local recurrences and six (21.4%) systemic metastases.

There were also 11 (39.2%) deaths in our series of patients. Two (7.1%) died of systemic metastases and two (7.1%) from local recurrences. Another seven (25%) died of causes not related to recurrent NPC, including cardiac arrests and strokes.

DISCUSSION

In a landmark study, Wei et al. examined a series of whole-neck dissections in 40 patients whose RND specimens contained tumour tissue.[5] The total number of suspicious lymph nodes detected clinically, with or without preoperative CT scan, were 59 with a range of 1 to 5 (mean, 1.5) per patient. The number of lymph nodes that actually contained tumour were 294, with a range of 1 to 62 (mean, 7.4) per patient. In a follow-up study, the authors[9] further found that all neck levels had the potential to be involved with levels II and V being the most common (53%). Extracapsular spread was evident in over 60% of metastatic lymph nodes. These findings reflect the aggressive nature of recurrent NPC in the neck. The authors thus concluded that RND with removal of surrounding sternocleidomastoid, internal jugular vein and spinal accessory nerve is the treatment of choice to achieve curative resection. This conclusion is supported by various other earlier studies.[2,3]

Radical neck dissection, however, is associated with high rates of functional and cosmetic defects. These included postoperative shoulder syndrome in cases of CN XI sacrifice, skin flap necrosis, shoulder syndrome, surgical site infection and delays in wound healing.[11,18] Since the landmark trials almost 20 years ago, more recent studies by Yen et al. and Liu et al. reported similar 5-year survival and neck control rates for patients treated with more limited neck dissections.[7,24, 25] Another recently reported large series by Zhang et al[17] analysed 355 patients and recommended selective neck dissection be considered for patients with a single residual node. Other studies have also shown that metastatic lymph nodes appear to be primarily located at levels II and V.[20] With the refinement of surgical techniques and imaging modalities over the last decades, the requirement of a routine RND is under scrutiny.[1,20,24] The concept of sparing unaffected levels has also been applied in the treatment of other head and neck cancers.

Over the past decades, there have been significant advances in imaging with the advent of MRI for evaluating nodal metastases and planning radiotherapy in patients with head and neck cancers. MRI has become the preferred modality of assessment of primary nasopharyngeal cancers because of better contrast resolution and less prominent motion artefacts compared to CT scans.[12] Other authors have also purported that MRI, compared to CT, offers equivalent or superior sensitivity, specificity and accuracy in detecting nodal recurrences and soft tissue extension beyond the nasopharynx (P Olmi et al., 1995).[6]

Our present study is a series of recent (2002 to 2017) recurrent NPC cases treated with neck dissections. All cases underwent preoperative MRI to identify levels with suspicious lymph nodes. Histopathology was subsequently used as a postoperative gold standard to affirm if a neck level was involved. We sought to determine whether we could safely treat NPC neck nodal recurrence with selective neck dissection by demonstrating a high sensitivity of MRI, using histopathology as the gold standard.

In William Wei's study, for the 40 patients analysed, a total of 59 clinically-suspicious lymph nodes were detected on CT and physical examination preoperatively with a range of 1 to 5 lymph nodes (mean, 1.5) per patient. In contrast the number of lymph nodes that actually contained tumour on histopathology was 294, with a range of 1 to 62 (mean, 7.4). This represents a histology: clinical ratio of 4.6 times difference between the two groups.

In our study, for the 28 patients analysed, a total of 105 radiologically-suspicious lymph nodes were detected by MRI with a range of 0 to 10 lymph nodes (mean, 3.8) per patient. In contrast, the number of positive nodes that actually contained tumour on histopathology was 91, with a range of 0 to 5 per patient (mean, 3.6). This represents a histology: clinical ratio of 0.95 times between the two groups, demonstrating a marked improvement in nodal detection with the routine use of preoperative MRI in the detection of disease from 4.6 times in William Wei's study (Table VI). In fact, with MRI, as opposed to clinical examination and CT in William Wei's study, there were more nodes deemed as suspicious on preoperative assessment compared to those found on final histology.

Despite the superiority of MRI over CT scan, the sensitivity and specificity do not approach 100%. Of note, the use of size itself does not definitely discriminate disease. Nodes larger than 10 mm are conventionally considered abnormal. However, 20% of nodes that exceed 10 mm harbour no metastatic deposits and histologically show only hyperplasia. On the other hand, 23% of nodes that show extracapsular spread measure less than 10 mm.[4] It Is clear that no imaging modality, including MRI, is able to depict all of the micrometastases of small recurrent lymph nodes.[17] Specificity can also be affected by the presence of suppurative nodes that show central areas of low attenuation. Assumptions that these nodes are cancerous are further confounded that such inflammatory nodes can sometimes have irregular and ill-defined margins.[10]

Despite the improved sensitivity of MRI over CT, further analysis showed that the sensitivity of MRI for NPC nodal disease ranged from 25 to 100% by levels and was 76% overall (Table IV). This means that out of the 28 patients (140 neck levels) operated upon, we would be missing 10 (7.1%) diseased lymph node levels in a total of eight patients (28.6% of patients). Hence, based on our study, MRI was not able to allow for an ontologically safe image-guided selective neck dissection.

There are several limitations to this study. First, our study is a retrospective study with a small sample size. Despite the fact that data is examined over a 15-year period, our study was limited by the relative paucity of recurrent nodal metastases in nasopharyngeal cancer in general. Second, the results of this study are based on the definition of what constitutes a radiologically suspicious node, as defined by our paper. It is recognized that different institutions may have different criteria for what constitutes a radiologically suspicious node. However, we envisage that the results of this study should provide a close approximation of the relative sensitivity and specificity of preoperative MRI in the majority of centres. Thirdly, some recent studies have purported improved metastatic lymph node detection over MRI by using more contemporary imaging modalities such as the 18 flurodeoxyglucose-proton emission tomography CT or MRI (18F PET-CT or MRI) with resultant improved sensitivity of 90% with PET-CT over 77% with MRI alone in detecting nodal recurrence. This can be attributed to the superior ability of PET-CT or MRI to distinguish recurrence NPC from local scar or fibrous tissue following irradiation.[5,26] However, a significant proportion of our patients from earlier years did not undergo routine preoperative PET scans, thus this was not included in our study. PET scans still require a critical volume of disease to pick up tumour, and has its own limitations.

CONCLUSION

Regional neck recurrence after (chemo) radiation of primary nasopharyngeal carcinoma (NPC) can involve all five levels of the neck. Salvage surgery is indicated as first line therapy for such cases. Our study suggests that even with modern-day MRI, we are unable to fully eliminate false negatives to allow safe selective neck dissections. This is of clinical importance as salvage surgery is deemed as a last resort to achieve tumour clearance. Hence, a comprehensive neck dissection should continue to be the first line treatment for recurrent NPC to achieve salvage.

FUNDING INFORMATION

No funding information to declare for this study.

CONFLICTS OF INTEREST

No conflicts of interest to declare for this study.

INSTITUTIONAL REVIEW BOARD (IRB)

This study is approved by Tan Tock Seng Hospital IRB

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Rebalancing of the skin microbiome with an emollient 'plus' for effective management of atopic dermatitis: A mini review

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ABSTRACT

A balanced and diverse skin microbiome is pivotal for healthy skin. Dysregulation of the skin microbiome could disrupt the skin barrier function and result in the development of atopic dermatitis (AD), a common chronic and relapsing inflammatory skin disorder. Given the role that the skin microbiome plays in the initiation and maintenance of AD, maintaining a healthy skin microbiome is crucial for effective disease management. Specifically, current guidelines recommend emollients as the treatment mainstay in maintaining a functional skin barrier across disease severity. Emollient 'plus' or therapeutic moisturisers have recently emerged as the next-generation emollients that specifically aim to rebalance the skin microbiome and subsequently improve AD lesions. This article provides a quick overview of an emollient 'plus' or therapeutic moisturiser, discussing the clinical efficacy and tolerability of Lipikar Baume AP+M as a companion in AD management.

KEYWORDS:
Skin microbiome, barrier function, atopic dermatitis, emollient 'plus', therapeutic moisturiser

INTRODUCTION

Human skin is colonised by an abundant and diverse population of microorganisms, called microbiome, that coexist with human skin cells in an intricately controlled environment.[1] These microbial communities support the overall skin health through their interaction with the host, such as by reinforcing the physical and immunological barriers of the skin.[1] The skin uses several mechanisms to control its microbiome, including regulation of pH, water content, lipid composition and antimicrobial peptides (AMPs).[1]

Dysregulation in any of these systems could cause an imbalance in the skin microbiome, represented by an overabundance of one microbial species or a decrease in overall microbial diversity, a condition known as 'dysbiosis'.[1] In many instances, dysbiosis could disrupt skin homeostasis and lead to the development of many chronic skin diseases, including atopic dermatitis (AD).[1]

AD is a chronic relapsing and remitting inflammatory skin disorder characterised by dry skin, localised erythema, pruritus and skin pain. AD is a common condition that affects up to 10% of adults and up to 20% of children worldwide.[2] AD exacts a substantial burden on patients and their families through its effect on health-related quality of life (HRQoL) and socioeconomic costs,[3] making it an important public health problem worldwide.

Skin Microbial Dysbiosis and AD

Dysbiosis is well documented in patients with AD, with evidence showing heavy colonisation of *Staphylococcus aureus* and loss of microbial diversity in AD skin compared with the skin of healthy individuals.[4] Specifically, *S. aureus* is associated with and often preceded AD flares,[5] and the degree of *S. aureus* colonisation correlates with disease severity.[5]

S. aureus initiates and exacerbates AD by exploiting mechanisms that affect the skin barrier function and skin immunity.[1,6] In a nutshell, *S. aureus* colonisation on the skin can lead to biofilm production, causing disruption in the skin barrier function and permitting entry of infectious agents into the dermis, resulting in chronic inflammation and skin immunity impairment.[1,6] Therefore, maintaining a balanced and diverse microbial population is crucial for overall cutaneous health.

Current Guidelines for AD Management

International,[7] regional[8] and local[9] guidelines recommend a stepped-care approach for AD management, involving regular use of emollients and additional therapies based on disease severity. As the quantity of emollients is essential for effective AD control, the European guidelines recommend prescribing a minimum amount of 250 g per week for adults.[7] Meanwhile, the Asian guidelines recommend prescribing 120 to 225 g per week for adults and 40 to 75 g per week for children aged 4 years.[8]

While current guidelines do not offer specific recommendations on targeted support to improve the skin microbiome as an initial treatment approach, various AD therapies have been shown to reduce the abundance of *S. aureus* and improve microbial diversity, leading to effective disease control. Accordingly, the Malaysian guidelines and others recommend identifying and managing aggravating factors, such as microbial colonisation, for better AD control.[9] More specifically, the European guidelines have now recognised the role of emollient 'plus' or therapeutic moisturisers in improving AD lesions and regulating skin microbiome in patients with AD.[7]

Skin Microbiome Rebalancing with an Emollient 'Plus': Evidence of Clinical Efficacy and Tolerability

Lipikar Baume AP+M (La Roche-Posay Laboratoire Dermatologique, France) is an emollient 'plus' specifically formulated for AD skin. Multiple studies of patients with

This article was accepted: 19 February 2024
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mild-to-moderate AD demonstrated that Lipikar Baume AP+M has higher efficacy in modulating the skin microbiome compared with commercial emollients.[10,11] In particular, patients receiving Lipikar Baume AP+M had a higher reduction of the *S. aureus* population and a significant increase in the *Xanthomonas* genus than those receiving the usual emollient, despite using less product.[10]

Compared with the usual emollient, Lipikar Baume AP+M monotherapy led to significant improvement in the average Scoring Atopic Dermatitis (SCORAD) level, corresponding with an 11% reduction in SCORAD level at Day 28 ($p = 0.018$).[10] A recent longer-term follow-up study showed that Lipikar Baume AP+M monotherapy significantly improved the SCOARD, signs and symptoms at Day 168 versus the baseline period in patients with mild-to-moderate AD (all $p < 0.05$).[12] Notably, patients receiving Lipikar Baume AP+M were twice less likely to experience relapse within 28 days of follow-up than with usual emollients.[10] Lipikar Baume AP+M also reduced the number and intensity of flares in the longer-term follow-up study.[12]

A significant steroid-sparing effect was also observed with Lipikar Baume AP+M without affecting its efficacy.[13] In patients with mild-to-moderate AD receiving topical corticosteroids (TCS), the addition of Lipikar Baume AP+M significantly reduced TCS use by 34% compared with a routine emollient ($p = 0.041$), driven by the decrease in the number of TCS applications per days and the number of days of TCS use.[13] When used as an adjunct to systemic agents, Lipikar Baume AP+M led to a significantly greater reduction in current pruritus of moderate-to-severe AD at Week 10 ($p = 0.0277$), even with less product use.[14] In addition, the improvement in patient global assessment and SCORAD scores were greater with Lipikar Baume AP+M versus the usual emollient.[14]

Importantly, daily use of Lipikar Baume AP+M monotherapy for 6 months resulted in a significant improvement in the HRQoL of patients with mild-to-moderate AD over time ($p <0.001$).[12] Similarly, patients with moderate-to-severe AD receiving adjunct Lipikar Baume AP+M had a 20% reduction in the Dermatology Life Quality Index (DLQI) score than the control group, with patients receiving Lipikar Baume AP+M reporting significantly better responses for DLQI items #6 and #7.[14] The studies showed that Lipikar Baume AP+M as monotherapy or adjunct therapy has a good safety profile,[12,14] with high overall tolerance and satisfaction rate of over 96%.[15]

Notably, two cost-effectiveness analyses conducted in the UK (including lost productivity cost)16 and France (only direct healthcare costs)17 showed that Lipikar Baume AP+M was the more cost-effective strategy for relapse prevention than other commercially tested emollients and no emollients. Compared with emollients of a similar price range, patients using Lipikar Baume AP+M will have an additional 1.08 to 4.92 months without flares over 6 years of follow-up.[17] Similarly, Lipikar Baume AP+M will generate a respective gain of 1.08, 3.84 and 6.12 months without flares compared with less costly, more costly and no emollients over 6 years.[17]

The microbiome maintenance action of Lipikar Baume AP+M is thought to be driven by the active ingredients *Vitreoscilla filiformis* and microresyl.[18] The *V. filiformis* biomass extract has been shown to activate endogenous cutaneous antioxidants and increase the secretion of AMPs via the toll-like receptor 2 and protein kinase C signalling pathway to effectively control inflammation in AD.[18] Extracted from Ophiopogon japonicum tuberous roots, microresyl has been shown to reduce the inflammatory markers on the skin cells (such as thymic stromal lymphopoietin and interleukin 8) and limit *S. aureus* adhesion to the skin.[19]

Another emollient 'plus', Dermoflan AD cream (Meda Pharma, Sweden), has also been shown to exhibit microbiome maintenance properties, attributed to the selective antibacterial and prebiotic activities of galacto-oligosaccharides and xylitol.[20] Dermoflan AD cream significantly increased microbial diversity in treated areas at Day 28 versus baseline among participants predisposed to AD.[20] The author concluded that larger studies are needed to study the correlation between changes in the skin microbiome after Dermoflan AD cream treatment and clinical improvement of AD.[20]

CONCLUSION

Skin microbiome dysbiosis is a key component of atopic dermatitis (AD) disease initiation and progression. Therapies that aim to rebalance the skin microbiome can reduce S. aureus abundance, increase microbial diversity in AD skin could help maintain a functional skin barrier and improve disease management. By rebalancing the skin microbiome, Lipikar Baume AP+M has been shown to be effective as monotherapy or adjunct therapy in AD management, representing the most cost-effective strategy in AD relapse prevention.

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SYSTEMATIC / NARRATIVE REVIEW ARTICLE

Intraocular pressure measurements in paediatric glaucoma: A narrative review on accuracy, tolerability, and ease of use

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ABSTRACT

Introduction: Numerous tonometers are available to measure intraocular pressure (IOP) in children with glaucoma. This review aims to discuss IOP measurement techniques and principles and compare the accuracy, tolerability and ease of use of available tonometers in measuring IOP in paediatric glaucoma patients.

Materials and Methods: A review of observational studies was conducted to discuss the accuracy, tolerability and ease of use of tonometers in measuring IOP in children with glaucoma.

Results: Goldmann applanation tonometry (GAT) and its portable handheld versions remain the gold standard in measuring IOP. Tono-Pen (Reichert Ophthalmic Instruments, Depew, New York, USA) and rebound tonometer (RBT) both correlate well with GAT. Although both tonometers tend to overestimate IOP, Tono-Pen overestimates more than RBT. Overestimation is more remarkable in higher IOP and corneal pathologies (such as but not limited to scarred cornea and denser corneal opacity). RBT was better tolerated than other tonometers in children and was easier to use in children of all ages.

Conclusions: RBT is the preferred tonometer for measuring IOP in children with glaucoma, as it is less traumatic, time efficient and does not require fluorescein dye or anaesthesia. However, examiners should use a second tonometer to confirm elevated IOP readings from the RBT.

KEYWORDS:
Intraocular pressure, measurement, paediatric, glaucoma, tonometry

INTRODUCTION

Glaucoma can cause severe vision loss and blindness and can affect people of all ages, including children.[1] Diagnosing paediatric glaucoma is challenging, as perimetry examinations and optic disc evaluation in children are difficult due to a lack of cooperation.[2,3] Usually, raised intraocular pressure (IOP) is the most common feature of paediatric glaucoma and the most important risk factor in glaucoma progression and development.[4]

Precise and accurate IOP measurement depends on several factors, including but not limited to patient cooperation, the use of anaesthesia and the application of fluorescein dye.[5,6] These pose a challenge, as children tend to cry, hold their breath and squeeze their eyes during examination.[7,8] Furthermore, the use of anaesthesia may cause pain and the application of fluorescein may cause discomfort.[6]

This literature review aims to discuss IOP measurement techniques and principles, and compare the accuracy, tolerability and ease of use of available tonometers in measuring IOP in paediatric glaucoma patients.

MATERIALS AND METHODS

A comprehensive medical literature search was conducted on PubMed and through manual cross-referencing (n = 144). The search terms used alone or in combination were IOP measurement, tonometers, paediatric glaucoma, accuracy, tolerability and ease of use. The review included full-text observational studies in the English language published from inception to April 2022 that discussed the accuracy of various tonometers in measuring IOP in children with glaucoma, as well as studies that investigated the tolerability and ease of use of tonometers in children with glaucoma and healthy children (n = 26). The review also excluded studies that recruited adult subjects (n = 2). Two reviewers performed the search, assessment and data extraction processes. This narrative review includes 14 studies, with 10 focusing on the accuracy of tonometers and four examining the tolerability and ease of use in children (Figure 1).

IOP Measurement Techniques and Operating Principles

IOP is a dynamic equilibrium of aqueous humour production and outflow, which are nearly equal under normal conditions. IOP can be evaluated by transpalpebral, manometry and tonometry.[9] Tonometry is performed with tonometers. The purpose of tonometers is to obtain accurate IOP measurement with the least disturbance of the eyes. Based on its operating principles, tonometers can be classified into (1) applanation, (2) indentation, (3) applanation-indentation and (4) rebound tonometers (Table I).[9]

Goldmann applanation tonometry (GAT) remains the gold standard amongst other tonometers in measuring IOP.[5,10] Perkins applanation tonometer is one of the GAT's portable handheld versions, thus enabling IOP to be measured in both upright and supine positions. Its handheld design is ideal for babies, young children and bedridden children. General anaesthesia is required for IOP measurements with GAT and

This article was accepted: 07 March 2024
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Table I: Operating principles of tonometers

Operating Principles	Explanation	Tonometers (Production year)
Applanation	Operated based on the Imbert-Fick Law (P= F/A), which states that the pressure inside a thin-walled sphere is equal to the force needed to flatten its surface divided by the area of the flattening.[9,10] Can be divided into non-contact tonometers (no physical contact between the eye and tonometer, such as (pneumotonometer, air-puff tonometry, and Ocular Response Analyzer [ORA]).) and contact tonometers (GAT and Perkins tonometer).[10] Most widely used and reliable tonometers.	Goldmann applanation tonometer [GAT] (Haag Streit and Reliance Medical Products, Mason, Ohio, USA) (1955) Perkins tonometer (Haag Streit and Reliance Medical Products, Mason, Ohio, USA) (1965) Pneumotonometer (Reichert, Buffalo, New York, USA) (1969) Air-puff tonometer (1973) ORA (Reichert Ophthalmic Instruments, Depew, New York, USA) (2005)
Indentation	Operated based on the basic principle that a known force will indent a fluid- or gas-filled object to a greater extent if the internal pressure is low, as opposed to high. The force can be provided digitally or by a known weight.[9] Although it is no longer used in developed countries, it is still widely used in developing countries.[10]	Schiøtz tonometer (1905) Bailliart tonometer (1923) Maurice electrical tonometer (1958) Mueller electronic tonometer (1960)
Applanation-Indentation	Operated based on the principle of applanation and indentation.[9,10]	Tono-Pen (Reichert Ophthalmic Instruments, Depew, New York, USA) (1989) Corvis ST (Oculus, Wezlar, Germany) (2011)
Rebound	Analysis of motion parameters of a bouncing probe from the tonometer caused by an electrical pulse generator that creates a magnetic field after impact with the cornea. When the probe makes contact with the cornea, it bounces back to the instrument, causing a voltage change. The solenoid inside the tonometer detects voltage changes. The greater the IOP, the shorter the time the probe is in contact with the cornea and the faster it returns to the tonometer.[3] One of the most commonly used tonometers in clinical practice today.	Icare tonometer (Icare Finland Oy, Helsinki, Finland) (1997)

handheld applanation tonometers. There have been no studies that compare the accuracy of handheld applanation tonometry and GAT, however, in adults, the IOP measurements obtained with handheld applanation tonometer are closely comparable to those obtained with GAT.[18,19]

The applanation principle is also used in non-contact tonometry (NCT), in which the cornea is flattened with a puff of air.[3,10] NCT eliminates the possibility of contamination because it does not make contact with the cornea, thus ideal for cooperative children at increased risk of infection.[2,10] Another notable advantage is that NCT does not require topical anaesthesia's instillation.[3,10] NCT is available in handheld and stationary models.[3] Only a few studies investigated the accuracy of NCT, especially in children with glaucoma. Chan et al. in 2015 discovered that in the eyes of children with anterior segment pathology, including those with congenital glaucoma, the mean IOP measured by NCT was 3.9 mmHg lower than the IOP measured by Icare (Icare Finland Oy, Helsinki, Finland) rebound tonometry (RBT), and this difference became more significant at higher levels of IOP. The authors did, however, mention the possibility of IOP variation in their cohort due to stress on the cornea when measuring IOP with NCT to RBT, thus resulting in the lower IOP measurement with NCT.[20] More robust studies on the accuracy of NCT in children with glaucoma are warranted.

Tono-Pen is a battery-powered tonometer that operates on the principles of applanation and indentation. Tono-Pen is equipped with a disposable latex cap to reduce cross-infection. A more recent tonometer, Icare RBT, is a lightweight, portable handheld instrument with a disposable probe. Unlike Tono-Pen, RBT does not require topical anaesthesia.[3,10] RBT has high reproducibility, both intraobserver and interobserver.[4,21] IOP measurements with Tono-Pen and RBT correlate well with GAT, although both tonometers tend to overestimate the IOP. Studies have consistently shown that the IOP measured by RBT is higher than GAT (Table II).[4,7,12,13,17] When comparing the accuracy of RBT and Tono-Pen, numerous studies have found that the overestimation by Tono-Pen is greater than RBT.[5,14–16]

Table II: Summary of accuracy from included studies

Author (Year)	Study population	Sample size	Tonometers used	Mean IOP measurements
Levy et al. (2005)[11]	PCG (IOP measured ~3 minutes after inhalation anaesthesia)	16 children (28 eyes)	Perkins tonometry and Tono-Pen XL	Perkins: 18 ± 6 mmHg Tono-Pen XL: 22 ± 8 mmHg
Martinez-de-la-Casa et al. (2009)[12]	PCG	47 children (47 eyes)	Perkins tonometry and RBT	Perkins: 19.1 ± 5.4 mmHg RBT: 22.1 ± 7.7 mmHg
Flemmons et al. (2011)[13]	Known or suspected glaucoma	71 children (71 eyes)	GAT and Icare	GAT: 18.7 ± 6.8 mmHg Icare: 21.1 ± 8.4 mmHg
Gandhi et al. (2012)[7]	Known or suspected glaucoma	60 children (60 eyes)	GAT and Icare ONE	GAT: 16.9 ± 5.7 mmHg Icare ONE: 19.0 ± 8.4 mmHg
Dahlmann-Noor et al. (2013)[4]	Glaucoma	102 children	GAT and RBT	GAT: 18 ± 6.45 mmHg RBT: 21.1 ± 8.19 mmHg (observer 1); 21.14 ± 8.41 mmHg (observer 2)
Dosunmu et al. (2014)[14]	Known or suspected glaucoma and healthy children	47 children (94 eyes)	GAT, Icare PRO and Tono-Pen	Sitting position GAT: 16.4 ± 4.2 mmHg Icare PRO: 17.5 ± 3.5 mmHg Tono-Pen: 18.0 ± 3.9 mmHg Supine position Icare PRO: 18.4 ± 4.5 mmHg Icare PRO: 18.8 ± 4.2 mmHg
McKee et al. (2015)[5]	Glaucoma with/without corneal pathology and healthy children (IOP measured immediately after inhalation anaesthesia)	50 children (100 eyes)	Icare PRO and Tono-Pen XL	Icare PRO: 16.7 ± 7.1 mmHg Tono-Pen XL: 16.9 ± 7.5 mmHg
AlHarkan et al. (2016)[15]	Glaucoma and other eye pathologies (IOP measured ~20 minutes after oral sedation)	28 children (52 eyes)	Icare PRO, Tono-Pen XL and Pneumotonometer	Glaucoma group Icare PRO: 17.6 ± 6 mmHg Tono-Pen XL: 20.5 ± 6.8 mmHg Pneumotonometer: 20 ± 6.4 mmHg Control group Icare PRO: 13.54 ± 3.07 mmHg Tono-Pen XL: 14.6 ± 3.3 mmHg Pneumotonometer: 15.25 ± 3.3 mmHg
Mendez-Hernandez et al. (2020)[16]	Glaucoma	46 children (91 eyes)	Perkins, Icare PRO, and Tono-Pen XL	Perkins: 17.99 ± 6.24 mmHg Icare PRO: 19.3 ± 6.10 mmHg Tono-Pen XL: 23.5 ± 10.65 mmHg
Angmo et al. (2021)[17]	Glaucoma (Patients were under general anaesthesia)	105 children (200 eyes)	Perkins and Icare IC200	Clear cornea Perkins: 15.05 ± 8.8 mmHg Icare IC200: 15.83 ± 10.4 mmHg Corneal haze Perkins: 19.1 ± 10.8 mmHg Icare IC200: 18.59 ± 10.74 mmHg Corneal haze Perkins: 23.71 ± 11.6 mmHg Icare IC200: 26.05 ± 15.09 mmHg

PCG = Primary congenital glaucoma; IOP: Intraocular pressure; RBT = Rebound tonometer; GAT = Goldmann applanation tonometer

Table III: Summary of tolerability of different tonometers in children from included studies

Author (Year)	Study population	Sample size (Age range)	Tonometers used	Tonometers used
Lundvall et al. (2011)[26]	Healthy children	39 children (3 to 18 months)	Icare	No child shows discomfort.
Rodrigues et al. (2014)[27]	Children with horizontal strabismus and healthy children	50 children (3 to 21 months)	Icare PRO and Perkins tonometry	Icare PRO is more tolerable than Perkins tonometry. Three infants (6%) were distressed and cried during examination with Icare PRO, compared to 31 infants (62%) with Perkins tonometry.
Sahin et al. (2007)[21]	Healthy children	152 children (7 to 15 years)	RBT (Icare) and GAT	RBT is more tolerable than GAT. Ten (6.6%) children felt slight pain and/or discomfort, and the remaining 142 (93.4%) children experienced no pain or discomfort.
Gandhi et al. (2012)[7]	Known or suspected glaucoma	60 children (5 to 17 years)	Icare ONE and GAT	Icare PRO is more tolerable than GAT. Forty parents (78%) rated Icare ONE as equal or more tolerated than GAT.

GAT = Goldmann applanation tonometer; RBT = Rebound tonometer

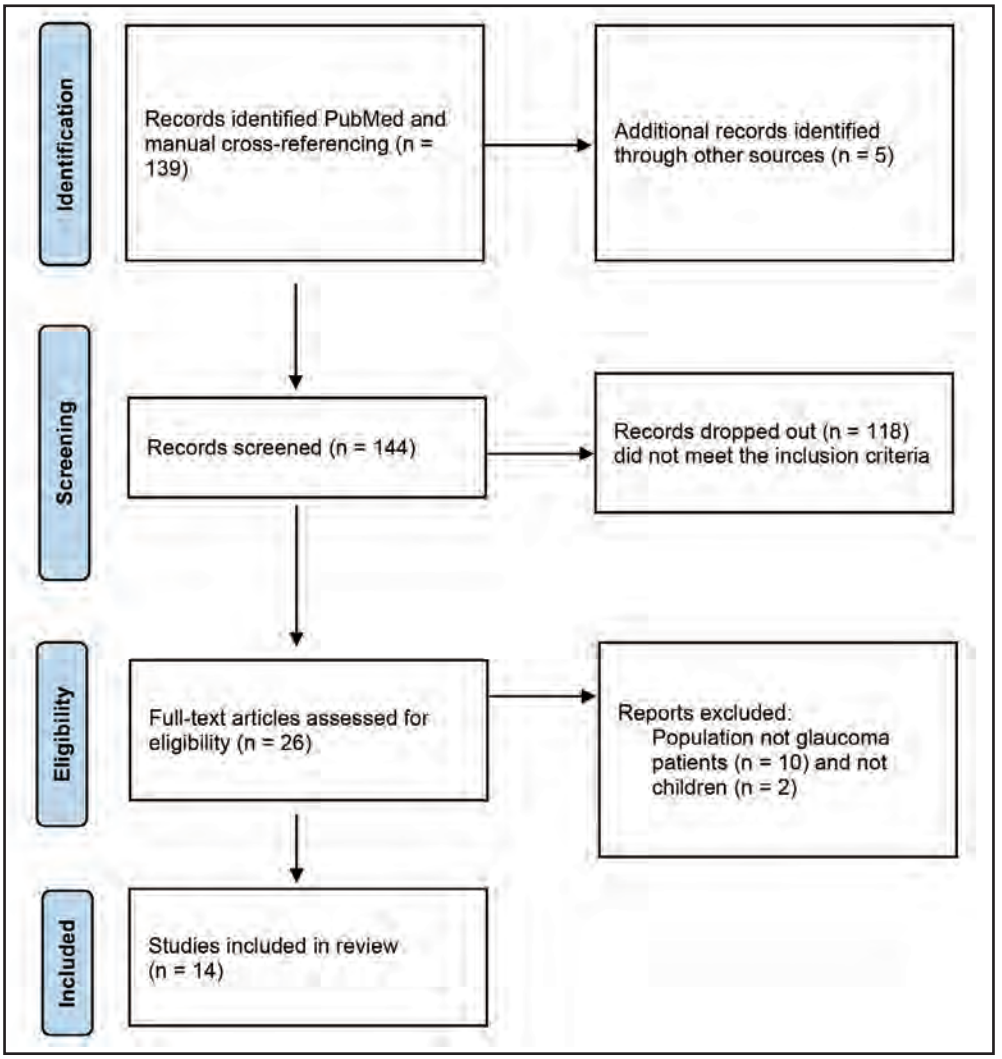

Fig. 1: Flow chart of the study selection process.

The mean difference between IOP readings with Tono-Pen and RBT is more significant in eyes with corneal oedema or abnormalities.[5,22] According to Levy et al., the overestimation with Tono-Pen is greater than with handheld applanation tonometry when the IOP exceeds 16 mmHg.[11] A study by Mendez-Hernandez found that the overestimation by Tono-Pen is even more remarkable if measurements by handheld applanation tonometry are greater than 20 mmHg.[16] When comparing RBT and handheld applanation tonometry, overestimation with RBT is more pronounced in eyes with an IOP of ≥19 mmHg and scarred cornea.[6,17] Angmo et al. discovered that the scarred cornea group (2.34 mmHg) had significantly higher IOP overestimation with RBT than the clear cornea group (0.78 mmHg).[17] These findings imply that RBT IOP values are less reliable in eyes with higher IOP and denser corneal opacity. Three case reports concluded that high IOP readings obtained with RBT should be interpreted with caution in cases of congenital corneal opacity with corneal fibrosis and that examiners should always consider the possibility of false-positive glaucoma diagnosis in these patients.[23] The accuracy of Tono-Pen over other tonometers in children with paediatric glaucoma presenting with oedematous cornea is still in question. However, several studies have stated that Tono-Pen is superior to GAT in adults with glaucoma and oedematous cornea.[10] Thus, more studies should be conducted to validate the accuracy of Tono-Pen in the oedematous cornea in children.

The notable challenge when measuring IOP in children with suspected or known glaucoma is the need for repetitive measurements. This has been shown to influence IOP readings in adults.[24] However, this is not true for children, as Dosunmu et al. found that the mean IOP difference between the initial and final (eighth) measurements with RBT was similar among the 20 eyes of 10 children recruited for the study. This could be because the RBT tip measures only 1 mm in diameter and makes only a small and brief contact with the cornea, hence, it does not appear to affect IOP.[25]

Another noteworthy challenge is the effect of body position during examinations and measured IOP. IOP measurements in infants are usually taken in supine positions, and it was questioned whether IOP measurements in older children in seated positions would be significantly different. Dosunmu et al. found that supine IOP readings with RBT and Tono-Pen were higher than seated readings in children. However, the IOP increases of 0.9 and 0.7 mmHg with RBT and Tono-Pen were considered insignificant and unlikely to change treatment plans in children with or without glaucoma.[14]

Tolerability and ease of use are two essential features of a tonometer, especially in children with paediatric glaucoma. As previously mentioned, GAT, handheld applanation tonometer, and Tono-Pen readings require topical anaesthetic drop and general anaesthesia which may be daunting to younger children.[3,13] The Tono-Pen has a relatively large tip that may intimidate children. Although no prior topical anaesthetic is required for IOP measurement with NCT, the puff of air may be frightening to children. With its small tip diameter, RBT's design is tolerable for children.[3]

Numerous studies have investigated the tolerability of various tonometers in infants and school-aged children without general anaesthesia (Table III). Lundvall et al. discovered that 39 healthy infants aged 3 to 18 months experienced no discomfort using RBT during or after an IOP examination.[26] A later study by Rodrigues et al. found that measurement with RBT was better tolerated in infants, causing distress and crying in only 6% of infants, compared to 62% with handheld applanation tonometer.[27]

In children between 5 to 17 years of age with known or suspected glaucoma in clinical settings, majority of patients' parents rated RBT as equally or more tolerable than GAT.[7] In a study by Sahin et al., school going children aged 7 to 15 years were asked to rate their level of discomfort during IOP measurements using RBT. According to their testimonies, 93.4% of the children experienced no pain or discomfort during IOP measurement with RBT, while the remaining children felt minor discomfort.[21]

In terms of ease of use, a survey of current paediatric tonometry practice in 2012 that included 144 paediatric ophthalmologists in the UK discovered that rebound tonometry (77.8%) is the most preferred method to measure IOP in children, followed by GAT/Perkins (44.4%), Tono-Pen (5.6%) and air-puff NCT (5.6%). 85.7% of participants rated rebound tonometry as 'very easy' and 'moderately easy'.[4] Another study found that examiners rated RBT higher than handheld applanation tonometer, regardless of the child' age.[12]

CONCLUSION

The primary goal of paediatric glaucoma diagnosis is to avoid irreversible eye damage that can lead to blindness. Goldmann applanation tonometry (GAT) is the gold standard for measuring intraocular pressure (IOP) but can only be used on older, cooperative children. Many newer tonometers have been developed, including handheld applanation tonometer (Perkins), rebound tonometer (RBT) (Icare), Tono-Pen, and air-puff non-contact tonometry (NCT) (in descending order of accuracy), each with distinct advantages over GAT. In children with suspected or known glaucoma, choosing the right tonometer is crucial, considering the accuracy, tolerability and ease of use. This review suggests that RBT is a better option than other tonometers in paediatric glaucoma patients because it is less traumatic, time-efficient and does not require anaesthesia or fluorescein dye. However, high readings with RBT, especially in patients with scarred cornea, should prompt the examiner to confirm findings with a second instrument. Further studies should be done in large, multi-centred cohorts to assess the accuracy of tonometers (and their various versions) in different anterior segment abnormalities in patients with paediatric glaucoma.

ACKNOWLEDGMENTS

None declared.

FUNDING ACKNOWLEDGEMENTS
Authors receive no financial support for this article's research, authorship and/or publication.

DECLARATION OF CONFLICTING INTERESTS
None declared.

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SYSTEMATIC / NARRATIVE REVIEW ARTICLE

Interventions to Improve Adherence to Medication on Multidrug-Resistant Tuberculosis Patients: A Scoping Review

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ABSTRACT

Introduction: Inappropriate treatment and non-adherence use of anti-tuberculosis (TB) drugs trigger the spread of multidrug-resistant tuberculosis (MDR-TB) strains and causes an emerging public health threat worldwide. Therefore, non-adherence to MDR-TB treatment leading to prolonged medication period, increase incidence of adverse event and financial burden, thus it requires interventions to achieve a therapeutic outcome.

Objective: This scoping review aims to provide an overview of interventions to improve the adherence level to medication of MDR-TB patients.

Materials and Methods: A review of observational studies was conducted to discuss the accuracy, tolerability and ease of use of tonometers in measuring IOP in children with glaucoma.

Three databases (PubMed, Web of Science, Scopus) were used in a scoping review. The data were synthesised using Rayyan AI. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were used to guide this review.

Results: A total of 11 articles were included in this review to describe the various interventions in MDR-TB treatment adherence. Psychological counselling or education intervention was the most popular intervention, and it significantly increased adherence levels among MDR-TB patients. Increased adherence level patients also reported by interventions with Medication Event Reminder Monitor (MERM), Video Directly Observed Therapy (VDOT), 30-day recall and Visual Analogue Scale (VAS), Financial Support, mHealth Application and directly observed therapy, short course (DOTS) and DOTS-Plus programs. However, we found that Electronic Dose Monitoring (EDM) device intervention has less effect on MDR-TB patients' adherence. Conclusion: The recovery of patients can be facilitated through MDR-TB treatment adherence interventions. It is acknowledged that the studies included in this review exhibit heterogeneity, with a majority showing significant improvement. Therefore, further study was required to investigate the specific on developing highly personalised interventions tailored to specific population or context, as well as to assess the cost-effectiveness of such interventions.

KEYWORDS:
Adherence intervention, scoping review, therapy MDR-TB

INTRODUCTION

Tuberculosis (TB) is an infectious disease caused by Mycobacterium tuberculosis which has existed for millennia and remains a major global health problem for approximately 10 million people each year, and is one of the top 10 causes of death worldwide.[1] Treatment of TB is even more complex and challenging with the emergence of multidrug-resistant tuberculosis (MDR-TB).[2,3] Multidrug-resistant tuberculosis (MDR-TB) is caused by Mycobacterium tuberculosis strains resistant to at least isoniazid and rifampicin, two first-line medicines used to treat TB.[4]

The prevalence of multidrug-resistant/rifampicin-resistant tuberculosis (MDR/RR-TB) was estimated to be 3.3% in new cases and 18% in previously treated cases globally in 2020. Overall, an estimated 465,000 incident cases of MDR/RR-TB were reported, and the global proportion of RR-TB cases estimated to have MDR-TB was 78%.[1] Despite considerable advances in therapy in the last decade, treatment outcomes remain poor for individuals with MDR-TB, with treatment success rates of 56% worldwide and 48% in India for the 2017 patient cohort.[5] Although some of the variability in treatment outcomes may be attributable to the composition of the patient's drug regimen,[7,8] suboptimal medication adherence may be another critical problem contributing to poor MDR-TB treatment outcomes.[9]

Medication non-adherence is well recognised as a leading cause of health problems and a financial burden.[10-12] Therefore, a robust assessment of adherence to the treatment regimen MDR-TB is needed to assess progress towards the treatment goals and inform policy and practice.[13] Recent data

This article was accepted: 13 March 2024
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Table I: Keywords used in each database

No.	Database	Keywords
1	PubMed	(intervention program) AND (multidrug resistant tuberculosis) AND (adherence)

from a global meta-analysis explained that non-adherence to treatment regimens was associated with a higher prevalence of MDR-TB and poor treatment outcomes.[14,15] Socioeconomic, health care systems, conditions, treatment and patient knowledge factors are closely related to adherence level.[16,17] Previous studies on interventions to increase adherence in TB patients have outlined various approaches.[18–22] These encompass TB interventions, education, counselling, incentives, community-based initiatives, and mixed interventions, all linked to several active TB care cascade outcomes. However, the selection of strategies requires accounting for cost-effectiveness and local contexts due to their substantial diversity. Despite these investigations, there is not comprehensively review study addressing interventions targeted specifically at MDR-TB patients. This scoping review aims to provide an overview of interventions to improve the adherence level of MDR-TB patients.

MATERIALS AND METHODS

A scoping review was conducted to assess the articles interventions to improve adherence among MDR-TB patients. The review encompassed articles published between January 2012 to November 2022. This period was specifically chosen to encompass the latest advancements and initiatives in MDR-TB treatment and adherence strategies, reflecting a decade of significant progress and innovation in this field. This scoping review was reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[23] The review specifically emphasised the PICOS criteria which included the population (patient with MDR-TB, infected with strains resistant to isoniazid and rifampicin), intervention, comparator, outcomes and study design. Only interventions specifically targeting medication adherence and treatment outcomes for MDR-TB were considered in this review. The intervention included in this review required a comparison group to assess their effectiveness of the intervention, such as a comparison between intervention groups or a control group. Additionally, the review examined treatment outcome in relation to improvements in adherence level or the absence of no impact after the intervention.

Searching Strategy

Initial searches were conducted using three electronic databases (PubMed, Web of Science, and Scopus). A broad literature search was undertaken to identify keywords in the field. Literature search uses the primary term to expand the search. Key terms used for the search were as follows (Table I).

Eligibility Criteria

This review uses inclusion and exclusion criteria for specific journals as material for this review. The inclusion criteria included an original study with adult MDR-TB patients receiving continuous anti-TB treatment, supplemented with adherence tools interventions. The exclusion criteria were review articles, commentary articles, handbooks, guidelines and study protocol.

Study Selection

The title and abstract of the articles were screened by the authors, and then the full text of the articles was assessed for eligibility and quality by the authors. Data screening was conducted using Rayyan Intelligent Systematic Review software (https://www.rayyan.ai/). Duplicate papers were excluded from the study. Abstracts were read, and relevant full articles were reviewed for data extraction. Any uncertainty or conflict was discussed at regular check-ins until a consensus was reached among the authors. While Rayyan's AI screening and highlighting feature were utilised, each record was still individually screened. In cases of uncertainty, a more inclusive approach was adopted. Independent screening of full-text articles was conducted by at least two researchers, and conflicts or uncertainties were resolved through further discussions until a consensus was reached among all researchers conflicts and uncertainties were resolved through further discussion until a consensus was reached among all researchers.

Charting the Data

We developed data extraction templates to map data to each research question. To define these conceptual areas, we adopted the World Health Organisation's guidance on ethics and governance of MDR-TB for health definitions (based on the recommendations of the Artificial Intelligence Council of the Organization for Economic Cooperation and Development states.[5,6] The following data were extracted:

- General information: Authors, publication year, country, intervention, participants, duration of intervention, outcome measurement and conclusion of the intervention effect.
- Types of intervention: Psychological Counselling or Educational Intervention, Medication Event Reminder Monitor (MERM)/Electronic Dose Monitoring (EDM), Video Directly Observed Therapy (VDOT), 30 day recall and Visual Analogue Scale (VAS), Financial Support, mHealth Application, directly observed therapy, short course (DOTS) and DOTS-Plus program.

Collating, Summarising, and Reporting the Results

The analysis used data related to the research questions to summarise implementation motives and elements in the implementation process. Articles were read and re-read, with initial ideas sorted into domains of explanations for improved adherence for MDR-TB patients. Next, initial codes were identified within each article. The codes were compared based on similarities and differences and organised into potential themes, which were then compared to generate the interventions used to come up with clear definitions and names for each intervention in each of the domains of adherence levels of MDR-TB patients. Data analysis was conducted in pairs, and any uncertainties or differences were discussed among all authors until a consensus was reached.

Table II: Overview of articles included in the scoping review (N = 11)

No	Author	Year	Country	Intervention	Participants	Participants type	Duration of intervention	Outcome measurement	Conclusion of the interventions effect
1	Baral et al.[25]	2014	Nepal	A mixed-method study comprising a qualitative formative survey, pilot intervention study, and explanatory qualitative study better to understand barriers to completion of treatment for MDR-TB	49 registered people with MDR-TB for interview	Patients	18 months	The MDR-TB treatment causes extreme social, financial, and employment difficulties. The pilot intervention study resulted in cure rates for those receiving counselling, combined support, and no support of 85%, 76% and 67%, respectively. Compared with no support, the (adjusted) risk ratios of a cure for those receiving counselling and receiving combined support were 1.2 (95% CI 1.0 to 1.6) and 1.2 (95% CI 0.9 to 1.6), respectively.	Financial and counselling support appear to improve MDR-TB treatment outcomes and cure rates.
2	Tola, et al.[33]	2016	Ethiopia	A structured questionnaire, psychological counselling, and adherence education.	698 TB patients, who were in treatment	Patients	30 minutes	Non-adherence level decreased among the intervention group from 19.4 (at baseline) to 9.5% (at endpoint), while it increased among the control group from 19.4% (baseline) to 25.4% (endpoint).	Psychological counselling and educational interventions, which were guided by HBM (Health Belief Model), significantly decreased treatment non-adherence levels among the intervention group
3	Malini et al.[28]	2021	Indonesia	The study used a quasi-experimental design with a pretest-post-test without a control group. The program intervention of health education uses with lecture method and group discussion using flipcharts and video as media	29 respondents	Patients	4 months	The result of this study shows that 65.5% of patients take medication regularly. The provision of health education on MDR-TB prevention behaviour emphasises motivation and self-efficacy.	The effect of health education in improving respondents' knowledge of MDR-TB preventive health behaviour.
4	Calligaro et al.[31]	2021	South Africa	questionnaires and conducting qualitative interviews	60 patients	Patients	3 months	Qualitative interviews revealed participants' perceptions of the value of the intervention. From baseline to follow-up, patients reported reductions in substance use severity, symptoms of depression, distress, and functional impairment.	Participant retention in the study was moderate. Randomized studies are needed to demonstrate the efficacy of this intervention before considering the potential for wider implementation.
5	Walker et al.[26]	2018	Nepal	This feasibility study used a mixed quantitative and qualitative approach. Counselling, using educational materials and group interaction	135 patients	Patient	30 to 60 minutes	All aspects of the intervention package were acceptable to patients. Researchers successfully trained individuals with no psychological counselling experience to deliver HAP (Health Activity Program).	This psychosocial support package is acceptable to patients.

No	Author	Year	Country	Intervention	Participants	Participants type	Duration of intervention	Outcome measurement	Conclusion of the interventions effect
6	Thomas et al.[9]	2021	India, US	Interviews with patients (MDR-TB) multidrug resistance-tuberculosis and health care providers (HCPs)	65 patients with MDR-TB and 10 HCPs.	Patients and HCPs	45 minutes	HCPs reported that MERM implementation resulted in fewer in-person interactions with patients and thus allowed HCPs to dedicate more time to other tasks, which improved job satisfaction.	
7	Bateman et al.[30]	2022	South Africa	Patients on ART and starting MDR-TB treatment with bedaquiline were enrolled at a public hospital in KwaZulu-Natal, South Africa (PRAXIS Study). Participants received separate EDM tools measuring adherence to bedaquiline and ART (nevirapine or lopinavir/ritonavir).	198 persons with MDR-TB and HIV	Patients	6 month	A total 11% of people with MDR-TB and HIV had multiple resistance at baseline, and 7.5% developed ART resistance.	Adherence to ART was independently associated with ART resistance and mortality
8	Casalme et al.[29]	2022	Philippines	Healthcare workers (HCWs) monitored adherence by watching videos via a web-based dashboard with the VOT (video-observed therapy) mobile app.	308 patients converted to MDR-TB cases	Patients and treatment providers	-	The treatment success rate was 88%, and the loss to follow-up rate was 8.1%. All HCWs agreed that VOT data accurately reflect the medication intake of the patients; 88/89 (99%) mentioned benefits of VOT, notably convenience, sense of comfort, privacy, and security	VOT (video-observed therapy) is feasible and acceptable for both patients and HCWs (Healthcare workers)
9	Stephens et al.[32]	2019	South Africa	3-day recall, 30-day recall, and Visual Analogue Scale (VAS) and examined adherence to monthly study visits (months 0–12).	200 patients	Patients	30 days	Adherence to medications (81–98% fully adherent across all measures) and clinic visits (80% missed ≤1 visit) were high, irrespective of HIV status. Adherence to antiretroviral therapy (ART) was significantly higher than to MDR-TB treatment by all self-reported measures (3-day recall: 92% vs. 84%, respectively. Adjusted risk ratio (aRR) of unsuccessful MDR-TB treatment increased with every missed visit: 1.50, 2.25, and 3.37 for unsuccessful treatment, for 1, 2, ≥3 missed visits.	Adherence to ART was significantly higher than MDR-TB treatment by all self-reported measures. Less effect of the intervention on MDR-TB patients.
10	Chaiyachati[34]	2013	South Africa	Trained five Health Care Workers (HCWs) in one location and given mobile phone HCWs' mobile usage patterns were electronically tracked for seven months and analysed	Five HCWs (one of five HCWs is female, two mobile HCWs were nurses; three completed secondary schooling without additional training)	Healthcare Workers and patients	7 months	Mobile HCWs submitted nine of 33 (27%) expected adverse events forms, conflicting with qualitative results in which mobile HCWs stated that mobilise improved adverse events communication, helped their daily workflow, and could be successfully expanded to other health interventions.	Explore the motivations of HCWs in the context of the limitations of their workflow and better technology for closer and real-time performance monitoring to create scalable interventions
11	Chien et al.[27]	2013	Taiwan	Researchers conducted a retrospective analysis of resistance profiles among MTB isolates obtained from 2160 consecutive patients with culture-confirmed pulmonary tuberculosis (pulmonary TB).	2160 patients	Patients	month	Trend analysis revealed that the rates of acquired MDR-TB were significantly lower after implementing the DOTS and DOTS-Plus programs ($p < 0.01$). The rates of resistance to rifampicin, isoniazid, ofloxacin, moxifloxacin, levofloxacin, and para-aminosalicylic acid decreased significantly during the study period.	DOTS and DOTS-Plus are both effective at preventing the acquisition of MDR-TB in Taiwan

Table II: Study interventions characteristics

	Intervention	Studies
1	Psychological counselling or educational intervention	Baral et al. 2014;[25] Tola et al., 2016;[33] Walker et al, 2018;[26] Malini et al., 2021;[28] Calligaro et al., 2021[31]
2	Medication event reminder monitor (MERM)/electronic dose monitoring (EDM)	Thomas, et.al, 2021;[9] Bateman, et al., 2022[30]
3	Video Directly Observed Therapy (VDOT)	Casalme et al., 2022;[29] Malini et al., 2021[28]
4	30-day recall and VAS	Stephens et al., 2019[32]
5	Financial Support	Baral et al., 2014[25]
6	mHealth Application	Chaiyachati et al, 2013[34]
7	Directly observed therapy, short course (DOTS) and DOTS-Plus programmes	Chien et al, 2013[27]

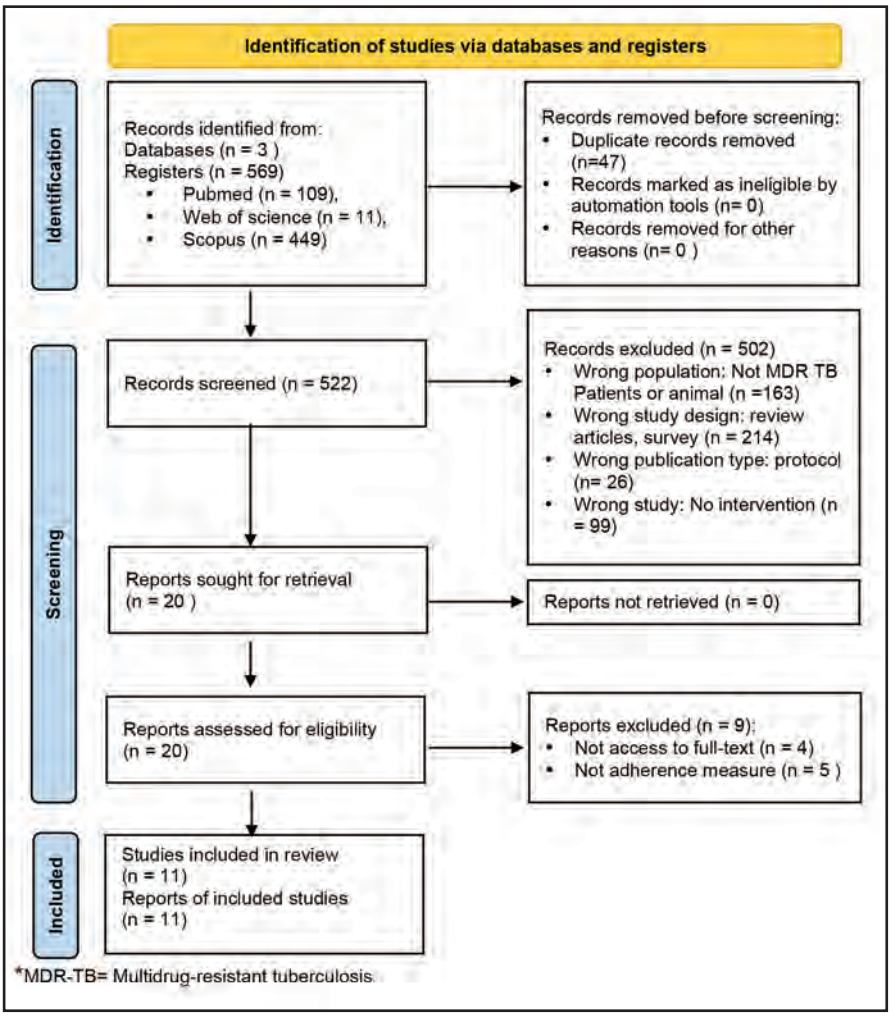

Fig. 1: PRISMA diagram of this review.

RESULTS

Study Selection

All original studies are assessing the intervention to improve adherence to medication MDR-TB. We use journals published for the period January 2012 and November 2022 that were selected for this systematic review. During the search, we found 569 articles divided into 109 articles from the PubMed database, 11 articles from the WoS database and 449 articles from Scopus. We identified 47 duplicate articles using the Rayyan AI® software.[24] A total of 522 articles were screened for the title and abstract. This initial screening excluded 502 irrelevant articles then, the full-text screening process was continued for 20 articles. In the full-text screening, nine articles were excluded, consisting of no access to full-text articles (n = 4) and no adherence measure (n = 5). We finally analysed 11 articles for qualitative synthesis. The flow diagram, literature search and screening process following the inclusion and exclusion criteria using the PRISMA diagram23 can be seen in Figure 1.

Study Characteristic

We found 11 studies related to improving the adherence in MDR-TB patients. In this review, we included studies on two continents, i.e. Asia and Africa. The studies from Asian

countries, i.e., India,[9] Nepal,[25,26] Taiwan,[27] Indonesia[28] and Philippines,[29] while the African studies from South Africa,[30-32] and Ethiopia[33] (Table II).

Study Interventions

The implementation of an intervention for MDR-TB patients is essential to improve adherence (20). Some interventions are very influential in improving the adherence level of MDR-TB patients. The results of the intervention can be seen in Table II.

From all the intervention studies we identified, psychological counselling or educational interventions were found to be are the most popular interventions for improving adherence in MDR-TB patients because as indicated by several.[25,26,28,31,33] It has been shown that psychological counselling increases the adherence rate of MDR-TB patients and promotes regular medication intake.

Furthermore, the electronic-based monitoring system using specifically MERM/EDM has also garnered. The implementation of MERM has been demonstrated to improve adherence in MDR-TB patients[9], while EDM had less effect on adherence levels in the same patient group.[30] VDOT is also one of the effective methods to improve adherence levels in MDR-TB patients. Recent study show that VDOT methods enhance the adherence of MDR-TB patients because it provides a sense of ease, comfort, privacy and safety.[28,29] Recent study with interventions such as 30 day recall and VAS,[32] Financial,[25] mHealth application,[34] DOTS and DOTS-Plus programs[27] also had a significant in improving adherence to MDR-TB patients.

DISCUSSION

Principal Findings

To the best of our knowledge, this is the first study of adherence to explore the adherence level of MDR-TB patients. We found eleven intervention studies in the research literature that mostly supported adherence rates in MDR-TB patients. Some intervention studies, such as psychological counselling and educational intervention, were more widely used by researchers in the literature sources. Focusing on the implementation process of adherence in MDR-TB patients still seems to be an important topic in research.

Study Characteristics

Regarding our findings, based on the studies published in 2012 to 2022, the research on the intervention to increase the adherence level of MDR-TB patients were dominated by lower-middle countries such as South Africa (four studies). In low- and middle-income countries, TB is often linked to poverty, poor living conditions and lack of access to healthcare.[35] Our findings are supported by the fact that more than 90% of notified tuberculosis infections occur in low-income and middle-income countries. Two-thirds of the estimated 10 million new active tuberculosis cases globally are accounted for by eight countries: India (26% of global cases), Indonesia (9%), China (8%), the Philippines (6%), Pakistan (6%), Nigeria (4%), Bangladesh (4%) and South Africa (4%).[36]

Study Interventions

Interventions aimed at improving to treatment adherence in patients with multi-drug resistant tuberculosis (MDR-TB) in low- and middle-income countries can pose challenges due to various factors such as poverty, lack of access to healthcare, and poor understanding of the disease.[36] Regarding our findings, psychological counselling or education intervention were identified as the most popular interventions, especially in low- and middle-income countries. MDR-TB treatment is a long and complex process that often leads to psychological distress for patients, including anxiety, depression and stigma.[35] The implementation of psychological counselling and health education interventions resulted in a significantly reduction in non-adherence levels among the intervention group. Moreover, unlike those studies that reported contradictory results, our findings were consistent with many other studies findings. For instance, Liefooghe et al. reported limited impact on adherence improvement despite intensive patient counselling.[37] However based on the evidence from five studies using psychosocial were found to be the most effective, efficient and cost-effective making them suitable for implementation in low-income countries. This conclusion with the study conducted by Kaliakbarova et al. which revealed significant decrease in treatment non-adherence levels with the provision of psychological support to MDR-TB patients.[38] Furthermore, Lee et al. found that physical education significantly reduced cumulative non-adherence levels among the intervention group compared with the control group.[39] Thiam et al. also reported an improvement in TB treatment adherence levels following an intervention focused on enhancing communication between health care workers and patients.[40]

Psychological and social factors that can affect treatment adherence can be addressed through counselling which provides emotional support, coping strategies and disease-related information to patients.[9,41] One approach utilised is cognitive-behavioural therapy (CBT), which assists patients in identifying and modifying thought patterns and behaviours affecting their adherence to treatment. CBT also in the development of coping strategies for managing medication side effects and the physical and emotional impacts of the disease.[42] Another approach is motivational interviewing (MI), an employs patient-centred counselling method to helps patients explore and resolve ambivalence about treatment adherence. MI also facilitates the identification of personal motivations for adherence and the establishment of treatment goals.[25,33] Group counselling can also prove effective for MDR-TB patients, as it allows patients to share their experiences with others facing similar challenges. Offering emotional support and reducing feelings of isolation and stigmatisation.[26,28] It is important to note that psychological counselling should be provided by trained professionals and integrated into the comprehensive treatment plan for MDR-TB patients. In summary, psychological counselling was valuable intervention for increasing treatment adherence in MDR-TB patient by addressing psychological and social factors, providing emotional support, coping strategies and disease related information.[9,40,41]

The improvement of MDR-TB adherence can be achieved through the utilisation of MERM. Positive outcomes were observed in studies conducted by Thomas et al., demonstrating the effectiveness of MERM in improving treatment adherence among MDR-TB patients.[9] MERMs serve as reminders for patients to take their medication at the designated time and generate electronic records of medication adherence. Patients greatly appreciated the reduction in clinic visits, resulting in time and cost savings, as the frequency of routine clinic visits for patients with MDR-TB was reduced during the pilot implementation of MERM.[41] Despite the decreased in face-to-face interactions with healthcare providers (HCPs), some patients expressed a feeling more cared for. This feeling stemmed from the perception that HCPs were remotely monitoring their clinical progress and the from positive responses to receive through actual phone or in-person outreach based on adherence data. The study also highlights the advantage of MERM as the reminders prompt patient to access their medication storage area, increasing the likelihood of prompt medication intake and promote habit-forming medication-taking behaviour.[45,46]

Furthermore, the impact of MERM monitoring in this population will contingent upon the development of interventions to address issues such as drug toxicity, depression, stigma and substance use disorders, which frequently contribute to non-adherence.45 Therefore, the utilisation MERMs is deemed to have a good impact on adherence in MDR-TB patients. In a study conducted in India, the implementation of a mobile phone-based system with text message reminders improved treatment adherence among MDR-TB patients by more than 20%.[41] However, a study on EDM in South Africa[30] shows that EDM has less effect on improving adherence among MDR-TB patients, and there are several reasons why studies on EDM may have indicated limited effectiveness. One reason is the potential inadequate utilisation of EDM systems by patients, healthcare providers or both. For example, patients may forget to use the device or may not understand how to use it properly. Similarly, healthcare providers may not properly integrate the device into their care and follow-up practices.[47] Another reason is that EDM systems may not be appropriate or feasible for all patients, especially those residing in low- and middle-income countries with limited access to technology.

Additionally, some patients may not have access to the necessary infrastructure to support EDM, such as electricity or mobile phone networks.[48] Another reason is that EDM systems alone may not improve adherence in patients with MDR-TB. Treatment adherence is a complex issue influenced by many psychological, social, and economic factors. Therefore, it's important to consider a multifaceted approach that includes psychological counselling, social support, and financial support.[39,40] Finally, some studies may have limitations that affect the results' accuracy and generalisability of the findings. Therefore, it's important to consider the design and methodology of studies when interpreting their results. While EDM systems such as MERMs can be an effective approach to improve adherence to treatment in patients with MDR-TB, they may not be as effective in specific populations or when used in isolation. It's important to consider the context and the patient's needs and to use a multifaceted approach when addressing adherence to treatment in MDR-TB patients.

VDOT is a technology-based approach that can improve adherence to treatment in patients with MDR-TB. VDOT involves video conferencing technology, allowing healthcare workers to observe patients taking their medication remotely. Additionally, it allows for more frequent monitoring of medication adherence, which can improve treatment outcomes. Our findings show this approach positively enhanced the adherence of MDR-TB patients to treatment who have difficulty attending in-person clinic visits, such as those who live in remote areas or have mobility limitations.[28,29] Garfein and Doshi[50] and Chen et al.[51] stated that the combination of media (audio-visual) and effective communication while delivering health education programs could be effective in improving knowledge and behaviour for TB control.[52–54] A randomised clinical trial in Moldova showed that VOT increased adherence to TB treatment.[55] A much earlier study on asynchronous VOT at five sites in California showed that VOT reduced stress on the TB programs and enabled a quicker return to daily activities. It also reported that VOT was beneficial for patients in remote areas as it does not require consistent network connectivity.56 VDOT can effectively improve adherence to treatment in patients with MDR-TB by increasing accessibility to care, allowing healthcare workers to observe patients taking their medication remotely, and providing more frequent monitoring of medication adherence.

The 30-day recall method and VAS are two methods that can be used as interventions to improve adherence to treatment in patients with multi-drug resistant tuberculosis (MDR-TB).[32] Both methods can be used with other interventions, such as directly observed therapy (DOT) and psychological counselling to improve treatment adherence. For example, the 30-day recall method can monitor medication adherence over time, while VAS can assess patients' attitudes and beliefs about their treatment and adherence.[32] However, a study conducted by Wilson et al. stated that the closer correlation between the 3-day recall measure and TB treatment outcomes compared to the 30-day recall measure is consistent with evidence suggesting that self-reports during shorter recall periods (2 to 4 days) tend to be more accurate compared to more extended recall periods.[57] We agree that in addition to more accurate results with shorter recall periods, the results may also provide adherence for MDR-TB patients.[57,58] The 30-day recall method and VAS are two methods that can be used as interventions to improve adherence to treatment in patients with MDR-TB. Still, they should be used in conjunction with EDM or DOT to get a more comprehensive picture of a patient's adherence.

Another approach is financial support, which can help to reduce the burden of treatment-related costs and increase treatment adherence. Providing counselling and financial support reduces their vulnerability and increases recovery rates.[25] Another study in India showed that providing financial support through transportation vouchers improved treatment adherence among MDR-TB patients by more than 15%.[59] A recent study in Thailand shows no significant difference in medication adherence rates after financial

support.[60] It is important to note that financial support should be provided in a way sensitive to the patient's needs and cultural context. It can be an effective intervention for improving adherence to treatment in patients with MDR-TB by reducing the burden of treatment-related costs and making it easier for patients to adhere to their treatment regimen.

Furthermore, an approach through mHealth applications is mobile phone-based health interventions that can provide patients with reminders to take their medication, information about the disease and its treatment, and the ability to communicate with healthcare providers.[34] Additionally, mHealth applications can be integrated with financial incentives for adherence, such as mobile phone credit or other rewards, to motivate patients to adhere to their treatment regimen.[25] The mHealth applications should be designed with the patient's needs and cultural context in mind, and they should be easy to use and accessible to patients with limited literacy and technology skills.[61]

The classical way to improve the adherence level of MDR-TB patients was DOTS and DOTS-Plus program approaches.[27] DOTS is a World Health Organisation (WHO) recommended strategy for the treatment of TB, which involves providing patients with daily supervised therapy.[62] DOTS-Plus is an extension of the DOTS strategy that includes using second-line drugs to treat MDR-TB. It is a comprehensive package of care that provides for the provision of medicines, diagnostic services, and other support services. DOTS-plus also includes components such as psychological counselling, social support, and financial assistance, which can help to improve adherence to treatment.[63] The rationale is that the social interaction and peer pressure involved in DOT can motivate patients to more adhere to prescribed treatment.[64] However, DOT raises several ethical and legal issues.[65,66] Some studies have shown that frequent DOT can reveal a patient's TB status, which is stigmatised in many cultures.[67,68] Despite the unfavourable stigma, continued use of DOTs will yield positive results. This is because, in some countries, DOT is provided by trained private observers such as volunteers or specialized DOT providers employed by the government.[69,70]

There are several limitations that may be encountered when studying interventions to improve adherence to treatment in patients with multi-drug resistant tuberculosis (MDR-TB). The results of studies may not be generalisable to other populations or settings. The interventions may be effective in specific contexts but may not be appropriate or feasible in others. MDR-TB is a complex disease that requires a multifaceted approach to address treatment adherence. It's important to consider the length of treatment and side effects when addressing adherence to treatment in patients with MDR-TB. In addition, it's important to acknowledge the challenges associated with different interventions to study limitations. These include scalability, cost-effectiveness, cultural considerations and implementation barriers. However, similar evaluation should apply to other interventions to comprehensively understand their real-world impact.

CONCLUSION

Our review implies that interventions to improve adherence to treatment for multidrug-resistant tuberculosis (MDR-TB) are essential for successful outcomes. These interventions can include directly observed therapy (DOT), counselling, education and provision of social support. Additionally, involving community members and traditional healers in the care and treatment of patients with MDR-TB can increase trust and understanding, leading to better adherence. Overall, a combination of interventions tailored to the patient's and community's specific needs and cultural context is likely to be most effective in improving adherence to treatment for MDR-TB. Further study is required to investigate the specific on developing highly personalized interventions for a particular population or context, and examining the cost-effectiveness of interventions to help policymakers, and health systems make informed decisions about which interventions to implement.

ACKNOWLEDGMENT

This study is supported by Indonesian Education Scholarship and Harapan Bangsa University Purwokerto.

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SYSTEMATIC / NARRATIVE REVIEW ARTICLE

Exploring measurement tools to optimise hospital physician distribution

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ABSTRACT

Introduction: Equitable healthcare delivery is essential and requires resources to be distributed, which include assets and healthcare workers. To date, there is no gold standard for measuring the correct number of physicians to meet healthcare needs. This rapid review aims to explore measurement tools employed to optimise the distribution of hospital physicians, with a focus on ensuring fair resource allocation for equitable healthcare delivery.

Materials and Methods: A literature search was performed across PubMed, EMBASE, Emerald Insight and grey literature sources. The key terms used in the search include 'distribution', 'method', and 'physician', focusing on research articles published in English from 2002 to 2022 that described methods or tools to measure hospital-based physicians' distribution. Relevant articles were selected through a two-level screening process and critically appraised. The primary outcome is the measurement tools used to assess the distribution of hospital-based physicians. Study characteristics, tool advantages and limitations were also extracted. The extracted data were synthesised narratively.

Results: Out of 7,199 identified articles, 13 met the inclusion criteria. Among the selected articles, 12 were from Asia and one from Africa. The review identified eight measurement tools: Gini coefficients and Lorenz curve, Robin Hood index, Theil index, concentration index, Workload Indicator of Staffing Need method, spatial autocorrelation analysis, mixed integer linear programming model and cohort-component model. These tools rely on fundamental data concerning population and physician numbers to generate outputs. Additionally, five studies employed a combination of these tools to gain a comprehensive understanding of physician distribution dynamics.

Conclusion: Measurement tools can be used to assess physician distribution according to population needs. Nevertheless, each tool has its own merits and limitations, underscoring the importance of employing a combination of tools. The choice of measuring tool should be tailored to the specific context and research objectives.

KEYWORDS:
Review, physicians, resource allocation, delivery of healthcare

INTRODUCTION

Equitable allocation of health resources is crucial for ensuring optimal healthcare delivery, characterised by providing equal opportunities for individuals to access healthcare services.[1] This principle is particularly important during the ongoing COVID-19 pandemic,[2,3] which has further intensified the challenge of allocating limited resources in healthcare systems already under strain. The impact of the pandemic has been particularly severe in lower-income countries, leading to disruption in essential services, including maternal and childcare, vaccination programs and cancer care.[4-6]

Healthcare delivery systems encompass public health, community care and hospital care, each with distinct resource needs. In hospital settings, a multidisciplinary approach has been widely adopted to provide comprehensive and patient-centred care, with physicians often assuming clinical leadership roles. Hence, it is important to ensure an equitable distribution of physicians across hospitals.[7] However, achieving this equity remains a global challenge influenced by various factors. Typically, urban regions with higher living standards tend to have a higher physician density.[8]

Several measurement tools have been employed to assess the distribution of physicians across hospitals. However, a universally accepted standard measure is currently absent. Policymakers face the task of carefully selecting appropriate measuring tools to facilitate human resource planning. The selected tool should be straightforward and provide timely information to effectively guide the allocation of physicians to suitable geographical areas. Therefore, this rapid review aimed to explore the various measurement tools specifically designed or adapted to guide the allocation of hospital physicians and evaluate their respective advantages and disadvantages.

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MATERIALS AND METHODS

Ethics Approval

This review was prospectively registered with National Medical Research Register (NMRR-22-02136-2S5) and obtained exemption from the Medical Research and Ethics Committee, Ministry of Health Malaysia as all data used in this review is publicly available.

Stakeholder Engagement

This review was conducted to provide guidance for policymaking in response to a request from the Committee of Internal Medicine, Ministry of Health Malaysia, with a strict timeline for completion. Multiple meetings were held with the head of service for internal medicine, senior consultants, physicians and health system researcher to develop literature search strategies, assessment methods and a data extraction plan. Stakeholders were regularly updated on the progress of the review, and all decisions were made in close consultation with them.

Search Strategy

The research question was formulated using the problem-concept-context format. Primary research articles published in English between January 2002 and June 2022, which described the use of at least one measurement tool to assess the distribution of hospital physicians, were considered eligible for inclusion in the review. Literature search was performed in three databases (PubMed, EMBASE and Emerald Insight) using search strings as follows: (placement OR distribution OR allocation OR planning OR equity OR fairness) AND (tool OR method OR index OR measure) AND (physician OR hospital-based internal medicine OR specialist). Additionally, a search of grey literature was conducted using Google Search.

Study Selection

The article selection process involved a two-level screening approach. In the level 1 screening, a pilot screening was independently conducted by three authors (RAR, SAS, NAA) on 5% of the records using titles and abstracts. Any inconsistencies in decision-making were resolved through discussions to reach a consensus. Subsequently, the same researchers screened the titles and abstracts for the remaining 95% of records. In the level 2 screening, the full texts of the records selected in the level 1 screening were retrieved and independently assessed for eligibility by two other authors (MAMS and KAAA). Any disagreements during the article selection were resolved through discussions and consensus.

Data Extraction and Synthesis

A data extraction form was created and pre-piloted on two selected articles. Two authors (RAR and MAMS) independently extracted the following information into the form: author and publication date, country of origin, measurement tools used to assess hospital physician distribution and the specific variables used. Any uncertainties during the data extraction process were discussed until consensus was reached. Subsequently, data extraction was conducted on all included articles in the review using the form for narrative synthesis.

Quality Appraisal

Study appraisal employed an assessment tool by Hawker et al., which evaluates each study's reporting quality for elements such as the abstract, title, introduction, objectives, methods, sampling, data analysis, ethics approval, researcher reflexivity, population generalisability and findings' implications.[9] Scores for each element range from 1 (very poor) to 4 (good). One author (MAMS) appraised all studies, while another author (RAR) evaluated 10% of the studies. Both authors' assessments demonstrated 95% agreement, with the remaining 5% of discrepancies resolved through discussion.

RESULTS

Included Studies

The initial literature search identified a total of 7,199 records, with an additional record retrieved from grey literature sources. After the removal of 1,460 duplicate records, the remaining 5,739 titles and abstracts underwent thorough screening. Subsequently, 46 articles were considered for full-text review. During this phase, 33 articles were excluded based on the predefined criteria, leaving with a final selection of 13 articles for the review.[10-22] The reasons for excluding articles during the full-text review primarily revolved around ensuring relevance to the specific focus of this study on hospital-based physician distribution and the evaluation of measurement tools. In details, a subset of the excluded articles (seven in total) did not pertain to hospital-based physicians, three articles were excluded due to a lack of explicit mention or discussion regarding the specific formula or method employed in the distribution of physicians, and a significant portion of the excluded articles (23 in total) did not delve into the subject of physician distribution. A detailed breakdown of the article search, selection process, and reasons for exclusion is presented in Figure 1. It's noteworthy that literature search also identified one relevant record from grey literature, which offers valuable insights into the intricate dynamics of physician supply and demand.

Study Characteristics

The selected articles are predominantly from Asian countries, particularly Thailand, Japan, China, Iran and Taiwan, reflecting a geographical emphasis in the literature on hospital physician distribution. It is worth noting that there is representation from Africa, albeit with only one article included in the review. A notable aspect is that five out of the 13 articles took a comprehensive approach by employing a combination of measurement tools. This methodological choice enhances the depth of understanding, offering a more nuanced evaluation of the dynamics involved in hospital physician distribution within populations. The characteristics of the selected articles are summarised in Table I.

Measurement Tools Used to Assess the Distribution of Hospital Physicians

A total of eight distinct measurement tools used to assess the hospital physician distribution: the Lorenz curve and Gini coefficient, the Robin Hood index, the Theil index, the concentration index, the Workload Indicator of Staffing Need method, the mixed integer linear programming model, the cohort-component model and the spatial autocorrelation

Table I: Summary of included articles for data synthesis

No.	Title	Year Published	Country	Tool/measure(s) used
1.	Equity of health workforce distribution in Thailand: an implication of concentration index.[13]	2019	Thailand	Concentration index
2.	Examining changes in the equity of physician distribution in Japan: a specialty-specific longitudinal study.[14]	2017	Japan	Gini coefficients and Lorenz curve
3.	Equity analysis of Chinese physician allocation based on Gini coefficient and Theil index.[11]	2021	China	1. Gini coefficients and Lorenz curve 2. Theil index
4.	Physician distribution across China's cities: regional variations.[20]	2021	China	Gini coefficients and Lorenz curve
5.	The cost of health workforce gaps and inequitable distribution in the Ghana Health Service: an analysis towards evidence-based health workforce planning and management.[21]	2021	Ghana	Workload Indicator of Staffing Need method
6.	Model for allocation of medical specialists in a hospital network.[19]	2018	Thailand	Mixed integer linear programming model
7.	Future projection of the physician workforce and its geographical equity in Japan: a cohort-component model.[16]	2018	Japan	Cohort-component model
8.	What about the health workforce distribution in rural China? An assessment based on eight-year data.[22]	2019	China	1. Gini coefficient and Lorenz curve 2. Theil index
9.	Equity in distribution of health care resources; assessment of need and access, using three practical indicators.[12]	2013	Iran	1. Gini coefficient and Lorenz curve 2. Concentration index 3. Robin Hood index
10.	Comparing regional distribution equity among doctors in China before and after the 2009 medical reform policy: a data analysis from 2002 to 2017.[10]	2020	China	1. Gini coefficient 2. Theil index
11.	Incorporating spatial statistics into examining equity in health workforce distribution: an empirical analysis in the Chinese context.[17]	2018	China	1. Spatial autocorrelation analysis 2. Theil index
12.	Examining sufficiency and equity in the geographic distribution of physicians in Japan: a longitudinal study.[15]	2017	Japan	Gini coefficient and Lorenz curve
13.	Measuring inequality in physician distributions using spatially adjusted Gini coefficients.[18]	2016	Taiwan	Gini coefficient and Lorenz curve

analysis. Table II summarised all the measurement tools found including data requirements, standard formulations, advantages and limitations for each tool.

1. Lorenz curve and Gini coefficient

The Lorenz curve (LC) is often regarded as equivalent to the Gini coefficient. The LC serves as a graphical representation illustrating the distribution of health resources, specifically physicians. It is constructed by plotting the cumulative percentage of physicians, categorised into different levels based on the populations or regions, on the vertical axis against the cumulative percentage of the population on the horizontal axis. The LC appears as a diagonal line when physicians are equally distributed. Deviations from the diagonal line indicates the degrees of disparities in physician distribution.

The Gini coefficient, derived from the LC, is a numerical measure to quantify health resource inequality in a population with a single value. It is a commonly used measurement tool by studies included in this review. A population with total inequality has a Gini coefficient of 1, while a population with a perfect distribution has a value of 0. The Gini coefficient is calculated by comparing the area between the LC and the line of perfect equality (a diagonal line) to the total area under the line of perfect equality. A higher Gini coefficient indicates a more unequal distribution of physicians.

Gini coefficients and LC are applied to assess inequality in physician distribution, revealing if specific regions or specialties dominate concentration. They are effective in visually representing distribution disparities and identifying areas or specialties with disproportionate physician concentration. In this review, their application can be seen in eight studies conducted in various countries, including Japan and China.[10-12,14-15,18,20,22] Common variables for analysis include the number of physicians per population and population data. The application of Gini coefficient and LC allows the visualisation of a decreasing trend in physician numbers per population over time, with some specialties experiencing increases.[12,14,15] In other studies, results from Gini coefficient and LC analyses can highlight disparities between urban and rural areas, emphasising the importance of balancing medical resources.[10,11,20,22] An additional study conducted in Taiwan proposed spatially adjusted Gini coefficients, integrating the use of Geographic Information Systems (GISs) to analyse the impact of geographic accessibility (travel distance and travel time) in relation to the utilisation of health services.[18] This study concludes that by increasing physician numbers in medium-sized cities and improving transportation infrastructure, one can address geographical maldistribution effectively.

In terms of advantages, both the Gini coefficient and LC are sensitive to changes in the distribution of physicians. They can capture even small shifts in the distribution and detect

Table II: Summary of measurement tools for hospital physician distribution

No	Method	Brief Description	Data Requirements	Standard Formulation*	Advantages	Limitation
1	Lorenz curve, Gini coefficient	Measure and compare cumulative percentage of physicians that ranked according to different populations or regions and the cumulative percentage of the population. Gini coefficient took values between 0 and 1, with higher values indicating higher levels of inequality. The standard of Gini-coefficient in health resource allocation is as follow; Gini coefficient <0.2 indicates in highly fair distribution; 0.2-0.3, relatively fair; 0.3-0.4 indicates reasonable distribution; 0.4-0.5 indicates a large gap; and >0.5 indicates a high degree of unfairness [11].	1. Number of physicians in different populations or regions. 2. Total number of physicians. 3. Population of units or region.	The Lorenz curve is a graphical representation and doesn't have a single mathematical formula. It is created by plotting the cumulative percentage of the population (x-axis) against the cumulative percentage of physician in the population (y-axis). Gini coefficient = A / (A + B), where A is the area between the Lorenz curve and the line of equality, and B is the area under the line of equality.	1. Generally regarded as gold standard in economic work. 2. The Lorenz curve provides a visual assessment of how physician availability is distributed across different regions or population groups. 3. Both the Gini coefficient and Lorenz curve are sensitive to changes in the distribution of physicians, meaning it can capture even small shifts in the distribution and detect improvements or deteriorations in fairness over time. 4. Enable comparisons of physician distribution across different regions or time periods.	1. May not fully capture the complexities of healthcare access and disparities that go beyond income considerations as they primarily designed to measure income or wealth inequality. 2. Able to provide an overall summary of inequality in a population but does not capture disparities within specific subgroups or regions (within or between group comparison). 3. Do not consider non-health factors that influence healthcare resource allocation, such as disease prevalence, healthcare needs, and efficiency of healthcare systems.
2	Robin Hood index	Measures proportion of physicians to be redistributed from areas with above-average provision to areas with below-average provision to achieve equal distribution. Based on the Lorenz Curve, it is equivalent to the maximum vertical distance from the Lorenz curve to 45° equality line and is denoted as a vertical line. The index value ranges from 0 (complete equality) to 100 (complete inequality).	1. Physician distribution data across different geographical areas or population groups. 2. Population data for the same geographic areas or population groups.	Robin Hood index = (Vertical Distance / Total Area Under Lorenz Curve) * 100	1. Result is easier to understand compare with Loren curve and Gini coefficient outcome. 2. It highlights the potential for redistribution to achieve a more equal distribution.	1. Although the index primarily addresses the redistribution of resources based on health needs or socioeconomic status, other dimensions of equity (geographic disparities, cultural factors, or specific health requirements of different population groups) may not fully capture.
3	Theil index	Measure the equity of physician distribution within and between different populations or regions. Theil index took values between 0 and 1, with higher values indicating higher levels of inequality.	1. Number of physicians allocated in different populations or regions. 2. Total number of physicians. 3. Population of units or region. 4. Total population.	Theil index = Σ (Xi) * log (Xi/Yi) where Xi is the proportion of population in the ith city / state accounting for the total population. Yi is proportion of physician in the ith city / state accounting for the total physician.	1. Well reflect the contributions to inequality by within group and between group and is complementary to the Gini coefficient.	1. Not intuitively interpretable as some other inequality measures. Thus, the result interpretation could be challenging. 2. Cannot directly compare populations with different sizes as calculation depends on the number of physicians in the population or region.

No	Method	Brief Description	Data Requirements	Standard Formulation*	Advantages	Limitation
4	Concentration index	Measures whether the number of physicians is distributed fairly across different socioeconomic groups. The CI value ranges from -1 to +1. CI=0 indicates equal physicians' distribution among socioeconomic groups; CI>0 indicates physicians' distribution is disproportionately concentrated on higher socioeconomic groups; CI<0 indicates physicians are more concentrated among lower socioeconomic groups.	1. Ranked data of socioeconomic status such as income of individuals or households. 2. Physician to population ratio.	Concentration index = 2 *Cov (Y, R)/μ, where Y is the health variable of interest (e.g., physicians per population), R is the rank of individuals by socioeconomic status, Cov is the covariance, and μ is the mean of Y (the variable).	1. Helps assess the concentration of physicians in specific areas and reveals the extent to which the distribution is skewed towards certain regions or socioeconomic groups. 2. Allows for comparisons across different regions, demographic groups, or time periods.	1. Can only be applied if a strict ranking socioeconomic variable, like income, is available. 2. Unable to make comparison within and between income/socioeconomic group.
5	Spatial autocorrelation analysis	Measure the distribution of physicians across different geographic areas and examine any spatial patterns or clustering in their allocation. Global Moran's I and the local Moran's I were used to evaluate the degree of spatial autocorrelation and estimate the local autocorrelation between a single area and its neighbours, respectively.	1. Data that represents the geographic boundaries and spatial units of the study areas such Geographic Information System (GIS) data. 2. Number or density of physicians in each geographic area. 3. Population data for each geographic area.	Spatial autocorrelation analysis involves various statistical tests, and the specific formulae may depend on the method used.	1. Can gain insights into the spatial relationships between different locations. It helps determine whether nearby locations tend to have similar or dissimilar values, indicating potential patterns or trends. 2. Can highlight areas where there might be disparities or uneven access to healthcare services, enabling policymakers to identify areas that require attention and intervention. 3. Helps in targeting areas that require additional healthcare infrastructure, recruiting more physicians, or implementing policy interventions to improve access to healthcare services.	1. Require data on spatial units or boundaries which may not readily available or inaccurate. 2. Choice of spatial units or boundaries used in the analysis can significantly impact the results. Different levels of aggregation may reveal different patterns of physician distribution. 3. Only provides a snapshot of physician distribution at a specific point in time. Many factors can influence the distribution patterns over time. 4. Require special software for spatial analysis and clustering map generation.

No	Method	Brief Description	Data Requirements	Standard Formulation*	Advantages	Limitation
6	Workload Indicator of Staffing Need (WISN) method	Assess physician distribution and determine the optimal number of physicians required in a particular setting or facility. Does not have specific values range applicable, but calculation typically result in ratio or percentage. This ratio represents the estimated physician requirement based on the workload demand. A ratio greater than 1 indicates that additional physician is needed to meet the workload, while a ratio less than 1 suggests an excess of physician relative to the workload.	1. Service profiles: types of services provided by physician including specific tasks and procedures, frequency to perform the tasks. 2. Work measurement: the time required to deliver different tasks. 3. Workforce data: number of physician available, working hours of physicians.	WISN ratio = Workload demand/available workforce	1. The approach to staffing decisions is more objective and evidence based. By matching workforce distribution with workload requirements, it helps prevent understaffing or overstaffing situations. 2. It is a flexible technique for labour planning since it take into consideration of variations in service profiles and working conditions.	1. Physician's task varies between facilities or study area and may not be reflective if categories under larger job scopes. 2. May not fully consider other elements such as population demographics, healthcare demands, or infrastructure availability because it focuses solely on workload and physician capability. 3. Data required are retrospective in nature, which may not accurately reflect current workload variations. 4. Require regular reviews and updates on various parameters to maintain results relevance and accuracy.
7	Mixed integer linear programming (MILP)	A mathematical optimisation model to measure and optimize physician distribution in a systematic and quantitative manner.	1. Healthcare system data, (e.g., number of healthcare facilities, capacity, and geographical coverage area). 2. Population data on the population served by the healthcare system, (e.g., demographics, geographical distribution, and healthcare needs). 3. Physician data on the available pool of physicians, their specialties, skills, and constraints (e.g., working hours, preferences). 4. Data on constraints (e.g., minimum staffing requirements, workload capacities and travel distances, or equity considerations).	Formulations depend on specific objectives, constraints, and decision variables chosen by the modeler. Involves equations representing population changes due to births, deaths, and migration, specific to demographic and workforce dynamics.	1. Offer a systematic approach to physician distribution. Due to the optimisation of resource allocation choices based on predetermined goals and constraints, better distribution outcomes are produced. 2. These models are flexible and can accommodate various constraints, objectives, and scenarios.	1. As a mathematical model, it requires computational resources and expertise in mathematical programming. 2. Large-scale problems cannot always be solved.
8	Cohort-component model	Measure physician distribution by projecting the future supply of physicians based on population characteristics and workforce dynamics.	1. Population data 2. Current physician workforce. 3. Population's birth and death rates. 4. Information on internal and external migration.	Involves equations representing population changes due to births, deaths, and migration, specific to demographic and workforce dynamics	1. The model able to estimate the future physician's distribution enables long-term planning. 2. Considers various demographic elements to help policymakers to match physician distribution to the population's changing demographics.	1. It is highly dependent on reliable birth, death, and migration data. Thus, it may be difficult to collect the information to apply this method. 2. Assumes that survival and birth rate and estimates of net migration will remain the same throughout the projection period.

*General formulations, and variations may exist in different studies or applications.

Table III: Quality of studies assessing hospital physician distribution

Study title	Abstract and title	Introduction and objectives	Method and data	Sampling	Data analysis	Ethics and bias	Finding and results	Transferability and/or generalisability	Implications and usefulness
Equity of health workforce distribution in Thailand: an implication of concentration index.[13]	4	4	4	3	4	1	4	4	4
Examining changes in the equity of physician distribution in Japan: a specialty-specific longitudinal study.[14]	4	4	4	3	4	4	4	4	4
Equity analysis of Chinese physician allocation based on Gini coefficient and Theil index.[11]	3	4	4	4	4	3	4	4	4
Physician distribution across China's cities: regional variations.[20]	4	4	4	4	4	4	3	3	3
The cost of health workforce gaps and inequitable distribution in the Ghana Health Service: an analysis towards evidence-based health workforce planning and management.[21]	4	4	4	4	4	4	4	4	4
Model for allocation of medical specialists in a hospital network.[19]	3	4	3	3	3	1	3	3	3
Future projection of the physician workforce and its geographical equity in Japan: a cohort-component model.[16]	4	4	4	4	4	4	4	4	4
What about the health workforce distribution in rural China? An assessment based on eight-year data.[22]	3	3	3	4	3	4	3	3	4
Equity in distribution of health care resources; assessment of need and access, using three practical indicators.[12]	2	3	4	3	3	4	3	3	3
Comparing regional distribution equity among doctors in China before and after the 2009 medical reform policy: a data analysis from 2002 to 2017.[10]	4	4	4	4	4	3	4	4	4
Incorporating spatial statistics into examining equity in health workforce distribution: an empirical analysis in the Chinese context.[17]	4	4	4	4	4	3	4	4	4
Examining sufficiency and equity in the geographic distribution of physicians in Japan: a longitudinal study.[15]	4	4	4	4	4	4	4	4	4
Measuring inequality in physician distributions using spatially adjusted Gini coefficients.[18]	4	4	3	4	4	4	4	4	4

Note: 1 = Very poor, 2 = Poor, 3 = Fair, 4 = Good

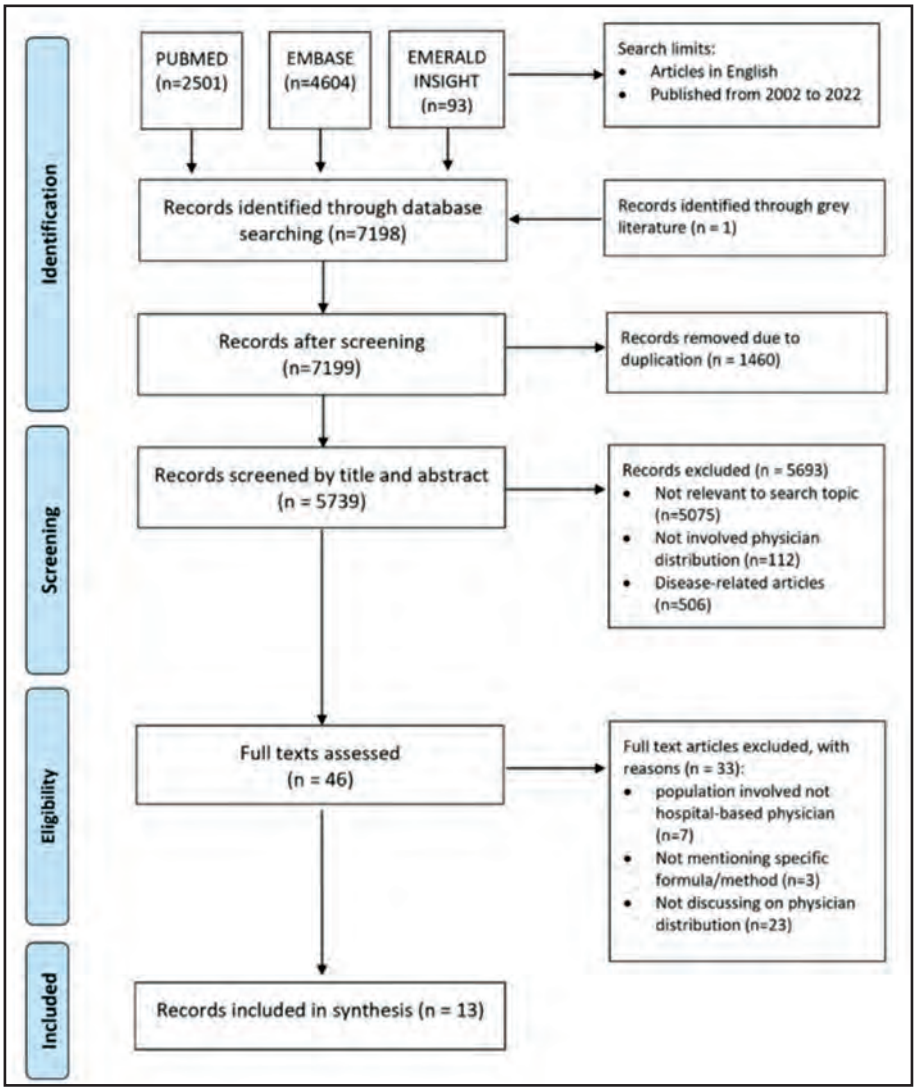

Fig. 1: PRISMA flow diagram of included studies.

improvements or deteriorations in fairness over time.[14] Additionally, both tools enable comparisons of physician distribution across different regions or time periods. However, these measurements may be sensitive to extreme values, potentially leading to misinterpretations if outliers significantly impact the distribution. Furthermore, they do not fully capture the complexities of healthcare access and disparities that go beyond income considerations.[12,20] Primarily designed to measure income or wealth inequality, they treat all the regions or areas equally and do not account for geographic disparities in healthcare access. Furthermore, the Gini coefficient is limited to assessing overall inequality without providing insights into its sources, whether originating between different regions or within each region.[22] Therefore, the incorporation of the Theil index (more information on Theil index can be found later) can complement the Gini coefficient by offering a means to measure and understand the specific sources of inequality.

2. Robin Hood index

The Robin Hood index, a measure derived from the LC and known as the Hoover index, the Pietra index and the Ricci-Schutz index, quantifies the proportion of resources to be relocated to achieve an equal distribution. It evaluates the impact of redistributive policies, indicating if certain areas or groups disproportionately benefit from physician resources. This index measures the vertical distance between the LC and the equality line. Only study by Omrani-Khoo et al used this index in this review.[12] In the context of physician distribution, it signifies the proportion of physicians to be redistributed from populations or regions above the mean to those below the mean, ranging from 0 (complete equality) to 100 (complete inequality).

In essence, elevated Robin Hood values signify greater societal inequality, suggesting that a larger proportion of physicians must be redistributed to attain equality. This tool offers a more intuitive interpretation than the Gini coefficient, emphasising the potential for redistribution based on health needs and socioeconomic status.[23] However, it is important to note a limitation of the Robin Hood index. Although the index primarily addresses the redistribution of resources based on health needs or socioeconomic status, it may not fully capture other dimensions of equity such as geographic disparities, cultural factors, or specific health requirements of different population groups.

3. Theil index

The Theil index, another valuable measure for assessing physician distribution disparities, was referenced in four articles.[10,11,17,22] It considers variations in physician allocation within populations or regions and between them. Moreover, it helps identify areas or groups experiencing more significant disparities in physician supply, contributing to a comprehensive understanding of distribution equality. For a given variable, it is calculated as the sum of the ratio of each subgroup's value to the overall average, multiplied by the natural logarithm of this ratio. When applied to physician allocation, the Theil index can pinpoint specific subgroups with significant gaps in access to physicians, aiding policymakers in comprehending the extent of these disparities for resource allocation decisions. One key advantage of the Theil index is its capacity to offer a detailed analysis, capturing disparities both within and between subgroups, well reflecting the contributions to inequality by within-group and between-group factors.[22] It serves as a complementary measure to the Gini coefficient. Like the Gini coefficient, the Theil index falls between 0 and 1, with higher values indicating greater inequality. However, the result from Theil index is less intuitive to interpret compared to some other inequality measures, making the interpretation of results potentially challenging.[24] Additionally, this index cannot directly compare populations with different sizes, as its calculation depends on the number of physicians in the population or region.

4. Concentration index

The concentration index (CI) is another tool to assess the fairness of physician distribution across different socioeconomic groups. The CI usually defined in relation to the concentration curve, which plots the cumulative percentage of the population, ranked according to living standards, starting with the low standard, on the x-axis, and the cumulative percentage of the health human resources or physicians, corresponding to each cumulative percentage of the living standard variable, on the y-axis.

The CI is calculated as twice the area between the concentration curve and the line of equality (the 45-degree line), with values ranges from -1 to +1. A value of 0 indicates an equal distribution of physicians among socioeconomic groups, reflecting equality. A positive index suggests that physicians are more concentrated among higher socioeconomic groups, reflecting an inequitable distribution. Conversely, a negative index indicates a concentration of physicians among lower socioeconomic groups, which signifies an inequitable distribution in the opposite direction. This tool is effective in understanding how specific factors influence the concentration of physicians in different regions. For example, Witthayapipopsakul et al. applied the CI to assess the equity of health workforce distribution in public hospitals in Thailand, and the CI values demonstrated equity in health workforce distribution, with doctors being relatively concentrated in wealthier provinces.[13] However, the applicability of the CI relies on the availability of strictly ranked socioeconomic variables, such as income.[25] Missing or unreliable income data can result in misleading interpretations of the CI.[26]

5. Spatial autocorrelation analysis

Many traditional methods used to measure the equity in health workforce distribution have ignored spatial location information.[27] Overcoming this limitation, Zhu et al. adopted spatial statistics into traditional methods through spatial autocorrelation analysis.[17] Spatial autocorrelation analysis identifies spatial patterns in physician distribution, showing if similar values cluster or disperse geographically. It is useful for understanding geographic clustering of physicians, particularly in scenarios where spatial patterns are crucial for equitable distribution. Zhu et al. applied this method for studying physician distribution patterns and detecting spatial clustering or dispersion of similar values across geographic regions in China.[17] It explores whether nearby locations exhibit similar physician allocation or non-random differences. This analysis yields two key indices: global Moran's I and local Moran's I.

Global Moran's I evaluates the overall spatial pattern of physician distribution across all study areas or geographical units, with values ranging from -1 to +1. A positive Moran's I indicates positive spatial autocorrelation, signifying the clustering of areas with similar physician densities. This suggests the presence of regions with concentrated physicians alongside those with fewer physicians. Conversely, a negative Moran's I suggests negative spatial autocorrelation, indicating that areas with contrasting physician densities cluster.[17,28] A value close to zero denotes no spatial autocorrelation, indicating a random pattern of physician distribution.

Local Moran's I, an extension of the global measure, examines local spatial patterns by calculating spatial autocorrelation for each area separately. It helps identify local clusters or outliers in physician distribution and categorises areas as having high-high (areas with high physician density surrounded by areas with high physician density), low-low (areas with low physician density surrounded by areas with low physician density), high-low, or low-high spatial autocorrelation. This analysis not only highlights areas with potential healthcare disparities but also aids in targeting regions that need additional healthcare infrastructure, more physicians, or policy interventions to enhance access to healthcare services. However, the accuracy and availability of spatial units or boundary data, as well as the need for advanced software for spatial analysis and clustering map generation, may limit the use of this analysis.[29]

6. Workload Indicator of Staffing Need

The Workload Indicator of Staffing Need (WISN) is a workforce planning tool used to determine the required number of physicians in a given area. It helps assess physician adequacy or shortages based on workload and population health needs in a specific region. Only study by Asama et al. conducted in Ghana applied WISN method to quantify the inequitable distribution of health workforce.[21] The WISN method require data on physician services (including specific tasks and their frequency), task durations and workforce details (physician numbers and working hours). Using these variables, the WISN method calculates physicians' needs by comparing workload demand to the available workforce, typically resulting in a ratio or percentage.

The resulting ratio reflects the estimated physician requirement based on workload demand. A ratio exceeding 1 indicates the need for additional physicians to meet the workload, while a ratio below 1 suggests an excess of physicians. The WISN method's core purpose is to align workforce distribution with workload requirements, preventing situations of understaffing or overstaffing. However, the complexity and diversity of physician tasks can introduce challenges and variability, potentially affecting staffing estimates' accuracy. Moreover, all data required for WISN are retrospective in nature, which may not accurately reflect current workload variations.[30] The number of physicians needed in a facility may evolve over time due to factors like population growth, changing healthcare needs, policy shifts, increasing healthcare demands, and new service requirements. Therefore, regular reviews and updates of these calculations are essential to maintain their ongoing relevance and accuracy.

7. Mixed integer linear programming models

Mixed integer linear programming (MILP) models offer a systematic approach to physician distribution, simultaneously considering multiple criteria and constraints. These models guide resource allocation decisions based on predefined goals and constraints, leading to improved distribution outcomes. They are effective in scenarios with diverse objectives and constraints. For example, Suppapitnarm and Pongpirol conducted a study on the model for the allocation of medical specialists in Thailand's hospital network.[19] They aim to enhance the systematic approach to physician distribution by leveraging the capabilities of MILP models.

Five MILP models were formulated, aiming to find an optimal solution for resource allocation, minimising transportation costs, while maximising physician engagement and meeting patients' needs. These models differed based on the inclusion of part-time medical specialists and the consideration of the case mix index. Based on data analysis, the Medical Services' executives favoured Model 5 due to its reported feasibility and practicality.[19]

While MILP models offer valuable insights into allocation strategies and policy changes, it is essential to recognise that, being mathematical in nature, they can pose computational challenges.[31] Implementing this method requires computational resources and mathematical programming expertise, particularly in large-scale healthcare systems or when dealing with numerous constraints. Policymakers should carefully explore different allocation strategies and conduct sensitivity analyses to assess the robustness of distribution outcomes.[32]

8. Cohort-component model

The cohort-component model is a commonly used technique for population projection.[33,34] In the context of physician distribution, this model employs demographic techniques to estimate physician distribution based on population dynamics and workforce characteristics. This model is useful for long-term planning, projecting future physician needs based on changes in population demographics. It examines the interplay between aging, population growth and physician supply, tracking distinct age and gender-based cohorts over time. This model considers migration, births, deaths and physician workforce changes, enabling predictions of physician distribution in various regions or healthcare settings.

This review identified one study conducted by Hara et al. that applied a cohort-component model to project the future geographical distribution of physicians and their demographics in Japan.16 The study projected that from 2005 to 2035, the absolute number of physicians aged 25 to 64 will decline by 6.1% in rural areas with an initially lower physician supply, while it will increase by 37.0% in urban areas with an initially lower supply. Despite an increase in the overall number of physicians in rural areas, the geographical disparity in physician distribution is expected to worsen, with physicians aged 25 to 64 becoming more concentrated in urban areas. By employing this model, policymakers can visualise regional disparities in physician supply and address them through effective measures to ensure equitable distribution.

However, to effectively use a cohort-component model for physician distribution, accurate data on population, current physician workforce, birth and death rates and migration, both internal and external, are crucial. Challenges in collecting comprehensive and reliable data for these variables may limit the model's accuracy.[16,35]

Quality Appraisal

All studies, except one,[12] featured informative abstracts with clear titles, as detailed in Table III. Each study received good or fair ratings for the introduction, aims, and well-described methods, including sampling and data collection. These aspects included specifics on targeted samples, recruitment processes and sample size justifications. Clear data analysis descriptions also earned good or fair ratings across all studies. Ethical and bias considerations were addressed adequately in all studies, except for two,[13,19] that did not mention these issues. The presentation of results was explicit and logically structured in all studies, with the exception of four[12,19,20,22] that require additional explanations for better comprehension. All studies, except for six,[12-14,19,20,22] offered sufficient context and setting descriptions, supporting generalisability. Furthermore, all studies contributed to generating new knowledge, offering ideas for future research and suggesting policy or practice implications, except for three.[12,19,20]

DISCUSSION

Statement of Principal Findings

The current review identified 13 published articles that utilised eight different tools to assess distribution of hospital physicians across populations or regions. Each tool, namely the Lorenz curve and Gini coefficient, the Robin Hood index, the Theil index, the concentration index, the Workload Indicator of Staffing Need method, the mixed integer linear programming model, the cohort-component model and the spatial autocorrelation analysis, possess its own strengths and limitations.

Interpretation within the Context of the Wider Literature

Interestingly, all but one of these 13 articles focused on work conducted in Asia, suggesting that imbalanced physician

distribution is a common issue in this region. Most Asian countries are characterised by their large size and challenging terrain, facing significant obstacles in providing equitable healthcare services and achieving balanced physician distribution. Within these countries, larger cities often offer more attractive opportunities for physicians, including career advancement, better employment prospects, active lifestyles, and enhanced educational opportunities for their children.[36-38] Geographical maldistribution of physicians also concerns European countries, as their physician density grew at a slower rate between 1990 and 2005 compared to the period from 1975 to 1990.[39] However, unlike low- and middle-income countries, most high-income countries have the capacity to mitigate the effects of maldistribution through strategies such as air medical services or the adoption of telemedicine technology.[40-42]

Among the eight measures identified, the LC, Gini coefficient, Theil index, CI and Robin Hood index are economic methodologies conventionally used to assess socioeconomic disparities within a population. While originally developed for income inequality analysis, these measures can be adapted for assessing fairness or inequality in various contexts,[43] including physician and healthcare resource distribution.[44] The Gini coefficient and LC are widely considered as gold standards in economic analysis due to their simplicity and interpretability.[17] This may explain their prevalent use in analysing geographical physician distribution disparities in eight articles from this study. Nevertheless, the traditional Gini coefficient fails to account for the fact that people living in adjacent regions may share medical services. Therefore, Hsu et al. recommended the use of spatially adjusted Gini coefficients, which incorporate factors like neighbourhood population density, travel distance and travel time, to effectively evaluate inequality in physician distributions.[18]

Selecting the appropriate tool for physician allocation relies on the availability of essential data. This review revealed that all methods require regional data on the population and the number of physicians. Researchers with this data can readily employ simple measurement tools, such as the Gini coefficient and LC, the Robin Hood index and the Theil index to measure physician distribution. However, other methods necessitate more complex information. For example, the CI method relies primarily on the selection of socioeconomic indicators, commonly utilising population or individual income data.[25] Income data is typically obtained from household surveys and must be used cautiously.[26] Challenges in accurately measuring income, such as recall bias or capturing all sources of income, can affect the reliability of CI interpretations. Difficulty in obtaining essential data, such as geographical boundaries (for spatial autocorrelation analysis), service profiles and work measurement (for WISN method), workload capacities and travel distance (for MILP) and information on population migration (for cohort-component model), also limit the use of these measurement tools.

Implications for Policy, Practice and Research

It is also important to note that no single measurement tool can fully capture the complex factors influencing physician distribution and equitable healthcare delivery. For policy makers and researchers, the choice of tool should be tailored to the specific context and research objectives. Furthermore, assessing physician distribution is just the initial step. The findings should ultimately inform evidence-based policy decisions and interventions aimed at addressing disparities and improving healthcare equity. Regular monitoring and evaluation of the distribution of hospital physicians are also crucial to assess the effectiveness of implemented strategies and identify the need for further adjustments.

STRENGTHS AND LIMITATIONS

Some limitations encountered in this review should be acknowledged. The review was conducted to provide stakeholders with timely evidence. Due to time constraints, the literature search was limited to a few databases and included only English-language articles, potentially leading to the omission of relevant data and selection bias. Additionally, the abbreviated timeframe restricted extensive data extraction and synthesis, potentially impacting the depth and accuracy of the findings.

CONCLUSIONS

In summary, this rapid review identified eight different measurement tools to assess the distribution of hospital physicians. Each tool has its own merits and limitations, underscoring the importance of employing a combination of tools. Adopting a comprehensive and evidence-based approach are crucial for policymaking to promote equitable healthcare. Additionally, advocating for ongoing evaluation and refinement of measurement tools is essential. Rigorous validation studies, comparative analyses and the incorporation of novel data sources can also further enhance the precision and reliability of these measurement tools.

ACKNOWLEDGEMENT

We would like to acknowledge the Ministry of Health Malaysia for permission to publish the study findings. We would also like to thank researchers from the Institute of Health System Research, National Institute of Health Malaysia for their assistance and support of this study. Our gratitude to Associate Prof. Dr Shaun Lee Wen Huey from Monash University for his valuable input during literature search and articles screening process.

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SHORT COMMUNICATION

Audit on data accuracy of the Malaysian Dialysis and Transplant Registry (MDTR)

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SUMMARY

Diabetes mellitus is the main aetiology of end stage kidney disease (ESKD) in Malaysia. However, there may be concerns of over-reporting of diabetes mellitus as the cause of ESKD in the Malaysian Dialysis and Transplant Registry (MDTR). The objective of this audit is to assess the accuracy of data collected in the MDTR. There were 151 centres/source data providers (SDP) with a total of 1977 patients included in this audit. The audit showed that 80.2% of doctors' records matched the MDTR data. The results were comparable with published validation studies in other countries.

INTRODUCTION

The Malaysian Dialysis and Transplant Registry (MDTR) of the National Renal Registry (NRR) collects data on all patients receiving kidney replacement therapy in Malaysia. There was a total of 9123 new dialysis patients in 2021, and diabetes mellitus remained the main cause (53.0%) of end stage kidney disease (ESKD), followed by hypertension (33.9%), unknown (4%) and glomerulonephritis/systemic lupus erythematosus (1.9%).[1] The proportion of diabetes mellitus appeared to have declined from 67.4% in 2016. This was probably artefactual due to the over-reporting of diabetes mellitus as the cause of ESKD, which was reviewed upon migration to a new deceased donor kidney transplant allocation system, the Malaysian Kidney Allocation System (MyKAS) in 2020.[2] The new system seeks to achieve the best use of scarce kidneys from deceased donors, applying ethical principles of utility and equity while retaining the principle of justice in the allocation process. Under MyKAS, a diagnosis of diabetes mellitus increases the 'estimated post transplant survival (EPTS)' score, and in effect excludes the patient from listing as a potential kidney transplant recipient. It is therefore important that all attempts are made to confirm the presence of diabetes mellitus.

The objective of this audit is to assess the accuracy of data collected in the MDTR on notification of new ESKD patients, specifically on the diagnosis of diabetes mellitus as cause of primary renal disease (PRD), in reference to patients' medical records.

Adult patients who were initiated on haemodialysis (HD) or peritoneal dialysis (PD) in year 2021 were included in the audit. Paediatric and transplant patients were excluded. A total of 177 centres/source data providers (SDP) were invited. Data collection was carried out from 1st November 2022 to 31st December 2022.

Doctors at each site reviewed the patients' medical records retrospectively and coded as 'Yes' if there was documentation of diabetes mellitus in the medical records, or 'No' if absent. Their results were then compared with the original data of PRD that was submitted by the SDP staff to MDTR.

Sub-group analysis was carried out to analyse the data accuracy according to sectors, HD versus PD, geographical regions as well as types of institution.

Descriptive statistics were used to describe demographics, primary renal disease, and comorbid conditions. Chi square tests were used to make comparisons between matched and unmatched data in subgroup analysis. The alpha level was established as $p \leq 0.05$. SPSS (version 25) and MS Excel were used for all calculations.

There were 151 (118 HD, 33 PD) centres/SDP from 12 out of 16 states/federal territories in Malaysia which participated in the audit, of which 139 were from the Ministry of Health (MOH), eight were from the Ministry of Education (MOE) and four were private HD centres. A total of 1977 patients were included, and their medical records were reviewed. Median age was 54.2 years (IQR 40.4, 62.7), 52.1% were male and 63.4% were on PD. Table I compares the characteristics of SDP and patients of the cohort we audited with the non-audited cohort in MDTR.

The audit showed that 80.2% of the doctor's record matched the MDTR data (Table II), with 0.6% of patients having untraceable records (missing data). There were 45.7% of patients with documentation of diabetes mellitus in the doctor's record and MDTR also confirmed the primary aetiology of kidney disease was diabetes mellitus.

There were 326 (16.5%) patients in which doctors documented the presence of DM, but MDTR did not indicate

This article was accepted: 29 January 2024
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Table I: Baseline characteristics of the audited and non-audited cohorts

	Audited cohort (n=151 SDP)	Non-audited cohort (n=752 SDP)	MDTR cohort (n=903 SDP)
Number of centres (SDP)			
Number of HD centres (SDP)	118	737	855
Number of PD centres (SDP)	33	15	48
Number of centres (SDP) according to geographical distribution			
West Malaysia			
East coast	46	93	139
West coast	59	605	664
East Malaysia	46	54	100
Number of centres (SDP) according to sectors			
MOH (Ministry of Health)	139	56	195
MOE (Ministry of Education)	8	4	12
MOD (Ministry of Defence)	0	5	5
NGO (Non-government organizations)	0	159	159
Private	4	528	532
Number of centres (SDP) according to types of institutions			
Tertiary institutions	31	6	37
Secondary institutions	105	132	237
Free-standing clinics	15	614	629
New dialysis patients in 2021			
Number	1 977	7 129	9 106
Age of patients (median, years)	54.2	59.1	58.3
Male patients (%)	52.1%	53.9%	53.5%
Patients on HD (%)	36.6%	94.9%	82.2%
Patients on PD (%)	63.4%	5.1%	17.8%

SDP: source data provider

Table II: Matching of doctors' records with Malaysian Dialysis and Transplant Registry (MDTR) data

	Matched result		Unmatched result	
	Dr's record: Yes; MDTR data: Yes	Dr's record: No; MDTR data: No	Dr's record: Yes; MDTR data: No	Dr's record: No; MDTR data: Yes
Patients (%)	904 (45.7%)	683 (34.5%)	326 (16.5%)	53 (2.7%)
Total patients	1587 (80.2%)		379 (19.2%)	

Untraceable/missing data: 11 (0.6%)

DM as the PRD. Further analysis showed that 123 (out of 326) patients had documentation of diabetes mellitus as 'co-morbidity' in the MDTR.

Sub-group analysis (Figure 1) showed that private centres or free-standing clinics had lower rate of matching data ($p < 0.05$) whereas no differences were detected among HD or PD centres/SDP, nor different geographical regions.

This is the first audit of accuracy of reported data in MDTR and it showed that 80.2% of the doctor's records matched the MDTR data. The results were comparable with other published validation studies. A pilot audit of the Australia and New Zealand Dialysis and Transplant Registry (ANZDATA) reported that the PRD data was correct for 86.3%.[3] The overall rate of accurate data entry of the Hong Kong Renal Registry was 81%.[4] Canadian Organ Replacement Register validation study reported a rate of 70.9%[5] and the United States Renal Data System (USRDS) validation result of 59.5%.[6]

In the group of unmatched results (Table II), 326 (16.5%) patients had documentation of diabetes mellitus in the doctor's notes, but MDTR did not reveal diabetes mellitus as the PRD. Although this could be due to inaccurate data submission, another explanation was related to diabetic patients having other causes of ESKD (e.g. glomerulonephritis, autosomal dominant kidney disease, etc). In this group of patients, further analysis showed that 123 (6.2%) patients had a record of diabetes mellitus as co-morbidity in MDTR, but PRD due to other causes. We believe the number may be higher, as it is not compulsory to report co-morbidity to NRR. Hence, the 'true' data inaccuracy of the MDTR was likely lower than 19.2% as shown in this audit. There were 2.7% of patients with an MDTR record as 'Yes' (diabetes mellitus as PRD) but the doctor's record did not concur. This small group of patients would require necessary correction in the MDTR to avoid being de-listed as kidney transplant recipients in MyKAS.

Over-reporting of diabetes mellitus in the past could be due to changes in the classification of diabetes as the PRD. In 2017 data collection migrated from a paper-based system to an electronic NRR, and it allowed more than one PRD. The NRR office adjudicated discrepancies in the data submitted to determine the PRD. For example, if the PRD was recorded as unknown and patient had diabetes mellitus as the secondary cause or co-morbidity, the PRD was amended to diabetes mellitus. However, since year 2021, only one cause of PRD is accepted. If PRD was unknown and diabetes mellitus is

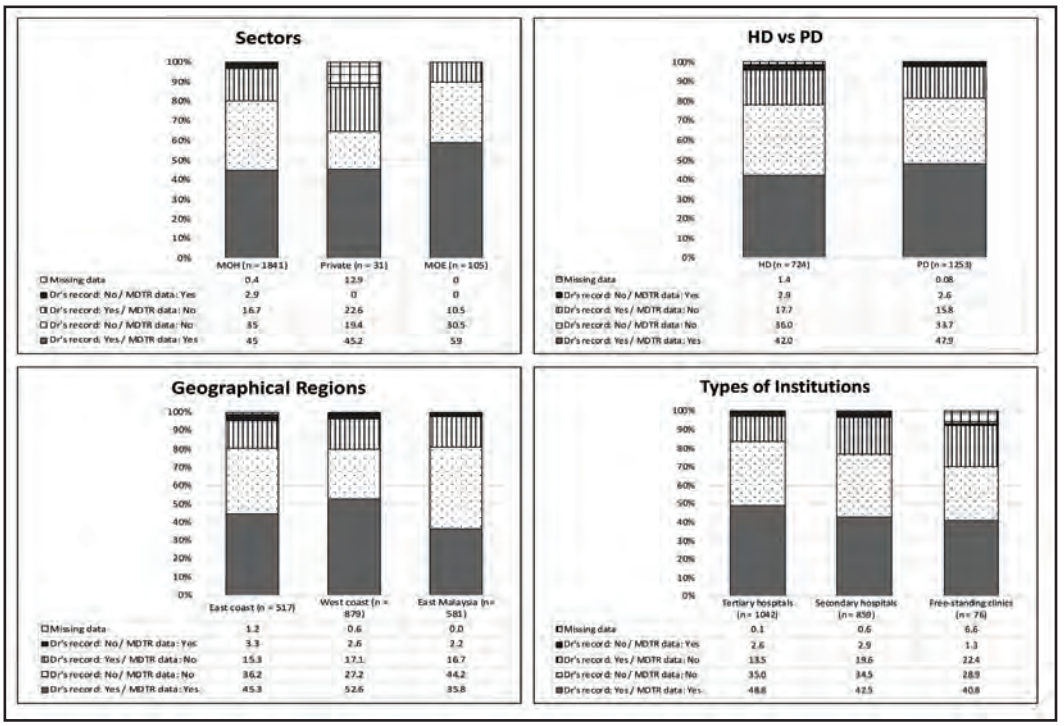

Fig. 1: Sub-group analysis according to sectors, dialysis modalities, geographical regions and types of institution

included in comorbidity at notification, 'unknown' PRD is maintained.

We recognise that our study has a both limitations and strengths. This limited audit involved mostly centres from MOH and MOE, although a large number of incident HD patients were in private HD centres. Although 63.4% were PD patients as opposed to 17.8% in MDTR, we audited 118 HD centres and 33 PD centres. We covered 12 states in Malaysia.

Our results were comparable with published validation studies in other countries. Strategies to improve data quality are on-going. These include providing guidance for diagnosis of diabetic nephropathy, educating staff in data submission and requiring a doctor to verify "primary renal disease" upon submitting data to MDTR.

ACKNOWLEDGEMENTS

The authors would like to thank the nephrologists, physicians, doctors and SDP staff for participating in the MDTR and this audit. Without their help, this report would not have been possible.

CONFLICT OF INTEREST

There is no conflict of interest or competing financial interests.

SOURCE OF FUNDING

Malaysian Society of Nephrology (MSN)

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A real-world experience of a prescribing policy for SGLT2-inhibitors in HFrEF in a Malaysian public tertiary cardiac centre

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SUMMARY

A prescribing policy for SGLT2-inhibitors was implemented in a local public tertiary cardiology centre in Sabah to improve access for heart failure (HF) patients. The study evaluated 169 HF patients with reduced ejection fraction (HFrEF) who met the policy criteria. After starting SGLT2-inhibitors, a significant proportion of patients experienced decreased NTproBNP levels, indicating a positive response. HF hospitalisation rates within 1 year were lower compared to the previous year. No adverse events were reported, suggesting that the treatment is safe. Findings demonstrates the benefits of implementing prescribing policies to enhance treatment accessibility and generate valuable real-world data at the local healthcare level.

KEYWORDS:
HFrEF, prescribing policy, empagliflozin, SGLT2-inhibitors, real-world

INTRODUCTION

Heart failure (HF) is a chronic and progressive condition that typically represents the end stage of various cardiovascular disorders, with high risk of readmissions and mortality.[1] In Malaysia, hospital admissions due to HF constitute approximately 6 to 10% of all the acute medical admissions.[2] Sodium-glucose cotransporter 2 inhibitors (SGLT2 inhibitors), an antihyperglycemic agent, has emerged as the fourth pillar of Guideline Directed Medical Therapy (GDMT) together with renin-angiotensin system (RAS) inhibitors, beta blockers and mineralocorticoid receptor antagonists (MRA) to reduce the HF burden of readmissions and mortality. However, given that Malaysia's healthcare system is mostly government-funded, introducing new therapy often requires careful planning to maintain a balance.

Malaysia is a part of Southeast-Asia, known for its cultural diversity. Of the estimated population of 33 million, the state of Sabah has the third highest population (10.4%) in Malaysia. The public tertiary cardiac centre in Sabah caters to the state's population, translating to approximately 3.5 million people.

However, access to SGLT2-inhibitors is limited in the public healthcare setting, where resources need to be carefully planned and fully maximised. Careful selection of patients who may reap greater benefit can improve access to this medication. We evaluated the outcome of HF patients prescribed with GDMT and SGLT2-inhibitors in a local public tertiary cardiac centre in Sabah, Malaysia, through the introduction of the centre's prescribing policy for SGLT2-inhibitors in HFrEF. Patient eligibility was determined based on the centre's prescribing policy, which include patients with HFrEF (LVEF ≤40%), optimised on GDMT, either NYHA II and above despite on GDMT, or NTproBNP levels > 600 pg/ml. Patients with eGFR<30 mL/min/1.732, known hypersensitivity to SGLT2-inihibitors, and known history of ketoacidosis were excluded.

In this observational study of patient enrolment from September 2020 to June 2022, 169 HFrEF patients with available records for review were initiated with SGLT2-inhibitors. Their baseline characteristics were analysed (Table I). Mean age was 53.8 year (SD13.02), with 83.43% males. Majority of ethnicity profiles were Sabah-natives (56.8%), Chinese and Malay. Patients were primarily initiated with SGLT2-inhibitor as outpatients (68.05%). Data available from 58 patients in this group showed an average eGFR of 61.358 ml/min/1.73m^2.

There were 33.14% (n = 56) patients with DeNovo HF, while 66.86% (n = 113) had a history of HF for 6 months and above. Common HFrEF aetiologies observed were ischemic cardiomyopathy, and non-ischemic dilated cardiomyopathy. More than 80% had co-morbidities, mainly hypertension, diabetes mellitus, coronary artery disease, dyslipidaemia and atrial fibrillation.

Baseline drug utilisation prior to initiation were also analysed. Majority were optimised on three GDMT drugs (85.8%). Overall, 95.27% patients were on RAS inhibitors (75.15% on ACEi, 10.65% on ARB and 8.88% on ARNi). Beta-blockers were prescribed for 97.6%, while 91.7% were prescribed for MRA.

NTproBNP levels were categorised to < 1000 pg/ml, 1000 to 3000 pg/ml and >3000 pg/ml. From 161 available readings, 62.11% had baseline NTproBNP levels >3000 pg/ml. Within 1 year following SGLT2-inhibitor initiation, 45.9% of these patients showed decreased NTproBNP levels, 10.56% had

This article was accepted: 19 February 2024
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Table I: Characteristics of the patients at baseline

Baseline demographics	Total no (%)
Gender	
Male	141(83.43)
Female	28(16.57)
Age (Mean)	53.8(SD 13.02)
Race	
Sabah-native	96(56.8)
Malay	22(13.02)
Chinese	35(20.71)
Others	16(9.47)
NYHA functional class	
I	74(43.79)
II	71(42.01)
III	9(5.33)
IV	15(8.88)
Cause of heart failure	
Ischemic	59(34.9)
Nonischemic	40(23.67)
Valvular heart disease	5(2.96)
Others	18(10.6)
Under investigation	52(30.77)
Co-morbidities	
Hypertension	89(52.5)
Diabetes mellitus	60(35.6)
Coronary artery disease	60(35.6)
Dyslipidemia	44(26.04)
Atrial fibrillation	33(19.53)
Others	18(10.65)
None	31(18.34)
NTproBNP levels (n = 161)	
<1000 pg/ml	14(8.7)
1000 to 3000 pg/ml	47(29.19)
>3000 pg/ml	100(62.1)
Heart failure medication	
RAS inhibitors	16(95.27)
Beta-blocker	165(97.6)
MRA	155(91.7)
Diuretics	104(61.54)

increased levels, while 43.48% lacked a repeat NTproBNP reading. The decrease in NTproBNP seen is consistent with findings from studies showing 5-13% reduction in HFrEF treatment with empagliflozin.[3] [However, a significant number of patients did not have subsequent readings while a minor subset of patients recorded elevated NTproBNP levels following SGLT2-I initiation, but this was not further explored. There were a total 107 patients with 1 year follow-up after SGLT2-inhibitor initiation, and 62 patients who did not attend the 1 year visit. In these 107 patients, 43% reported HFH within a year prior to initiating SGLT2-inhibitors. After SGLT2-inihibitors initiation, HFH within 1 year was reported in 15.9% of these patients. In this group of 107 patients, there were five deaths reported within the year. One was attributed to advanced HF, while the cause of death of the remaining four patients was undocumented.

There were no adverse events reported, suggesting drug safety although this may be under reported in cases where patients sought treatment elsewhere and failed to report the events during their clinic visits.

This communication was intended to describe the implementation strategy of providing empagliflozin to HFrEF patients, through a localised prescribing policy, matching closely to the study population seen in randomised-control trials such as the EMPEROR-REDUCED trial, where participants were above 18 years of age, with NYHA II, III or IV, with LVEF ≤40%, high levels of NTproBNP and receiving all appropriate treatments as available and tolerated.[4] Our findings demonstrate that the use of SGLT2 inhibitors echoes the similar benefits seen in randomised-controlled trials to reduce HF hospitalisation and death within 1 year.

The introduction of new therapies in any healthcare system comes with additional costs for healthcare providers or patients. Affordability, particularly in heavily subsidised public healthcare systems, can pose a barrier to accessing these new therapies, but it can be addressed through further economic evaluations. While treatment guidelines may provide strong evidence for implementing new treatments, barriers continue to exist in real-world practice. Although it may not always be feasible to fully translate new evidence into real-world practice, our findings support the benefits of initiating SGLT2-inhibitors in reducing HF hospitalisations and mortality and highlight the need for careful patient selection through prescribing policies to improve the access to new treatments in real-world practice, eventually benefitting a wider group of patients. Widespread implementation of this prescribing policy can also generate robust real-world,

diverse, Asian data and help inform healthcare policy at the local level.

CONFLICT OF INTEREST

The authors have no financial disclosure or conflicts of interest concerning materials in this article. This study has been approved by the Malaysia's Medical Research and Ethics Committee (NMRR-21-789-59532(IIR)).

SOURCE OF FUNDING

This article is not financially supported by any company or grant.

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Acknowledgement
March Issue 2024

The Editorial Board of The Medical Journal of Malaysia gratefully acknowledge the following individuals for reviewing the papers submitted for publication:

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