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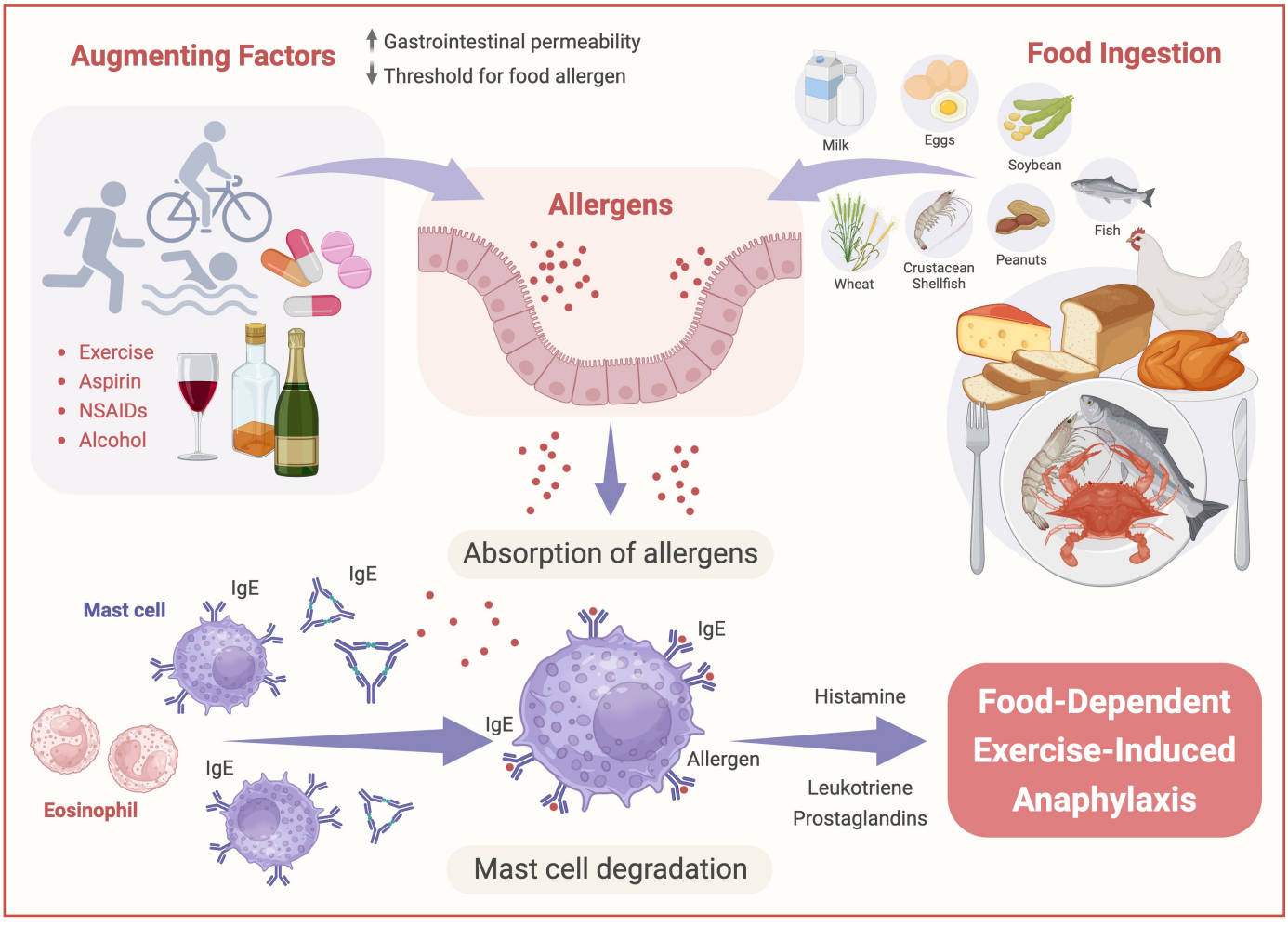

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A Study of Psychometric Properties of Difficulty in Emotion Regulation Scale – Thai Version among Thai Population

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ABSTRACT

Objective: Individuals with psychiatric disorders are found to struggle with emotion regulation, which is considered a transdiagnostic factor. However, due to a limitation in the assessment of emotion regulation in Thailand, this study aimed to translate the Difficulty in Emotion Regulation Scale (DERS) into Thai (DERS-Thai) and evaluate its psychometric properties.

Materials and Methods: The DERS-Thai was initially translated by one of the researchers before being re-reviewed. A pre-testing phase was then conducted to preliminarily evaluate the psychometric properties of the DERS-Thai. Subsequently, the testing phase involved 446 participants who completed an online questionnaire platform containing demographic data, DERS-Thai, the Emotion Regulation Scale (ERQ), and the Depression Anxiety Stress Scale 21 (DASS-21). The factor structure was then evaluated, along with its concurrent and criterion validity, as well as its internal consistency.

Results: DERS-Thai demonstrated acceptable content validity (I-CVI = 0.8 to 1.0, S-CVI/Ave = 0.85). In the testing phase with 446 participants (mean age = 29.19, SD = 8.50), predominantly female (81.8%), and mostly residing in central Thailand (81.31%), the original model did not fit well. After modification, fit indices were improved. DERS-Thai showed a negative correlation with ERQ and a moderate to strong correlation with DASS-21. Known-group analysis revealed significant differences in DERS-Thai scores between DASS-21 groups (p-value < 0.001). The scale exhibited excellent internal consistency ($\alpha = 0.94$, $\omega = 0.96$).

Conclusion: The DERS-Thai has demonstrated appropriate psychometric properties for assessing emotion regulation skills in individuals.

Keywords: Emotion regulations; psychometric; psychological tests; questionnaire (Siriraj Med J 2024; 76: 557-566)

INTRODUCTION

Psychiatric conditions encompass a wide array of challenges that affect an individual's functioning in academic, work, and social settings. In particular, there has been growing concerns about the increasing prevalence of mood (affective) disorders.[1,2] According to the World Health Organization (WHO), the global prevalence estimate for Major Depressive Disorder was approximately 280 million.[3] Psychiatric conditions arise from multifactorial causes, and research indicates that emotion regulation problems are one of the contributing factors.[4]

Emotion regulation refers to an individual's capacity to be aware of, identify the causes, and manage the timing of their emotional experiences, along with responding effectively to those emotions. It is considered a transdiagnostic factor because people facing various psychiatric conditions often struggle to regulate their emotions, leading to

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maladaptive coping strategies such as substance use disorder, social anxiety disorder, and borderline personality disorder. Maladaptive emotion regulation, as highlighted in studies, includes rumination, avoidance, and suppression, contributing to psychopathology.[4-8] Numerous studies have shown that people with psychiatric disorders face challenges in regulating their emotions, whether due to a lack of effective strategies or difficulty in engaging in adaptive behavior.[9-13]

Despite the attention given to emotion regulation in the research field, there remains a limited number of studies in Thailand, particularly in the area of assessment tools to assess emotion regulation. The Emotion Regulation Questionnaire has been used dominantly in Thai research as the gold standard assessment.[14-16] Although there have been studies aiming to develop assessment tools for emotion regulation, these have been limited to undergraduate students in terms of sample and objectives.[17,18] Therefore, the objective of this study was to translate the Difficulty in Emotion Regulation Scale into Thai and examine its psychometric properties in the Thai population.

MATERIALS AND METHODS

This study was carried out after receiving ethical approval from the Siriraj Institutional Review Board (SIRB), Faculty of Medicine Siriraj Hospital (COA no. Si 273/2023). The study design was cross-sectional.

Participants

The population included Thai individuals aged 18 to 60 years who could read Thai in a comprehensive way, who lived in Thailand, and who did not undergo psychological treatment or were diagnosed with any psychological condition. Samples were included through social networks and data was collected using an online platform. Participants who responded to the questionnaire randomly or incompletely (more than 10%), those currently undergoing treatment or diagnosed, or those who did not live in Thailand were excluded from the study. The study was conducted in two separate phases: the pre-testing phase and the testing phase. The pre-testing phase involved 30 samples for the preliminary evaluation of the DERS-Thai scale. The testing phase required a minimum of 403 participants, according to the sample size calculation for the structural equation model by Soper.[19] With a 20% increase in the response rate, the final sample size was 483.

Procedure

The recruitment process involved posting advertisements and invitations to participate in the study on social media platforms for instance Line, Facebook, and Instagram applications. To mitigate selection bias and ensure a more representative sample, efforts were made to reach diverse groups, including different age ranges, genders, educational levels, and regions of Thailand. All participants were informed in writing, covering the details of the study, possible risks, and benefits. Participants had to provide their consent before proceeding to the questionnaire sections. After completing the questionnaires, all participants received information on emotion regulation, mental health support contacts, and questionnaire results. This study was conducted in two phases: the pre-testing phase and the testing phase. The pre-testing phase was conducted for the initial evaluation of the DERS-Thai psychometric properties, while the comprehensive evaluation was held in the testing phase.

Measurement

The online questionnaire was constructed of various sections as follows: the demographic questionnaire, DERS-Thai, ERQ, and DASS-21. Demographic data was collected including the age and sex of the participant, province of living, educational level, marital status, and history of medical conditions both physical and psychological.

The Difficulty in Emotion Regulation Scale (DERS) consists of 36 self-report items assessing the multidimensional aspects of emotion regulation capacities, including Nonacceptance, Goals, Impulse, Awareness, Strategies, and Clarity subscales. DERS was developed by Gratz and Roemer (2004). The scale is rated on a 5-point Likert scale (1 = 'Almost never', 2 = 'Sometimes', 3 = 'Half of the time', 4 = 'Most of the time', 5 = 'Almost always'). The score will be counted in each area, a higher score in a particular aspect indicating greater difficulty in emotion regulation in that area.[20] DERS has been adapted to many cultures, translated into various languages, and has demonstrated good psychometric properties.[21-28] DERS was translated into the Thai version, named Difficulty in Emotion Regulation Scale – Thai version (DERS-Thai), by one of the researchers. Subsequently, DERS-Thai was translated back into English by the Translation and Interpretation Center (TICLA) of the Liberal Arts faculty at Mahidol University. Subsequently, all three versions were sent to five experts for review, comparing the original, Thai, and backtranslated versions using the content validity index (CVI) to evaluate their semantic and content validity. CVI required an expert of at least three to score each item range 1 to 4 (1 = 'not relevant', 2 = 'somewhat relevant', 3 = 'quite relevant', 4 = 'highly relevant'), then, I-CVI (content validity index for item) was

derived. Consequently, S-CVI/Ave (Sum I-CVI / number of items) and S-CVI/UA (I-CVI = 1 / number of items) were calculated. Moreover, in the pre-testing phase, all participants were asked to provide recommendations and rate its comprehensibility, divided into two categories: easy to comprehend and measuring a broad range of emotions.

The Emotion Regulation Scale (ERQ) is an assessment of emotion regulation comprising 10 items, developed by Gross and John (2003). This scale evaluates emotion regulation strategies based on the modal model of emotion regulation, which is categorized into two strategies: antecedent-focused and response-focused strategies. It includes reappraisal (6 items) and suppression strategies (4 items), with each item rated from 1 to 7 (strongly disagree to strongly agree). A higher score on each subscale indicates a higher frequency of using that strategy. The ERQ has been translated into Thai by Kumrod and Sunthornchaiya (2015).[14,16]

The Depression Anxiety Stress Scale – 21 is a self-report mental health questionnaire that assesses the symptoms of depression, anxiety and stress, developed by Lovibond and Lovibond (1995).[29] This scale consists of 21 items, each item scored on a 4-Likert scale (0 to 3) according to the severity of symptoms. Scores are then summed up in each aspect, with a higher score indicating a greater severity in those aspects. The DASS-21 was translated into Thai by Oei et al. (2013) and has demonstrated good to excellent internal consistency.[30]

Statistical analysis

Descriptive statistics were used to represent the demographic data and characteristics of the sample. The construct validity of DERS-Thai was evaluated using confirmatory factor analysis (CFA), correlation analysis with ERQ, average variance extracted (AVE), composite reliability (CR), and the known group technique (comparing mean scores between the normal to mild severity and severe to extremely severe groups). Criterion validity was examined through the correlation between DERS-Thai scores and DASS-21 scores. Reliability was assessed by analyzing Cronbach's alpha and McDonald's omega coefficients.

RESULTS

Semantic equivalence was ensured through a back-translation protocol, resulting in most items capturing the original concept of the scale with slight adjustments. Subsequently, the DERS-Thai was reviewed by five experts using the CVI, and the CVI evaluation was performed twice. After the initial evaluation, the expert panel suggested revisions for some items to be more familiar to the Thai population, specifically items 2, 3, 6, 8, and 31. The final results showed that the Item-CVI (I-CVI) for each item ranged from 0.8 to 1.0, and the Content Validity Index for Scale/Average (S-CVI/Ave), the average of I-CVI for the scale, was 0.85. This indicated that the scale demonstrated an acceptable level of semantic and content validity. It should be noted that the Content Validity Index for Scale/Universal Agreement (S-CVI/UA) requires all experts to agree on an item, and if one expert gives a score of 1 to 2 on that item, it could impact the total S-CVI/UA. As mentioned earlier, the use of three indicators was considered a conservative approach, and thus the S-CVI/Ave and I-CVI were given priority in this study as a liberal approach.[31-33]

Pre-testing phase

In the pre-testing phase, 30 participants were included to preliminarily evaluate the DERS-Thai internal consistency. The sample consisted of 27 females (90.0%) and 3 males (10.0%), with an average age of 29.7 (SD = 7.72). Most of the participants had a bachelor's degree (66.67%), and the majority were from central Thailand (83.34%). Participants reported that the DERS-Thai was easy to understand and measured a broad range of emotions (mean = 3.56 with median = 4 for easy comprehension and mean = 3.47 with median = 4 for measuring a wide range of emotions). The internal consistency was excellent (a = 0.93). However, item 34 was found to have a negative correlation from the corrected item-total correlation (CITC) on its subscale. Subsequently, the research team discussed and revised this item before proceeding to the testing phase.

Testing phase

In the testing phase, 483 participants were initially included, but after applying the exclusion criteria, the final sample size was reduced to 446. Most of the sample consisted of females (81.8%), individuals with a bachelor's degree (55.6%), and those who were single (85.2%). Similarly to the pre-testing phase, most of the participants resided in central Thailand (71.31%). Overall, the DASS-21 scores in the sample indicated a range of distress. Specifically, participants reported depression symptoms slightly higher than the cut-off point. Furthermore, stress symptoms were reported at a mild level and anxiety symptoms were reported at a moderate level (Table 2).

Construct validity

The DERS-Thai measurement model was initially investigated, resulting in an original model (6-correlated

TABLE 1. Demographic characteristics of the Sample in each phase.

Variables	Pre-testing phase (n=30) Number (%)	Testing phase (n=446) Number (%)
Sex		
Male	3 (10.0)	81 (18.2)
Female	27 (90.0)	365 (81.8)
Age	(M=29.70, SD=7.72)	(M=29.19, SD=8.50)
Education		
Primary school	-	1 (0.2)
Secondary school	-	3 (0.7)
High school or Vocational cert.	2 (6.67)	46 (10.3)
High Vocation cert.	1 (3.33)	8 (1.8)
Bachelor's degree	20 (66.67)	248 (55.6)
Master's degree	7 (23.33)	116 (26.0)
Doctor of Philosophy	-	23 (5.2)
Unknown	-	1 (0.2)
Province		
Bangkok	14 (46.67)	210 (47.09)
Central (exclude Bangkok)	11 (36.67)	108 (24.22)
North	3 (10.00)	38 (8.52)
Northeast	2 (6.67)	36 (8.07)
East	-	17 (3.81)
West	-	6 (1.35)
South	-	30 (6.73)
Unknown	-	1 (0.2)
Marital status		
Single	25 (83.33)	380 (85.2)
Married	3 (10.00)	60 (13.4)
Divorced	2 (6.67)	6 (1.3)

factors) that did not establish a good fit. Modification indices suggested some factor modifications. Subsequently, the model was modified (modified model) to improve fit, including allowing the measurement error to correlate, relocating item 30 to another subscale (Nonacceptance), and eliminating item 17 due to low factor loading, as depicted in Fig 1. The results showed that the modified model showed a better fit, as presented in Table 3, compared to the original model. The subsequent analysis was based on the modified model. The factor loading of each item ranged mostly between 0.53 and 0.86, except for the Awareness subscale, which had the lowest factor loading of 0.30 on item 10.

The correlation between subscales, in general, was moderate to strong (r = 0.43 to 0.78). However, the Awareness subscale demonstrated a very weak to weak correlation with other subscales (r = 0.10 to 0.22) except for the Clarity subscale which established a moderate level (r = 0.52)

Additionally, convergent validity was assessed through AVE and CR values. The results indicated that the DERS-Thai subscales have an AVE value range of 0.33 to 0.42 and a CR value range of 0.69 to 0.76. Nevertheless, the DERS-Thai showed a negative correlation with ERQ-reappraisal (r = -0.14 to -0.43) and a positive correlation with ERQ-suppression (r = 0.10 to 0.21). Additionally, the

TABLE 2. Descriptive data of psychological assessment of the sample in testing phase.

	Mean (standard deviation)	N (%)
DERS total score	88.53 (22.63)	
Nonacceptance	17.01 (6.32)	
Goals	14.52 (4.73)	
Impulse	13.93 (5.18)	
Awareness	13.22 (3.59)	
Strategies	18.82 (6.79)	
Clarity	11.03 (4.26)	
ERQ – Reappraisal	33.06 (6.11)	
ERQ – Suppression	17.09 (4.61)	
DASS-21 total score	42.30 (28.33)	
DASS-21 Depression	13.05 (10.93)	
Normal		**205 (45.96)**
Mild severity		**55 (12.33)**
Moderate severity		**84 (18.83)**
Severe severity		**35 (7.84)**
Extremely severe severity		**67 (15.02)**
DASS-21 Anxiety	12.55 (9.36)	
Normal		**150 (33.63)**
Mild severity		**40 (8.96)**
Moderate severity		**109 (24.43)**
Severe severity		**47 (10.53)**
Extremely severe severity		**100 (22.42)**
DASS-21 Stress	16.70 (10.67)	
Normal		**224 (50.22)**
Mild severity		**50 (11.21)**
Moderate severity		**69 (15.47)**
Severe severity		**61 (13.67)**
Extremely severe severity		**42 (9.41)**

known-group technique was performed by comparing DERS-Thai scores between two groups: the normal to mild severity group and the severe to extremely severe group. The outcome indicated that the DERS-Thai score in the severe to extremely severe group was significantly higher than in the other group ($p < 0.001$). These results suggest that DERS-Thai has established an appropriate level of convergent validity (Table 4).

Criterion validity

Criterion validity of DERS-Thai was examined. The correlation between the DERS-Thai score and the DASS-21 score and its subscale indicated a moderate to strong correlation ($r = 0.57$ to 0.70). On the contrary, the Awareness subscale established the lowest level of correlation ($r = 0.27$ to 0.35) (Table 4).

Internal consistency

The DERS-Thai established excellent internal consistency in the overall scale ($\alpha = 0.94$, $\omega = 0.96$). Furthermore, the subscales demonstrated acceptable to excellent levels of internal consistency considering both Cronbach's alpha and McDonald's omega values (Table 5).

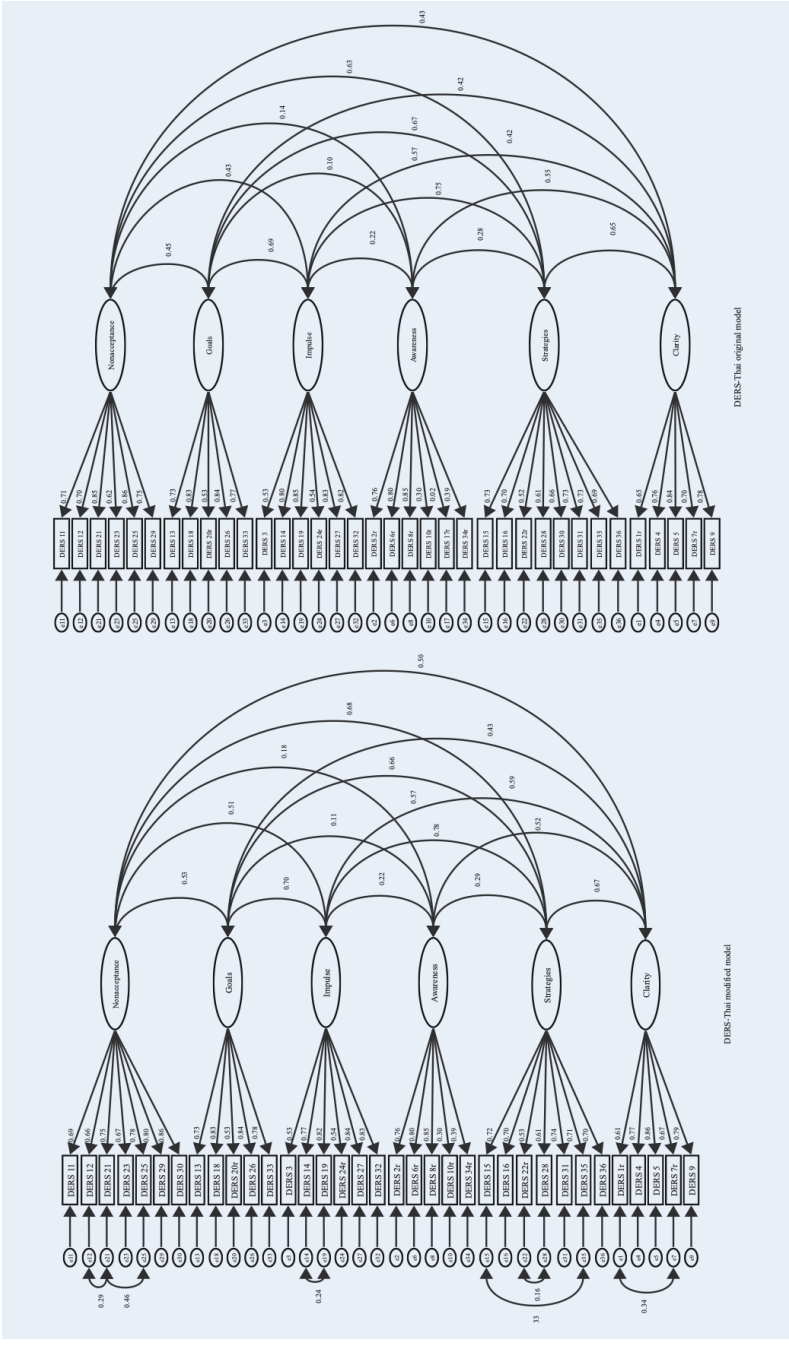

Fig 1. Factor structure of DERS-Thai between the original model and modified model

TABLE 3. Fit indices of the DERS-Thai both the original model and the modified model.

Fit indices	Acceptable fit criteria	Original model	Modified model
χ^2	-	2015.161	1469.260
df	-	579	539
χ^2/df	< 2.0	3.48	2.73
RMSEA (90% CI)	< 0.08	0.075 (0.071-0.078)	0.062 (0.058-0.066)
SRMR	< 0.08	0.080	0.064
CFI	≥ 0.90	0.84	0.90
TLI	≥ 0.90	0.83	0.88

TABLE 4. The correlation analysis between DERS-Thai, ERQ, and DASS-21.

	ERQ reappraisal	ERQ suppression	DASS-21 Total score	DASS-21 Depression	DASS-21 Anxiety	DASS-21 Stress
DERS-Thai	-0.43***	0.13**	0.70***	0.68***	0.57***	0.68***
Nonacceptance subscale	-0.14***	0.21***	0.51***	0.49***	0.42***	0.49***
Goals subscale	-0.27***	0.08	0.41***	0.41***	0.32***	0.39***
Impulse subscale	-0.38***	-0.07	0.55***	0.49***	0.43***	0.57***
Awareness subscale	-0.31***	0.03	0.33***	0.35***	0.28***	0.27***
Strategies subscale	-0.43***	0.16***	0.67***	0.63***	0.54***	0.66***
Clarity subscale	-0.34***	0.10*	0.57***	0.59***	0.48***	0.50***

*p-value < 0.05, ** p-value < 0.01, *** p-value < 0.001

TABLE 5. The internal consistency of DERS-Thai and its subscale.

Scale	Cronbach's alpha	McDonald's omega
DERS-Thai total	0.94	0.96
Nonacceptance	0.90	0.91
Goals	0.86	0.86
Impulse	0.87	0.87
Awareness	0.74	0.77
Strategies	0.86	0.86
Clarity	0.86	0.86

DISCUSSION

This study aimed to evaluate the psychometric properties of DERS-Thai in the Thai population, including from a cultural perspective. As a result, DERS-Thai demonstrated an acceptable level of semantics and content equivalent to the original version. However, there were some cultural difficulties, especially with the term 'upset' due to the fact that in Thai there was no direct meaning word that represents broad negative emotions. Subsequently, from the suggestion of the expert panel, the term upset was described in an instruction section to clarify this meaning to examinees. Moreover, after the pre-testing, the result indicated that item 34 had a negative correlation with other items in its subscale. Consequently, item 34 was revised to put more emphasis on the positive meaning of the term 'take time'. Statistical analysis in the pre-testing phase preliminarily indicated excellent internal consistency for the DERS-Thai.

The characteristics of the sample in this study consisted predominantly of women between 20 to 30 years old, with a significant living in central Thailand. This distribution might be attributed to the advertising strategy used on

social media platforms, this method was chosen for its convenient distribution across country, as the majority of users fall within the 18 to 45 age range. This skewness might be attributed to higher social media engagement among these demographics.[34,35] Data collection revealed that participants experienced various degrees of distress; however, it should be noted that DASS-21 is designed as a screening tool to aid in clinical practice.[29] On detailed examination, the cumulative percentage in the normal to mild severity group was higher than in the severe to extremely severe group. Moreover, considering the questionnaire's inquiries about participants' physical and mental conditions, in line with the exclusion criteria, it can be presumed that the sample in this study represented the characteristics of a normal population.

The factor structure of DERS-Thai was evaluated through CFA, indicating that the original model did not provide a good fit.[21,22,36-40] Subsequent modifications were made, including the reallocation of item 30 into the Nonacceptance subscale (originally under the Strategies subscale) and allowing measurement errors in the same subscale to correlate. Additionally, item 17 was excluded from DERS-Thai due to cultural considerations. In the Thai context, emotions are often not considered valid but rather irrational and undesirable, in accordance with the findings of previous studies.[21,22,41-43] After modification, overall, the DERS-Thai modified model demonstrated a better fit, even though the TLI was slightly below an acceptable level but still close to 0.90.[21,36,42]

The convergent validity of DERS-Thai was evaluated using AVE and CR values, along with correlations with ERQ and mean comparisons between the groups. In the modified model, the AVE values were mostly above the minimum requirement of 0.5, except for the Awareness and Strategies subscales. However, the CR values for all subscales were above 0.6, indicating maintained convergent validity.[44,45] Similar to the correlation between DERS-Thai and ERQ, the correlation between DERS-Thai exhibited a small to moderate correlation; however, the Awareness subscale showed a correlation with ERQ of small magnitude.[23,24,36,46] The mean comparison of DERS-Thai scores in two severity groups of DASS-21 revealed significantly lower scores in the normal to mild severity group in the three domains (p-value < 0.001). Furthermore, the criterion validity of DERS-Thai was assessed through its correlation with DASS-21, revealing a significantly positive correlation, even with the Awareness subscale, which exhibited the lowest correlation.

In conclusion, DERS-Thai has demonstrated an acceptable level of criterion validity.

In summary, DERS-Thai established an appropriate level of validity which can be utilized to predict psychopathology influenced by dysfunction of emotion regulation.[20,24,37,47-51]

The internal consistency of DERS-Thai was examined using both Cronbach's alpha and McDonald's omega. This study used two methods to assess internal consistency due to the nature of Cronbach's alpha, which requires certain assumptions to be met, including tau equivalence, unidimensionality, and uncorrelated error variance. As a result, McDonald's omega was considered a better method overall.[52-56] The findings indicate that the internal consistency of DERS-Thai was excellent, as observed by both methods.

This study has some notable limitations. First, the sample was predominantly female, with a limited age range, mainly located in central Thailand. This may restrict the generalizability of the findings to other populations. Additionally, the sample's educational level, predominantly consisting of bachelor's degree holders, might influence the findings and limit their applicability to populations with different educational backgrounds. Other potential confounding factors, such as socioeconomic status and regional differences, were not controlled for. To address these potential biases, future studies should consider additional recruitment strategies, such as offline methods and targeted outreach to underrepresented groups, including the male population, elderly and adolescent age groups, and individuals with lower educational levels. Second, the stability of the scale, particularly in terms of test-retest reliability, was not assessed.[24,36,38,40,41,57] Additionally, an alternative factor structure was not identified in this study. Therefore, future research with a more diverse population and an examination of the factor structure will enhance our understanding of emotion regulation. Although not conducted in this study, test-retest analysis can be carried out to establish the stability of the scale. However, the DERS-Thai shows promise as a valuable tool for clinicians in assessing emotion regulation difficulties within the Thai population. Clinicians can use the DERS-Thai to identify individuals at risk for various psychiatric conditions linked to poor emotion regulation, allowing for targeted interventions and support.

CONCLUSION

The DERS-Thai demonstrates good psychometric properties, making it a useful instrument for clinical practice and research on emotion regulation in the Thai context. Further studies with diverse populations and comprehensive analysis will strengthen its utility and reliability, ultimately contributing to better mental health outcomes in Thailand.

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Conflicts of interest

The author have no conflict of interest to declare.

Author Contributions

The authors confirm their contributions to the paper as follows: T.S. ; Initiated and designed the research, planned the study, collected data, performed statistical analysis, and was responsible for writing the manuscript. J.N. ; Contributed to co-conducting the research from its planning stages through data collection and statistical analysis, co-writing the manuscript, and served as the corresponding author. K.P. ; Provided essential intellectual contributions, including valuable content suggestions and guidance throughout the research process. All authors reviewed the results and approved the final version of the manuscript.

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Dexamethasone and Lidocaine Effects in 24 hours Post Cesarean Pain Reduction under Spinal Anesthesia: A Randomized Controlled Trial

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ABSTRACT

Objective: This study aimed to compare the efficacy of additional local infiltration of dexamethasone and lidocaine among post-cesarean parturient underwent spinal anesthesia compared to the control group.

Materials and Methods: This randomized controlled trial was conducted at Thammasat University Hospital, Thailand, between June and November 2022. Singleton pregnant women who underwent cesarean delivery were randomized into 3 groups: dexamethasone (D), lidocaine (L), and control groups (C). Before skin closure, D, L and C group received infiltration of 16 mg of dexamethasone, 2% lidocaine with adrenaline and none, respectively. A visual analog scale (VAS, 0-10) was used for the evaluation of post-cesarean pain at two, four, six, eight, twelve, and twenty-four hours. VAS, demographic, and obstetric data were collected for analysis. Additional opioid was recorded for secondary outcome.

Results: A total of 279 participants were recruited and divided into 3 groups. Half of the participants (151/279) were nulliparity. Other demographics were similar. Subjects in the D group had lower moderate to severe pain after 6 hours onwards and less additional opioid requirement compared to the C and L groups significantly. Subjects in the L group had lower moderate to severe pain than the C group at 4 hours after surgery. Postoperative complications were comparable among the groups.

Conclusion: Local dexamethasone infiltration could reduce and prolong post-cesarean pain relief within 24 hours after cesarean delivery.

Keywords: Cesarean delivery; pain; dexamethasone; lidocaine (Siriraj Med J 2024; 76: 567-572)

INTRODUCTION

The incidence of cesarean delivery is increasing widely, reaching 32 percent of births in 2021.[1] In Thailand, the rate increased from 25 percent over the past 15 years, with a further increase to 50 percent by 2023.[2-4]

According to a Cochrane review in 2020, half to three-quarters of cases who underwent cesarean delivery experienced moderate to intense pain after surgery.[5] Spinal nerve blocks with hyperbaric bupivacaine and opioids are routinely utilized during cesarean delivery.[6,7] However, postoperative pain is often reduced by various drugs, including opioids, lidocaine, and steroid derivatives.

Among postoperative pain reducers, opioids are often administered and cause many adverse reactions, such as

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nausea, vomiting, and sedation.[8] To minimize these side effects, multimodal analgesia is recommended. Additive and synergistic medications such as dexamethasone and lidocaine can reduce the required additional opioid doses. Even a minimal dosage of local dexamethasone infiltration could prolong the anesthetic effect of the local anesthetic infiltration at the surgical wound.[9,10] Dexamethasone has a 5-hour elimination half-life and acts to reduce tissue edema and inflammatory mediators.[11] Despite some studies reporting adverse effects of dexamethasone, such as an increased risk of infection in certain participant groups, a systematic review conducted by Maged revealed that the majority of studies supported its safety.[11]

Meanwhile, lidocaine, an amide-type local anesthetic used in wound infiltration, acts by blocking nerve-ending voltage-gated sodium channels with 2 hours of half-life.[12] This half-life extends to 5 hours with the addition of adrenaline.[13] Even though adding adrenaline affected tissue perfusion, there was no evidence of adverse effects on abdominal skin.[13]

Therefore, this study aimed to investigate the additional benefits of local infiltration of dexamethasone or lidocaine compared to the control group for pain reduction, additional meperidine requirement, and opioid side effects compared to the control group in parturients undergoing cesarean delivery via spinal anesthesia.

MATERIALS AND METHODS

This double-blind, randomized control trial was conducted at Thammasat University Hospital, Thailand, between June and November 2022. The study was approved by the Human Ethics Committee of Thammasat University (MTU-EC-OB-2-015/64) and the Thai Clinical Trial Registry (TCTR20220524002). We enrolled term singleton gravidas aged at least 20 years old. Participants who had indication for cesarean delivery during the study period were recruited. Exclusion criteria were allergy to lidocaine or bupivacaine, insulin-dependent diabetes mellitus, pre-existing chronic illnesses, and refusal to participate.

The sample size was calculated using 1.4 as the mean difference between the two groups as placebo versus dexamethasone[14] and 1.2 as the standard deviation from the previous studies.[15] With a 1% alpha-type error rate and a statistical power of 80%, the formula of $n_2 = \{(Z_{1-\alpha} + Z_{1-\beta/2})^2 \delta^2 (1+1/k)\} / (\delta - |\varepsilon|)^2$ was used with $\varepsilon = \mu_2 - \mu_1$, $k = n_1/n_2$ and $n_1 = kn_2$. The final sample size was at least 87 cases per group with ten percent was added to account for data loss, the total sample size was 300 cases. A total of 300 cases were recruited for this study and 18 cases declined attendance due to concerns about drug side effects, worries regarding post-operative pain control, and insufficient time to complete the survey.

After thoroughly explaining the protocol to the participants, either at the antenatal care clinic or in the labor room, they were then asked to sign the written consent form. Participants were randomized into three groups equally using a computer number generator after signing the consent form. Subjects received either 16 mg of dexamethasone (D; dexamethasone group), or 20 ml of 1:200,000 2% lidocaine with adrenaline (L; lidocaine with adrenaline group), or neither (C; control group) locally in addition to routine spinal nerve block.

Spinal anesthesia was administered using a combination of 2 ml of 0.5% hyperbaric bupivacaine with 0.2 mg morphine, delivered via the intraspinal route. Participants received general anesthesia if they were unable to undergo spinal anesthesia, then dropped out from this research. Before the closure of the subcutaneous fat, operating surgeons would locally infiltrate the medication, either dexamethasone, lidocaine with adrenaline, or none, according to the assigned group of D, L, or C group, respectively. The scrub nurse would allocate the participants in a queue and note the prescribed medication inside a sealed envelope, which would match the patient's identification and later be given to the researcher along with the result.

In the first 24 hours after surgery, participants were interviewed by registered nurses about their pain scores using the visual analog scale (VAS) ranging from 0 to 10 (0 = no pain, 10 = worst imaginable pain), at 2, 4, 6, 12, 18, and 24-hour post-operation. Pain scores were categorized into no pain (VAS 0), mild pain (VAS 1-3), moderate pain (VAS 4-6), and severe pain (VAS 7-10).[16] Participants with moderate-to-severe pain scores will be offered meperidine for pain control. After 24 hours, participants with persistent post-cesarean delivery pain and desiring adjunctive anesthesia, regardless of pain score, will be offered non-steroidal anti-inflammatory drugs. Thus, both the patient and the investigator who recorded the VAS were blinded.

The primary outcome of this study was the pain score within the first 24 hours. The secondary outcomes included meperidine requirement and prevalence of nausea, itching, abdominal distension, and demand for alternative medication after 24 hours post-surgery. After gathering the required information, data analysis was performed using the Statistical Package for the Social Sciences version 23 (SPSS Inc., Chicago, IL, USA). Continuous data were analyzed using one-way ANOVA, while categorized data were evaluated with the chi-square test.

RESULTS

Three hundred participants were enrolled. After consideration of the inclusion and exclusion criteria, 279 gravidas were randomized into three groups. Two cases in the dexamethasone group and one case in the lidocaine group dropped out during the time of operation because the patients were undergoing general anesthesia. None dropped out from the control group (Fig 1).

Most pregnant women were in their thirties. Half of the parturient (151/279) were nulliparous. One-third (103/279) of participants have a history of cesarean delivery. All groups show no significant differences in characteristics, as shown in Table 1.

Most cases underwent cesarean delivery with an operative time of less than one hour. There were two and four postpartum hemorrhage cases in D and C groups, respectively. One-quarter (72/279) of subjects underwent tubal resection procedures without differences among the three groups.

At 2 and 4 hours after surgery, all three groups had comparable pain scores. Postoperative after 6 hours onwards, the D group had a lower pain score than the C group with statistical significance. There was no difference in pain scores between the L and the C group. The number of cases with moderate to severe pain in the D group was lower than the C group significantly from 4 hours onwards after the operation. In contrast, the L group had fewer cases of moderate to severe pain at only 4 hours post-operation compared to the C group (Table 2).

Within 24 hours after cesarean delivery, meperidine required for pain control was used in only 38.5 percent (35/91) of participants in the D group. Meperidine requirements among L and C group were comparable at nearly 60 percent (54/92 and 53/93, respectively). There were no complications associated with the local infiltration of dexamethasone nor lidocaine. Moreover, there were also no differences in postoperative complications, and participants who required additional oral pain relievers were no different between groups after 24 hours post-operation (Table 2).

DISCUSSION

According to the pain scores in this study, the average pain score following postoperative cesarean delivery was 3.5 at 6 hours and 3.6 at 24 hours, respectively, which aligns with the results of the previous study.[17] Roughly half of the participants experienced moderate to severe pain in the initial 24 hours, which has the same result as Cochrane review.[5]

In the first 2 hours of the current study, the pain scores and the number of participants experiencing moderate to severe pain showed no difference among all participants. This result can be explained by the spinal nerve blocks with hyperbaric bupivacaine and opioids, which provide excellent pain control lasting up to 142 minutes, depending on the dose administration.[6,7] At 4 hours post-operation, although the pain scores show similar results among the three groups, the number of participants experiencing moderate to severe pain in both intervention groups was significantly less than in the control group. After 4 hours, there was no difference observed in any outcome between the L group and the C group, including pain score, number of moderate to severe pain incidence, meperidine usage, or additional pain relief. This can be explained by the duration of lidocaine with adrenaline, which lasts approximately 5 hours.[13]

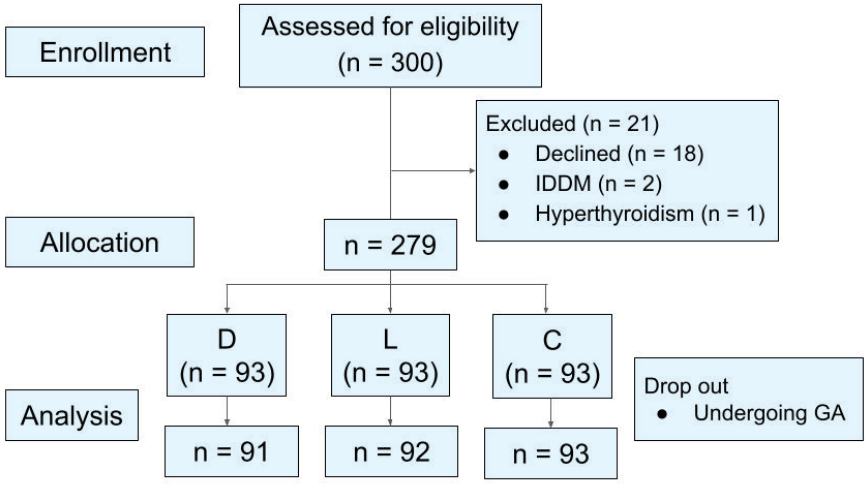

Fig 1. CONSORT flow diagram

Abbreviations: IDDM: Diabetes controlled with insulin, D: Dexamethasone group, L: Lidocaine with adrenaline group, C: Control group, GA: general anesthesia

TABLE 1. Baseline characteristics and operative data (93 cases per group for baseline data and 91,92, and 93 for D, L, and C group, respectively for operative data)

	D	L	C	*p*-value
Age (years) *	32.0 ± 4.8	31.7 ± 5.3	32.4 ± 4.8	0.634
GA (weeks) *	38.2 ± 0.8	38.1 ± 0.8	38.2 ± 0.7	0.557
Nulliparity **	46 (49.5)	47 (50.5)	58 (62.4)	0.147
BMI (kg/m^2) *	22.8 ± 3.8	23.9 ± 4.6	23.6 ± 4.1	0.211
Obesity (BMI kg/m^2) **				0.688
Underweight (<18.5)	9 (9.7)	8 (8.6)	8 (8.6)	
Normal (18.5-22.9)	44 (47.3)	42 (45.2)	40 (43.0)	
Overweight (23-24.9)	19 (20.4)	12 (12.9)	16 (17.2)	
Obese (≥25)	21 (22.6)	31 (33.3)	29 (31.2)	
Weight gain (kg) *	14.0 ± 5.2	14.2 ± 5.3	13.2 ± 4.8	0.337
AMA **	31 (33.3)	33 (35.5)	30 (32.3)	0.894
History of cesarean delivery **	38 (40.9)	36 (31.8.7)	29 (31.2)	0.357
Occupation **				0.101
Government	25 (26.9)	15 (16.1)	14 (15.1)	
Employee	30 (32.3)	30 (32.3)	36 (38.7)	
Self-employed	23 (24.7)	30 (32.3)	36 (38.7)	
Housewife	15 (16.2)	18 (19.4)	7 (7.6)	
Income (USD/month) **				0.089
<800	8 (8.6)	5 (5.4)	8 (8.6)	
800-1,400	64 (68.8)	80 (86.0)	73 (78.5)	
>1,400	21 (22.6)	8 (8.6)	12 (12.9)	
Operative data				
Time within 1 hour **	79 (86.8)	86 (93.5)	88 (94.6)	0.118
Board-certified **	71 (78.0)	80 (87.0)	75 (80.6)	0.272
EBL (ml) *	381.9 ± 173.4	381.5 ± 139.4	400 ± 230.0	0.363
PPH **	2 (2.2)	0 (0)	4 (4.3)	0.134
Tubal resection **	27 (29.7)	25 (27.2)	20 (21.5)	0.433

*: mean ± standard deviation, **: n (%)

Abbreviations: D: dexamethasone group, L: lidocaine with adrenaline group, C: control group, GA: gestational age, BMI: body mass index, AMA: advanced maternal age, USD: United States Dollar, Board-certified: board-certified obstetrician and gynecologist as the operator, EBL: Estimated blood loss, PPH: Postpartum hemorrhage

Despite its 5-hour elimination half-life, the effect of decreasing tissue edema and inflammatory mediators could explain how dexamethasone lowers the pain score.[18-21] While the VAS indicated a decrease in pain for the D group compared to the control group from 6 hours onwards, this reduction was not clinically significant. However, in D group, the number of participants experiencing moderate to severe pain was significantly lower than in the C group, ranging from 4 to 24 hours, consistent with previous research.[11] Furthermore, the use of opioids also showed a decrease compared to the C group, which correlates with previous studies.[22] This can be explained by the results of all groups experienced similarly low percentages of side effects which resulting in no difference in opioid use. Additionally, the incidence of post-operative complications was similarly low across both groups, indicating no significant difference.

A randomized controlled trial was chosen to select the sample group, along with double-blinded controls, which can be used to minimize bias in the outcomes.

TABLE 2. Outcome and complications.

	D (n= 91)	L (n=92)	C (n=93)	*p*-value		
				All	*D&C*	*L&C*
Pain score (hour)*						
2	3.1 ± 1.2	3.4 ± 1.4	3.1 ± 0.9	0.111	0.787	0.074
4	3.2 ± 1.0	3.2 ± 0.9	3.4 ± 1.1	0.261	0.278	0.121
6	3.0 ± 0.8	3.3 ± 1.0	3.5 ± 1.2	0.019	0.002	0.126
12	3.4 ± 1.3	3.8 ± 1.5	3.9 ± 1.2	0.003	0.006	0.778
18	3.5 ± 1.3	3.7 ± 1.1	3.9 ± 1.2	0.021	0.015	0.548
24	3.1 ± 1.0	3.7 ± 1.3	3.6 ± 1.1	<0.001	0.004	0.454
Moderate-to-severe pain (hour) **						
2	13 (14.3)	19 (20.7)	17 (18.3)	0.523	0.463	0.684
4	15 (16.5)	14 (15.2)	27 (29.0)	0.036	0.043	0.024
6	11 (12.1)	15 (16.3)	22 (23.7)	0.111	0.041	0.211
12	20 (22.0)	34 (37.0)	45 (48.4)	0.001	<0.001	0.116
18	29 (31.9)	34 (37.0)	45 (48.4)	0.020	0.010	0.116
24	16 (17.6)	35 (38.0)	30 (32.3)	0.007	0.022	0.410
Secondary outcome						
Mep use **	35 (38.5)	54 (58.7)	53 (57.0)	0.010	0.012	0.814
Add **	41 (45.1)	49 (53.3)	46 (49.5)	0.539	0.549	0.605
Post-op complication **						
N/V	7 (7.7)	10 (10.9)	15 (16.1)	0.195	0.078	0.295
Distension	25 (27.5)	24 (26.1)	22 (23.7)	0.835	0.533	0.702
Itching	10 (11.0)	3 (3.3)	7 (7.5)	0.130	0.417	0.199

*: mean ± standard deviation, **: n (%)

Abbreviations: D: dexamethasone group, L: lidocaine with adrenaline group, C: control group, Mep use: number of cases of meperidine use within 24 hours, Add: additional pain relieve after 24 hours post operation, N/V: nausea and vomiting

Furthermore, the frequency of measuring pain scores, pain level categorization, and meperidine use among the three groups was observed in our study, potentially enhancing the effectiveness of the results.

There was a limitation in our research due to the inability to blind the surgeon in the process, as the medication dosages are not equal. Furthermore, comparing dexamethasone to lidocaine was not feasible since the dosage of lidocaine is higher than that of dexamethasone, potentially leading to increased edema and pain. Additionally, the meperidine dose was fixed, making it challenging to assess whether patients use less of the opioid. Reevaluating the study design of patient-controlled anesthesia is necessary to evaluate the dosage of meperidine used accurately.

In conclusion, the local infiltration of dexamethasone among postoperative cesarean delivery showed to be effective in prolonging pain relief and reducing the moderate to severe pain and minimizing opioid use within 24 hours after cesarean delivery due to the reduction of inflammatory process. The findings of this study highlight the clinical benefits of implementing this approach.

What is already known on this topic

The incidence of cesarean delivery has been steadily rising globally and reaching nearly half of the parturients in 2023. Spinal anesthesia with hyperbaric bupivacaine and opioids is common practice in modern aesthetic. Adverse side effect of the opioid that commonly cause discomfort problems, include nausea, vomiting, and sedation. Various of medications namely, lidocaine, and dexamethasone are used to alleviate postoperative pain and minimize opioid-related adverse effects.

What does this study add

Local dexamethasone infiltration in post-cesarean delivery effectively prolonged pain relief, reduced moderate to severe pain, and minimized opioid use.

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Author Contributions

Conceived and designed the analysis, A.C., R.S.; Collected the data, R.S., Y.C.; Contributed data or analysis tools, D.P., K.S.; Performed the analysis, D.P., K.S.; Wrote the paper, R.S., Y.C., S.B., A.C. All authors have read and agreed to the final version of the manuscript.

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Comparative Evaluation of Imaging Modalities for Eligibility in Endovascular Treatment of Delayed Onset Acute Anterior Circulation Ischemic Stroke in Siriraj Hospital: A Retrospective Analysis

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ABSTRACT

Objective: The goal of this study is to evaluate the consistency between computed tomographic perfusion (CTP) according to the endovascular therapy following imaging evaluation for ischemic stroke (DEFUSE-3) criteria and other standard computed tomography (CT) imaging modalities, such as multi-phase CT angiography (MCTA) and unenhanced computed tomography (UECT), in assessing patient eligibility for EVT as determined by neurointerventionists evaluations.

Materials and Methods: This retrospective analysis included 64 patients with anterior circulation stroke and onset between 6 to 12 hours or unknown onset. Two neuro-interventionalists independently reviewed images and assessed eligibility for EVT based on the Alberta stroke program early CT score (ASPECTS) derived from UECT and collateral score obtained from MCTA. The results were then compared to CTP, utilizing the DEFUSE-3 criteria.

Results: Out of the 64 cases analyzed (mean age: 69 years ± 13.9 [SD]), 61 met DEFUSE-3 criteria for EVT by CTP, while 54 were deemed eligible based on an ASPECTS ≥ 6 and collateral score ≥ 3. Agreement between the modalities was moderate (Kappa coefficient score 0.4). When patients with ASPECTS score < 6 were excluded, concordance improved to perfect (Kappa coefficient score 1.0). Hence, concordance was significantly associated with ASPECTS scores ≥ 6 ($P < 0.001$).

Conclusion: In patients experiencing anterior circulation stroke with onset between 6 to 12 hours or unknown onset, excluding an ASPECTS score of 6 or higher, MCTA and UECT proved to be reliable for assessing endovascular treatment eligibility. These modalities may serve as substitutes for CTP and offer support in the clinical decision-making process.

Keywords: Endovascular thrombectomy; acute ischemic stroke; computed tomography; computed tomographic perfusion (Siriraj Med J 2024; 76: 573-580)

INTRODUCTION

Ischemic stroke is currently one of the leading causes of permanent disability in Thailand, especially when attributed to large vessel occlusion. Consequently, timely initiation of treatment during the acute phase is imperative to optimize the likelihood of complete or near-complete recovery.[1-3] Various therapeutic approaches are currently used to manage acute ischemic stroke, including intravenous thrombolysis, intra-arterial or combined thrombolysis, and mechanical recanalization techniques

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which involve various devices for thrombectomy and/or stent placement. Choosing the most suitable treatment approach often requires a customized combination of interventions based on each patient's individual factors.[4,5]

In recent years, notable strides in both technical and procedural aspects of endovascular therapy (EVT) for stroke have established it as an effective treatment modality.[5-7] Numerous studies have highlighted EVT's benefits which extend to patients treated in delayed time windows helping to amplify its therapeutic impact.[8] The development of imaging techniques has played a pivotal role in improving the selection process for EVT candidates, incorporating tools such as unenhanced computed tomography (UECT), single-phase CT angiography, multiple-phase CT angiography (MCTA), and magnetic resonance imaging (MRI).[9,10] These advancements have collectively contributed to enhancing the precision and efficacy of endovascular interventions in stroke management.

The standard protocol for assessing patients diagnosed with acute onset ischemic stroke due to large vessel occlusion within a timeframe of less than six hours involves using MCTA and UECT. This evaluation is conducted using the Alberta Stroke Program Early CT Score (ASPECTS) and collateral scoring.[9,11-13] However, for patients with unknown onset times or onset ≥ 6 hours, the ASPECTS and collateral scores are considered unreliable for evaluation. Numerous studies show that perfusion imaging outperforms conventional imaging in predicting excellent recanalization outcomes and favorable functional recovery.[14-20] Therefore, the incorporation of perfusion imaging into the diagnostic process is pivotal for enhancing the accuracy and reliability of assessments, particularly in scenarios involving uncertain onset times or delayed presentations.

The endovascular therapy following imaging evaluation for ischemic stroke (DEFUSE-3) clinical trials conducted by *G.W. Albers et al* in 2018 evaluated patients with occlusions in the proximal middle cerebral artery and internal carotid artery whose onset of symptoms occurred between 6 and 24 hours prior. In this study, computed tomographic perfusion (CTP) using RapidAI (iSchema View, Menlo Park, CA) software was utilized to determine the areas of penumbra and core infarction. Patients identified as suitable candidates proceeded with endovascular surgery, and clinical outcomes of this group showed a greater degree of favorability compared to cases treated solely with medical intervention.[14] This underscores the pivotal role of advanced imaging techniques, such as CTP, in extending the treatment window for endovascular interventions and improving clinical outcomes in specific patient populations.

At Siriraj Hospital, Mahidol University, Bangkok, Thailand, recent updates to stroke management guidelines include the use of UECT, MCTA and CTP with RapidAI software. These updates are in line with the guidelines from the DEFUSE-3 trials for making decisions about EVT, but with some minor modifications. The determination of EVT for delayed-onset strokes in the anterior circulation at Siriraj Hospital is based on the interventionist's assessment using CTP alongside other CT imaging modalities. While the American Heart Association's 2018 guidelines for acute ischemic stroke management recommend CTP criteria from the DEFUSE-3 trial for selecting delayed-onset patients for thrombectomy, certain patients who meet favorable CTP criteria may not undergo the procedure due to other factors, such as a low ASPECT score observed on UECT.[2] However, the widespread availability of advanced CTP with artificial intelligence (AI) remains limited across many primary, secondary, and tertiary hospitals. Consequently, this study seeks to evaluate the consistency between CTP and other conventional CT imaging modalities, namely MCTA and UECT, in assessing patient eligibility for EVT. The evaluation criteria adhere to the CTP criteria based on DEFUSE-3 and the clinical judgment of neuro-interventionists. The primary objective is to investigate whether the necessity for CTP in routine clinical practice can be minimized by comparing its results with those from more readily available imaging modalities. This comparative analysis seeks to enhance and streamline the decision-making process for EVT eligibility, particularly in environments where advanced CTP with AI technology is less accessible.

MATERIALS AND METHODS

This study aims to assess the agreement between CTP (DEFUSE-3 criteria) and other conventional CT imaging modalities (MCTA and UECT) in determining patients' eligibility for EVT based on the clinical judgement of neurointerventionists.

This study is designed as a single-center retrospective cohort study, involving a review of electronic medical records of patients with anterior circulation acute ischemic stroke with large vessel occlusion, including the M1 segment of middle cerebral artery (MCA), internal carotid artery (ICA) and common carotid artery (CCA), with symptom onset between 6-12 hours or of unknown onset. The review period spans from January 2018 to September 2022 at the Department of Interventional Neuroradiology, Siriraj Hospital.

Inclusion criteria

1) Patients diagnosed with anterior circulation

acute ischemic stroke with large vessel occlusion (CCA, ICA, M1 segment of MCA)
2) Age ≥ 18 years old
3) Onset between 6-12 hours or unknown onset[21]
4) Received evaluation with UECT, MCTA and CTP in same event.

Exclusion criteria

1) Poor image quality
2) mRS (modified Rankin Scale) ≥ 3
3) Inadequate clinical information or incomplete image study
4) Patient's National Institutes of Health Stroke Scale (NIHSS) score < 6
5) M2 segment of MCA occlusion

MCTA and UECT images for each patient were systematically collected and organized for review. Two neuro-interventionists, each certified by the Thai board of interventional neuroradiology for more than 10 years and with over a decade of experience in diagnostic imaging and neuro-interventional procedures, were recruited to independently assess the cases. Their task was to determine the eligibility of each case for endovascular treatment, guided by specific criteria — such as an ASPECTS score ≥6 and collateral score of ≥3.[9] To maintain objectivity, demographic details, and clinical history were concealed, with the evaluators having access only to information about the occlusion's location. Case reviews were conducted separately to avoid potential bias. The outcomes of these evaluations were subsequently compared to findings from CTP, where the ischemic core and penumbral regions were measured using the RapidAI software, which is an automated image postprocessing system. Eligibility for endovascular treatment was determined according to the DEFUSE-3 criteria. The goal of this comparative analysis was to measure the agreement between the neuro-interventionalists' clinical judgments based on conventional imaging and the results derived from advanced CTP enhanced by AI technology.

DEFUSE-3 criteria:[9,14]

1) infarct core volume <70 mL
2) penumbra volume ≥ 15 mL
3) penumbra/infarct core ratio ≥ 1.8

Statistical analysis was conducted using PASW (Predictive Analytics Software) Statistics 18 software. Quantitative data were presented as means, while qualitative data were expressed as frequencies with percentages. The Fisher Exact test was employed to explore the significant associations between risk factors and endovascular treatment. The agreement between CTP by RapidAI software and Multiple-phase CT angiography/UECT images, as well as interobserver variability regarding endovascular thrombectomy eligibility was assessed using Kappa correlation coefficients. A p-value <0.05 was considered statistically significant.

Given that this study was a retrospective analysis of existing medical records, the Institutional Review Board (IRB) of Siriraj Hospital, Mahidol University (Certificate of Approval number: Si 865/2022), granted exemption from the requirement to obtain individual patient consent. However, it is important to note that all patients included in this study had previously consented to their data being included in the hospital's institutional database and for research purposes during their initial clinical consultation. This consent was secured through a standard process, ensuring patients were informed about the potential use of their medical data for research purposes. The retrospective nature of the study ensured stringent adherence to patient privacy and confidentiality. There were no direct patient interventions or interactions, and all patient data were anonymized to safeguard protect patient identities. The study adhered to the principles set in the Declaration of Helsinki, the Belmont Report, the Council for International Organizations of Medical Sciences (CIOMS) Guidelines and the International Conference on Harmonization in Good Clinical Practice (ICH-GCP).

RESULTS

From January 2018 to September 2022, data of 64 patients was collected and reviewed. Baseline characteristics are shown in Table 1. At baseline, the median age was 68.9 years and an analysis of baseline characteristics and risk factors showed no significant relationship with endovascular thrombectomy according to DEFUSE-3 criteria.

Within the original group, 61 patients met the DEFUSE-3 criteria for endovascular treatment based on CTP analysis, while a joint evaluation using MCTA and UECT, identified 52 patients as suitable candidates. Of these, 52 patients received endovascular treatment. Follow-up data was available for 33 patients.

Among the 33 patients for whom follow-up data was available, 16 (48.5%) exhibited functional independence by day 90, as defined by a mRS score of 0 to 2. The collection of comprehensive follow-up information encountered obstacles due to the referral system, resulting in some incomplete records.

A subgroup analysis was carried out, excluding 15 patients with ASPECTS scores <6. In this refined group of 49 patients, all met the DEFUSE-3 criteria for

TABLE 1. Baseline characteristic and demographic data.

	All	Endovascular treatment by DEFUSE3	P-Value
Age (years), Mean±SD	69±13.9		
Sex (Female, Male) n, (%)	30, 34 (46, 54)		
Demographic Data			
DM n, (%)	20 (31)	19 (29)	.628
HT n, (%)	39 (90)	38 (59)	.414
DLP n, (%)	22 (34)	19 (29)	.393
AF n, (%)	15 (23)	13 (20)	.361
CAD n, (%)	8 (12)	7 (12)	.604
Smoking n, (%)	13 (20)	12 (19)	.484
Previous Stroke n, (%)	13 (20)	12 (19)	.432

Abbreviations: DM = Diabetes Mellitus, HT = Hypertension, DLP = Dyslipidemia, AF = Atrial fibrillation, CAD = coronary arterial disease, mRS = modified Rankin Scale

endovascular treatment, and 48 were considered eligible based on their ASPECTS and Collateral score (>2) as assessed through MCTA and UECT imaging.

The comparison of consistency between CTP and other standard imaging modalities, as assessed by neuro-interventionalists, revealed a Kappa coefficient score of 0.4. According to Landis & Koch's (1977) interpretation of Kappa values, this score is in moderate agreement, with a total concordance of 57 out of 64 cases and 7 discordant cases.[22] The interobserver agreement between the two neuro-interventionalists was deemed substantial, with a Kappa coefficient score of 0.7.

After a detailed consensus discussion, the consistency between CT perfusion and other standard imaging modalities improved from slight to fair agreement. A subgroup analysis was also conducted, which excluded patients with ASPECTS scores <6. In this refined subgroup, consistency between the modalities reached perfect agreement, as indicated by a Kappa coefficient score of 1.0. Additionally, it was observed that cases with concordant agreement were significantly associated with ASPECTS scores ≥6, and vice versa, with a p-value less than 0.001. (Diagram 1)

DISCUSSION

Recent stroke guidelines recommend mechanical thrombectomy in patients who present anterior circulation ischemic stroke within 6 to 16 or 24 hours of symptom onset with large vessel occlusion, according to the diffusion weighted image or CTP assessment with clinical mismatch in the triage of wake-up and late presenting strokes undergoing neurointervention with Trevo trial (DAWN) or DEFUSE-3 trial criteria.[4] The DAWN trial[15] identified candidates with large anterior circulation vessel occlusion for treatment with mechanical thrombectomy through a clinical-core mismatch based on the NIHSS score and imaging findings from CTP or diffusion-weighted MRI., Meanwhile, the DEFUSE-3 trial selected patients using perfusion-core mismatch and maximum core size as imaging criteria (infarct volume <70 mL, penumbra volume ≥15 mL and a penumbra/infarct core ratio ≥1.8[9,14]) to select patients with large anterior circulation occlusion 6 to 16 hours from onset l for mechanical thrombectomy, which required CTP for patient selection. Despite its advantages, CTP is not universally available. CT has many practical advantages over other cerebral perfusion imaging methods, including its wide availability. Thus, in prior studies[23-32] other modalities, such as UECT and MCTA, were used instead of advanced imaging to evaluate acute stroke patients with a late window period, with some questioning the need of perfusion imaging.[33] The recently published MR CLEAN LATE[34] demonstrated that patient selection in the late time window could be based on collateral circulation, making ASPECT score and CTP less critical. Studies by Wang et al.[24] and Dhillon et al. have suggested that MCTA can match CTP in predicting outcomes and that endovascular treatment is viable and safe without the

need for advance neuroimaging in acute ischemic stroke patients with delayed stroke onset.[28] However, conflicting findings persist, as some studies indicate that CTP can lower mortality, even though functional independence after late-window endovascular therapy appear similar to patients selected by UECT.[30] The evolving landscape of stroke management underscores the ongoing exploration of diverse imaging modalities and patient selection criteria in the extended time window, acknowledging the practical considerations and limitations of available technologies in different clinical settings.

In this study, our primary objective was to assess the consistency among different imaging modalities in establishing EVT eligibility. This involved comparisons between CT perfusion (utilizing the DEFUSE-3 criteria) and the combined use of multiple-phase CT angiography and unenhanced computed tomography. It should be noted that the guidelines at Siriraj Hospital are predominantly based on DEFUSE 3 trial criteria, with slight adjustments to the time window, which has been narrowed to 6-12 hours or of unknown onset.

Our study's findings indicate a slight agreement between CTP analyzed by RapidAI software and conventional imaging methods. Notably, discordance was noted in 7 out of 64 cases, predominantly due to two factors. In 6 out of the 7 cases, discordance was linked to an overestimation of the core infarction area during ASPECTS evaluation (Fig 1). This overestimation of the core infarction area is a significant concern when relying on UECT as it lacks the ability to differentiate between the penumbral and core infarction areas. A previous study conducted by Siegler et al.[26] also highlighted this issue, revealing that while nearly three-quarters of thrombectomy patients showed ischemic changes on UECT, about one-third of these cases had normal core volumes on CTP. This finding underscores the necessity of incorporating both perfusion and non-contrast scans to achieve a thorough and precise determination of endovascular treatment eligibility.

Moreover, the subjectivity in evaluating ASPECTS scores present another challenge. This subjectivity stems from the wide range of cerebral hypodensity attenuation

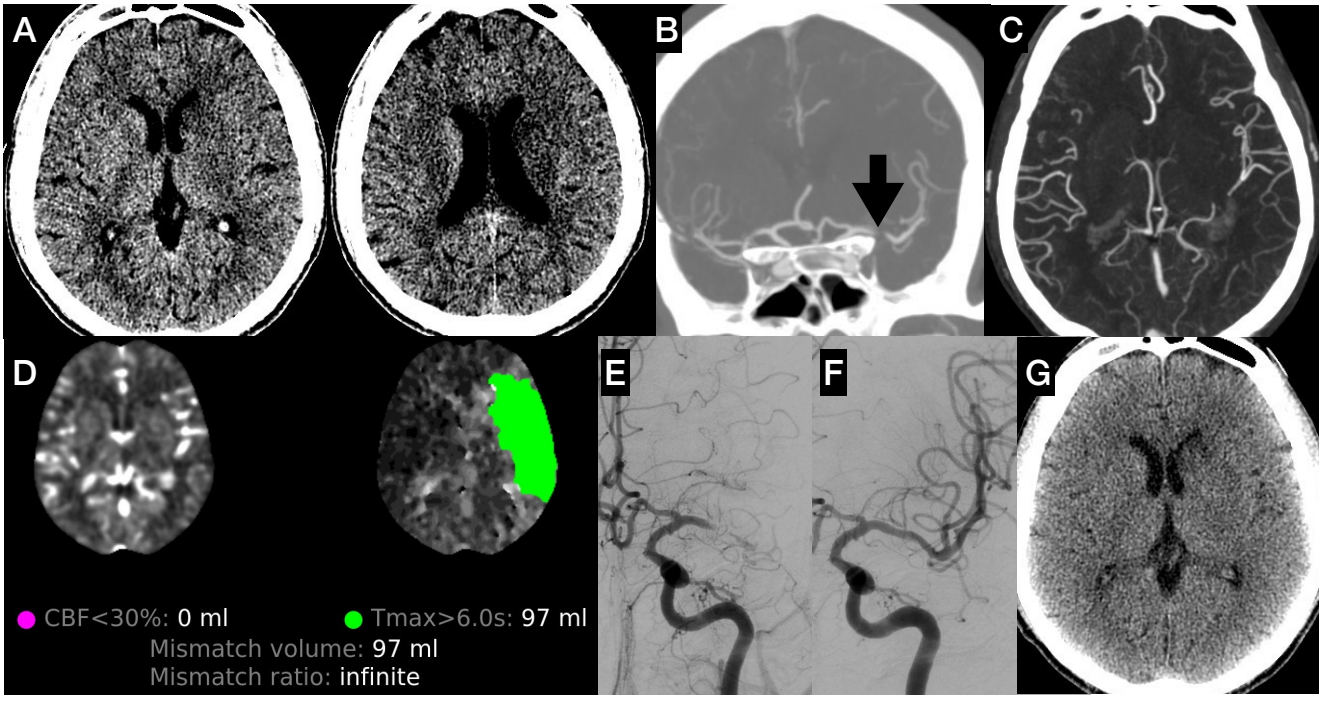

Fig 1. A 47 years old patient presented right-sided weakness for 6 hours, NIHSS = 11 A: NECT of the brain showed a hypodense area in the head of the left caudate nucleus, left internal capsule and left lentiform nucleus, with an ASPECTS score = 7. B: CTA source image shows total occlusion of the M1 segment of left MCA (black arrow). C: Multi-phase CTA during the 1st phase shows a collateral score = 5. D: CT perfusion shows no core infarct with a ischemic penumbra area about 97 ml, resulting in a mismatch ratio = infinite. Based on the DEFUSE-3 criteria from CT perfusion, the patient underwent MT E: Left ICA angiogram shows nearly total occlusion of the M1 segment of the left MCA. F: Post-MT left ICA angiogram shows recanalization of the left MCA. G: Brain CT, 24 hours post-MT shows subacute infarction in the head of left caudate nucleus but no hemorrhagic transformation. The patient exhibited improvement in weakness, NIHSS = 3. At the 3-month follow-up, the patient showed mRS = 0.

Abbreviations: NIHSS = National Institutes of Health Stroke Scale, NECT = Non-enhanced computed tomography, ASPECTS = Alberta Stroke Program Early CT Score, CTA = Computed Tomography Angiography, MCA = middle cerebral artery, CT = computed tomography, MT = mechanical thrombectomy, ICA = internal carotid artery, mRS = modified Rankin Scale

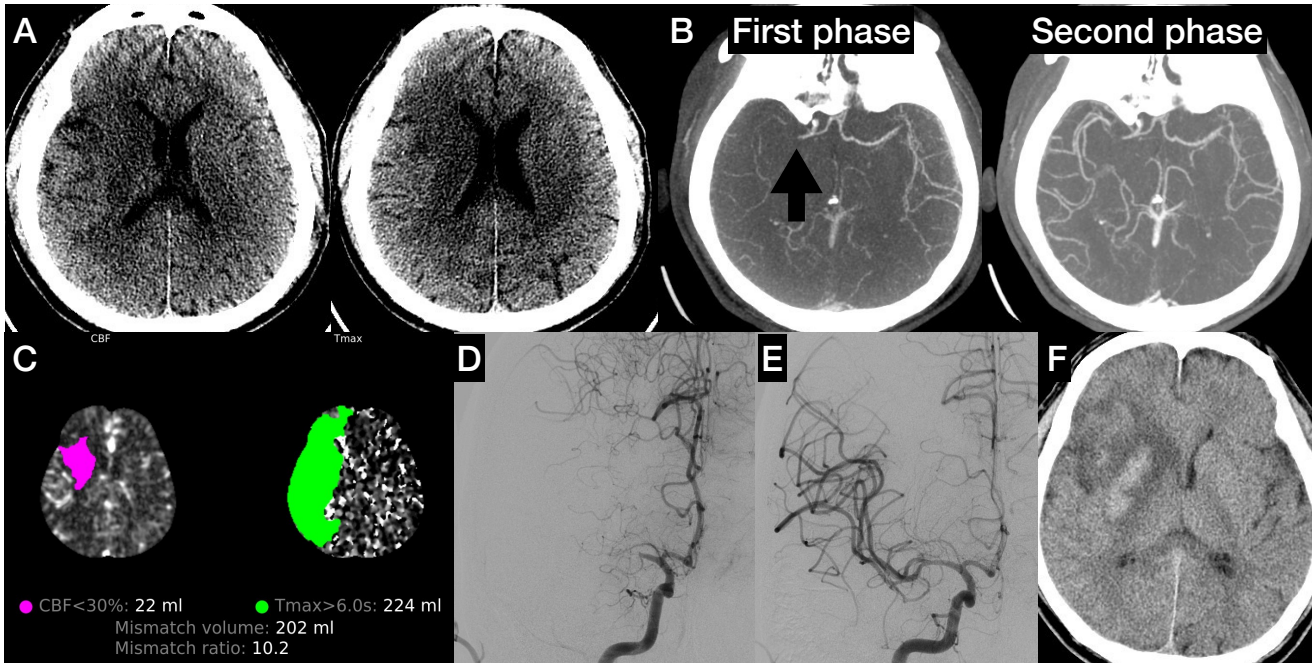

Fig 2. A 55 years old patient presenting left-sided weakness upon waking up, NIHSS = 10. A: NECT of the brain shows a hypodense area in the right caudate nucleus, lentiform nucleus, internal capsule, insular cortex, M1 and M4 areas, and an ASPECTS score = 4. B: Multiphase CTA in the 1st and 2nd phases shows total occlusion at M1 segment of the right MCA (black arrow) with collateral score = 4. C: CT perfusion shows a small area of core infarct, 22 ml, with a large ischemic penumbra area, mismatch ratio = 10.2. Based on the DEFUSE-3 criteria from CT perfusion, the patient was sent for MT. D: Right ICA angiogram shows total occlusion of the M1 segment of the right MCA. E: Post-MT right ICA angiogram shows recanalization of the right MCA. F: CT of the brain 24 hours after MT showed hemorrhagic transformation in the right basal ganglia. However, the patient improved in weakness, NIHSS = 2. At the 3-month follow-up, the patient showed mRS = 2.

Abbreviations: NIHSS = National Institutes of Health Stroke Scale, NECT = Non-enhanced computed tomography, ASPECTS = Alberta Stroke Program Early CT Score, CTA = Computed Tomography Angiography, MCA = middle cerebral artery, CT = computed tomography, MT = mechanical thrombectomy, ICA = internal carotid artery, mRS = modified Rankin Scale

values, measured in Hounsfield units (HU) on UECT, which can vary significantly when compared to MRI. ASPECTS scoring is predominantly utilized for assessing occlusions in the M1 segment of the MCA.

Furthermore, in one specific case, the complexity was further compounded by the presence of a concurrent posterior circulation occlusion, which was included in the penumbra volume calculation. This inclusion of additional pathology introduces challenges in accurately assessing the extent of ischemic damage and complicates the determination of treatment eligibility. These findings underscore the multifaceted nature of decision-making regarding EVT eligibility and emphasizes the importance of a comprehensive understanding of each patient's unique anatomy and pathology.

In this study, it was found that discordant cases (15 out of 64) were significantly associated with ASPECTS less than 6 (p-value < 0.001). Consequently, by excluding cases with ASPECTS scores below 6 revealed perfect concordance between imaging modalities.

This outcome suggests that by removing cases prone to overestimation of core infarction, UECT and MCTA could be emerged as reliable tools in the evaluation of delayed-onset acute anterior circulation stroke. The high level of agreement in this refined subgroup implies that these modalities, which are more readily available and less complex than advanced imaging techniques, could potentially serve as dependable alternatives in specific clinical scenarios.

Several limitations of this study should be acknowledged. First, the study's relatively small population was the result of the recent incorporation of CTP using RapidAI software into the institution's guidelines. This limited sample size may affect the broad applicability of our findings. Additionally, the lack of follow-up data for 20 out of 59 patients who underwent endovascular treatment posed additional constraints, potentially impacting the assessment of long-term outcomes and functional recovery.

Additionally, the study's reliance on quantification software from a single vendor could limit the generalizability of the results as the availability of quantitative core infarction/penumbra volume could be influenced by the specific characteristics and algorithms of the chosen software. The exclusive use of a single software may not

account for potential variations that may arise with different software solutions, potentially limiting the broader applicability of the study's results.

These limitations underscore the importance of cautious interpretation of the study's results. There is a clear need for future studies with larger and more diverse populations, alongside comprehensive follow-up data, to strengthen the robustness and generalizability of conclusion drawn from this research.

CONCLUSION

In conclusion, our study indicates that the highest level of agreement between CTP and other standard imaging modalities, including MCTA and UECT, occurs in patients with anterior circulation occlusion with onset between 6 to 12 hours or unknown onset, excluding cases with ASPECTS scores below 6. In cases where patients met these criteria, MCTA and UECT are dependable in assessments and can effectively act as alternative options to CTP analyzed by RapidAI software.

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Conflicts of interest

All authors declare that there are no conflicts of interest related to any aspect of this research.

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Author Contributions

BS and PW: Conceptualization.: RC, BS, EC, TA, AC and PW: Data curation.: RC and PW: Formal analysis.: RC, BS and PW: Methodology.: AC, BS and PW: Supervision.: RC and PW: Writing – original draft.: PW: Writing – review & editing.

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A Comparison of Wound Healing Efficacy between a Herbal-coated Lipidocolloid Dressing and a Paraffin-based Dressing in Pediatric Burn Patients - A Randomized Controlled Study

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ABSTRACT

Objective: Burn injuries are prevalent among pediatric patients and pose significant challenges in wound management. This study aimed to compare the effectiveness of a herbal-coated lipidocolloid dressing (SI-Herb) versus a paraffin-based dressing (Bactigras) in promoting wound healing in pediatric partial-thickness burns.

Materials and Methods: A randomized controlled trial was conducted at Nakhon Pathom Hospital, Thailand, enrolling patients aged 0 to 15 years with partial-thickness burns covering 20% or less of their total body surface area (TBSA) between November 2021 and July 2023. Patients were randomized into SI-Herb (Group S) or Bactigras (Group B) treatment arms. The primary outcome assessed was days to complete wound epithelialization, with secondary outcomes including pain, bleeding, and dressing removal difficulty scores.

Results: Of the 28 recruited patients, 25 were included in the analysis (13 in Group S, 12 in Group B). There was no significant difference in complete wound epithelialization between the groups overall (9.2 ± 3.1 days in Group S vs. 11.3 ± 5.2 days in Group B, $p = 0.242$). However, subgroup analysis of patients with burns ≥10% TBSA showed a significantly shorter epithelialization time in Group S compared to Group B (11.8 ± 1.5 days vs. 15.8 ± 1.6 days, $p = 0.007$). Additionally, Group S exhibited lower pain, bleeding, and dressing removal difficulty scores compared to Group B ($p = 0.042$, 0.009, 0.003, respectively).

Conclusion: The herbal-coated lipidocolloid dressing demonstrated superior efficacy in promoting faster wound epithelialization in pediatric patients with partial-thickness burns exceeding 10% TBSA compared to the paraffin-based dressing.

Keywords: Bactigras paraffin-based dressing; herbal-coated lipidocolloid dressing; partial- thickness skin burn; pediatrics (Siriraj Med J 2024; 76: 581-588)

INTRODUCTION

Burn injuries constitute a substantial contributor to pediatric trauma, aside from vehicle accidents, suffocation, and drowning.[1] Scald burn injuries are prevalent in toddlers and younger children, while flame burn injuries are more common in older children and adolescents, in contrast to chemical and electrical burns, which are infrequent in the pediatric population.[2,3] Extensive areas of burn injuries lead to mortality, with an incidence ranging metabolic derangements, and give rise to a diverse array of complications affecting multiple from 0.4-2.8%.[3] Severe burns induce significant stress responses, immune system alterations, and organ systems.[3] Wound dressing constitutes a crucial aspect of burn patient

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management. Expedited wound healing and mitigation of associated complications exert substantial influence on patient outcomes, duration of hospitalization, and the overall quality of life.[4] Numerous investigations on materials for burn dressings have been conducted. However, a predominant majority of these studies have been conducted on adult burn patients.

The former standard protocol for the management of burn wounds in the pediatric population at the principal investigator's center entailed the use of silver-zinc sulfadiazine cream. However, the application of silver-zinc sulfadiazine cream is linked to several disadvantages. Primarily, pediatric patients subjected to silver-zinc sulfadiazine cream dressings are required to undergo daily dressing changes, causing discomfort and distress during cream and dressing removal, in addition to recurrent dissatisfaction with the overall wound dressing experience. A study conducted in the past decade on Thai adult patients with partial-thickness burn wounds demonstrated a noteworthy reduction in the frequency of wound dressing changes and a decrease in pain scores in the group treated with an antibiotic-coated dressing (Acticoat™) compared to the group treated with a 1% silver sulfadiazine dressing.[5] Therefore, the innovative commercial dressings offer diverse advantages compared to the application of silver-zinc sulfadiazine cream.

A recently introduced "herbal-coated lipidocolloid dressing" incorporates a herbal extract formulation containing 2.5% *Aloe vera* and 5% *Centella asiatica* impregnated with lipidocolloid. This dressing is intended for use in adult burn patients in Thailand.[6] A comparative study in adults evaluating the effectiveness of the herbal-coated lipidocolloid dressing, incorporating *Aloe vera* and *Centella asiatica*, against a gauze dressing impregnated with paraffin and a 0.5% chlorhexidine acetate dressing has been conducted. The findings indicated a significantly reduced duration of wound healing and diminished pain during dressing changes in the herbal-coated lipidocolloid dressing group.[6] However, it is worth noting that investigations into the usage of herbal-coated lipidocolloid dressings in the pediatric population have not been undertaken.

The principal investigator's center, Nakhon Pathom Hospital, situated in the central region of Thailand, caters to a population of approximately one million. The facility receives a substantial number of pediatric trauma patients, including those with burn injuries, referred from six community hospitals and nearby regions. Consequently, the primary aim of this study is to compare the duration required for complete healing of partial-thickness burns in the pediatric population (aged 0 to 15 years) when treated with either a herbal-coated lipidocolloid dressing or a Bactigras paraffin-based dressing. The secondary objectives encompass assessing and evaluating pain scores and bleeding during dressing changes and determining infection rates.

MATERIALS AND METHODS

The study was a randomized, controlled trial approved by the Ethics Committee, Nakhon Pathom Hospital, Nakhon Pathom province, Thailand (approval number: 019/2021, date of approval: June 18, 2021). The protocol was registered with the Thai Clinical Trials Registry, registration number: TCTR20210822001, date of registration: October 21, 2021. We included patients aged 0 to 15 years old with partial-thickness skin burns from scald or flame burn injuries of less than or equal to 20 percent of the total body surface area (TBSA). The burn area was estimated in terms of percentage per total body surface area (% TBSA), using the original Lund and Browder chart.[7] The exclusion criteria were as follows: patients with chemical or electrical burn injuries; patients with full-thickness burn wounds requiring skin grafting; patients with burn wounds located in the facial, hand, foot, genital, and perineum areas; patients with known underlying diseases that may affect wound healing, e.g., autoimmune diseases, connective tissue diseases, diabetes mellitus, etc.; and patients taking current medication that may affect wound healing, e.g., corticosteroids. We also excluded patients with allergies to the study materials, including chlorhexidine (the Bactigras paraffin-based dressing contains chlorhexidine). Patients who were unable to attend a follow-up were withdrawn from the study.

Data collection took place from November 1, 2021, to July 31, 2023. Written informed consent was obtained from the guardians of all participants. Patients were randomized into one of two groups using computer-generated randomization of a block of four patterns. The allocation concealment was done by using a sealed file with sequentially numbered. The file is confidential and can only be accessed by the principal investigator.

The day that all patients arrived at the Emergency Department, Nakhon Pathom General Hospital, was noted (day 0), and all patients were allocated randomly to one of two groups and received a burn wound dressing: either a herbal-coated lipidocolloid dressing (SI-herb, Specialty Innovation Co., LTD., under the license of Bangkok Botanica Co., LTD., Thailand) (group S) or a Bactigras paraffin-based dressing (Bactigras, Smith & Nephew Medical Limited, Germany) (group B), which was then covered by dry gauze. The participants were blinded to the type of dressing. All patients received a

dose of 15 mg/kg oral acetaminophen as required, at six-hour intervals. Patients with burn wounds covering more than 10% of the TBSA underwent blister removal under general anesthesia in the operating theater on day 1.

Demographic data, including age, gender, cause of burn, weight, height, and underlying disease, were collected. The dressing change protocol was every other day in the first week, then, every 2 days until complete healing of the wound. The complete healing of the wound was defined as 100% epithelialization. The healed area and pain score were recorded on days 3, 5, 8, 11, 14, 17, 20, and 23, or until the wound had completely healed. The determination of complete epithelialization was made through direct visual inspection conducted by medical personnel, including doctors and nurses. The difficulty of dressing removal was graded by the nurse who removed the dressing according to a three-point grading system: 0 = easy removal, 1 = easy removal with soaking in normal saline, and 2 = difficult removal with soaking in normal saline. Additionally, bleeding from the burn wound while removing the dressing was divided into four grades: 0 = none, 1 = minimal bleeding, 2 = moderate bleeding, and 3 = heavy bleeding. Pain score and difficulty in dressing removal, and bleeding on the day of blister removal in the operating theater were not included in the analysis. In patients under 6 years old, the Face, Legs, Activity, Cry and Consolability (FLACC) scale was used to evaluate the pain score.[8] In patients over 6 years old, the Wong-Baker Faces Pain Rating scale was used.[9] The number of patients requiring oral or intravenous antibiotics as well as the rate of wound infection were also recorded throughout the healing duration. The outcome measurements were performed by doctors or nurses in the emergency department who were not involved with this trial.

Statistical analysis

The sample size calculation was derived from the results of Muangman et al.[6], which revealed the results of the usage of a herbal-coated lipidocolloid dressing compared to those of a Bactigras paraffin-based dressing in adult burn patients. The results revealed that the time of wound healing was significantly shorter in the herbal-coated lipidocolloid dressing group (18.53 ± 1.66 days) compared to the Bactigras paraffin-based dressing group (20.06 ± 2.51 days). The author determined that wound healing in the herbal-coated lipidocolloid group would hasten the time to complete wound healing by 2 days (mu1 – mu2), with a standard deviation of 1.66 days, a significance level of 0.05 (alpha), and a power of 80%, using the nQuery Advisor program. The calculated sample size of each group was 12 patients. The principal investigator increased the sample size by approximately 10% to compensate for possible subject loss in this study. Therefore, the total sample size of each group was 14 patients. Overall, there were 28 patients included in this study.

All analyses were performed using PASW Statistics (SPSS) version 18.0 (SPSS Inc., Chicago, IL, USA). The analyses were performed on an intention-to-treat basis. Categorical data are presented as numbers (percentage), while the continuous data are presented as mean ± standard deviation, range (minimum to maximum value), or median [interquartile range]. Chi-square test, independent T-test, and Mann-Whitney U test were used to compare between the two groups. Bleeding score and dressing difficulty score were compared using a linear-by-linear association test. Survival analysis was used and the Kaplan-Meier curve was presented to compare the duration of complete healing between the two groups. P-values lower than 0.05 were considered statistically significant.

RESULTS

In total, 28 patients were initially enrolled in the study. However, due to missing the follow-up, one participant from Group S and two from Group B were excluded. Consequently, a total of 25 patients were included in the final analysis (Fig 1). The average age of the entire group of patients was 2.4 ± 2.6 years, with an average burn area of 8.4 ± 5.0 % TBSA. Details of the demographic and clinical characteristics of both groups are shown in Table 1. All patients included in the study were of Asian ethnicity. No significant differences were observed in demographic characteristics between the two groups. All patients presented with scald burns resulting from boiling water, oil, or soup; none were caused by flame exposure. Burn injuries were distributed across various anatomical sites, including the forearm, arm, chest, abdomen, buttock, thigh, and leg. Table 2 shows the comparison of the time to complete epithelialization, pain score, bleeding grading, and difficulty in dressing removal. None of the patients were allergic to the dressings or developed an infection requiring antibiotics in either group. Nine patients required wound blister removal under general anesthesia in the operation theater on day 1 (group S = four patients, and group B = five patients). Table 3 shows the comparison of complete wound epithelialization between burn areas covering < 10% TBSA and ≥ 10% TBSA. Patients with burn areas more than or equal to 10% of the total body surface area in Group S exhibited

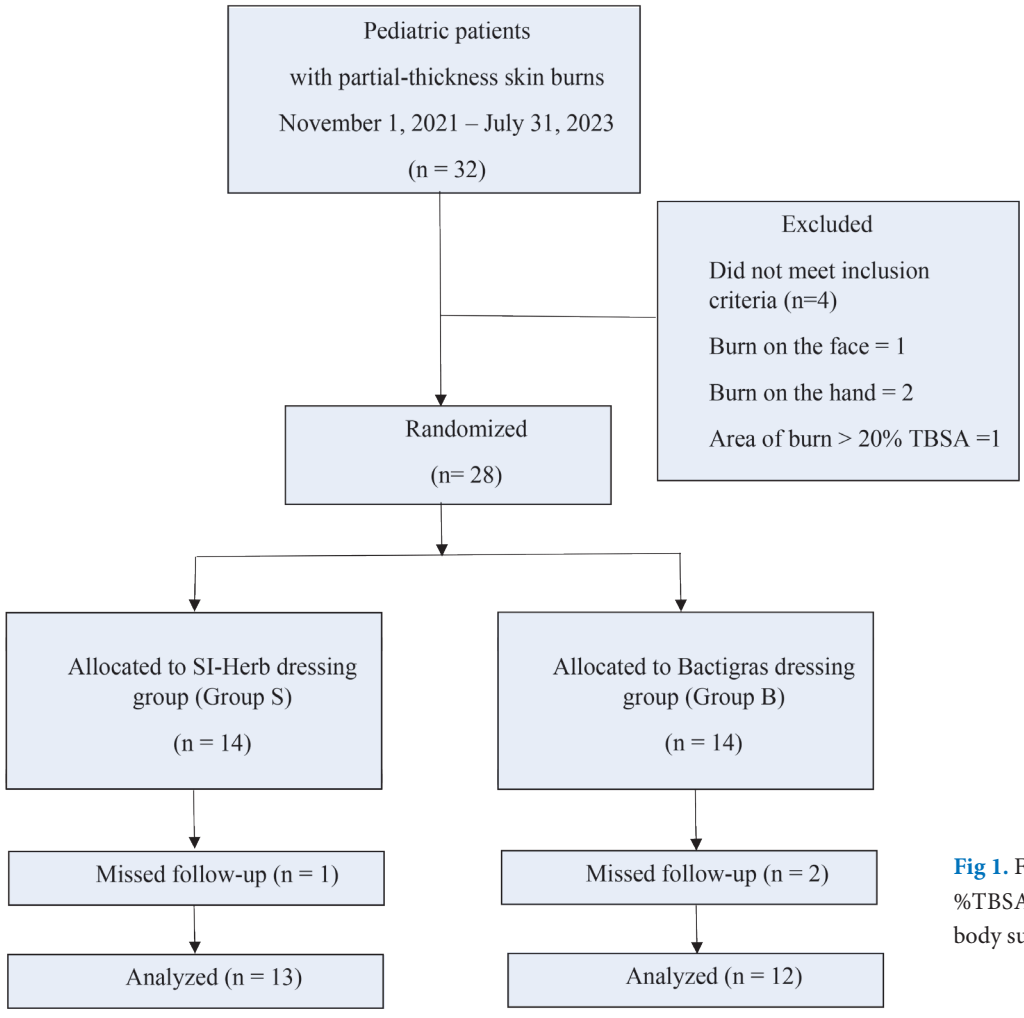

Fig 1. Flow of study
%TBSA: percentage of total body surface area

TABLE 1. Demographic and clinical characteristics (n=25).

Value	All patients N = 25	Si-Herb dressing (Group S) N = 13	Bactigras dressing (Group B) N = 12	P-value
Age (years)	2.4 ± 2.6 (0.4 – 10.4)	3.1 ± 2.9	1.8 ± 2.3	0.220
Male gender	12 (48.0)	4 (30.8)	8(66.7)	0.073
Body weight (kg)	13.1 ± 7.4 (6.0 – 35.0)	15.0 ± 7.8	11.6 ± 5.4	0.250
BMI (kg/m²)	17.2 ± 3.4 (10.4 – 24.7)	16.6 ± 3.6	17.91 ± 3.2	0.354
Burn area (% TBSA)	8.4 ± 5.0 (2.0 – 18.0)	7.7 ± 3.8	9.3 ± 6.2	0.451
Body surface area (m²)	0.52 ± 0.24 (0.30 – 1.08)	0.56 ± 0.24	0.48 ± 0.24	0.407
Cause of burn				
Hot water	18 (72.0)	9 (69.2%)	9 (75.0%)	
Hot oil	1 (4.0)	0 (0)	1 (8.3%)	0.645
Hot soup	6 (24.0)	4 (30.8%)	2 (16.7%)	

Data are presented as mean ± standard deviation (minimum – maximum value) or number (percentage).
Abbreviations: kg: kilogram; TBSA: total body surface area; m^2: square meter

TABLE 2. Comparison of wound epithelialization completion, pain scores, bleeding scores, and dressing difficulty scores between the two groups (n = 25).

	Si-herb dressing (Group S) N = 13	Bactigras dressing (Group B) N = 12	P-value
Wound epithelialization completion (days)	9.2 ± 3.1	11.3 ± 5.2	0.242
Pain score on days 3-8	3 [0, 4]	5.75 [6, 8]	0.042*
Pain score on days 9-17	0 [0, 2]	2.5 [3.5, 6.5]	0.096
Bleeding score on days 3-8			
0	12 (92.3)	5(41.7)	0.009*
1	1(7.7)	5(41.7)	
2	0(0)	2(16.7)	
Bleeding score on days 9-17			
0	5(100)	3(50)	0.093
1	0(0)	1(16.7)	
2	0(0)	2(33.3)	
Dressing difficulty score on days 3-8			
0	13(100)	5(41.7)	0.003*
1	0(0)	3(25.0)	
2	0(0)	4(33.3)	
Dressing difficult score on days 9-17			
0	5(100)	4(66.7)	0.455
1	0(0)	0(0)	
2	0(0)	2(33.3)	

Data are presented as mean ± standard deviation, median [interquartile range] or number (percentage).

TABLE 3. Comparison of completed wound epithelialization between burn areas < 10% TBSA and burn areas ≥ 10% TBSA.

	Si-herb dressing (Group S) N = 13	Bactigras dressing (Group B) N = 12	P-value
Burn area < 10%TBSA (days)	N = 9	N = 7	1.000
N = 16	8.0 ± 3.0	8.0 ± 4.2	
Burn area ≥ 10% TBSA (days)	N = 4	N = 5	0.007*
N = 9	11.8 ± 1.5	15.8 ± 1.6	

Data are presented as mean ± standard deviation.

Abbreviation: TBSA: total body surface area

a significantly shorter time to complete epithelialization of burn wounds. Survival analysis shows the probability of complete wound healing in group S compared to group B (Fig 2).

DISCUSSION

The present study conducted a comparative analysis of wound healing efficacy between a herbal-coated lipidocolloid dressing (group S) and a Bactigras paraffin-based dressing (group B). The findings revealed that the overall rate of complete epithelialization in patients within group S was comparable to that of group B. Nevertheless, in group S, there was expedited wound epithelialization observed in patients with burn areas exceeding 10% of the TBSA compared to such patients in group B. Furthermore, patients in group S exhibited a reduction in pain scores and bleeding scores during wound dressing procedures and reported fewer difficulties in dressing change from days 3 to 8 post-application.

Novel commercial dressings for burn wounds offer distinct advantages over silver sulfadiazine cream, including lower pain scores and reduced frequency of replacement. Dressings such as the Bactigras paraffin-based dressing or Aquacel Ag™ dressing typically require changing every other day or less frequently compared to conventional silver sulfadiazine cream dressings, which necessitate daily replacement.[5] These strategies also offer significant benefits for the pediatric population by minimizing the need for frequent dressing changes, thereby optimizing wound management, reducing the rate of wound healing, decreasing hospital length of stay, and reducing overall cost.[10]

Several studies have elucidated variations in wound healing rates among burn injuries treated with different dressings for partial-thickness wounds in adults. A prior comparative study underscored the efficacy of herbal-coated lipidocolloid dressings, incorporating *Aloe vera* and *Centella asiatica*, in significantly reducing the duration of wound healing and alleviating pain during dressing changes compared to Bactigras dressings.[6] The following study conducted in the adult population, which compared the efficacy of treatment with herbal-coated lipidocolloid dressings in conjunction with silver sulfadiazine cream to treatment solely with silver sulfadiazine cream (control group), demonstrated accelerated wound healing and decreased pain scores.[11] In this study, our focus was on pediatric populations, specifically the herbal-dressing group, where we also observed a decrease in the duration of wound healing in patients with burns to an extent equal to or greater than 10% of the TBSA. This threshold of 10% TBSA is considered indicative of an extensive burn area, aligning with the guidelines for burn management set forth by the American Burn Association and the American College of Surgeons, which recommend transferring patients with such extensive burns to specialized burn centers.[12]

The attributes of *Aloe vera* and *Centella asiatica* serve to hasten the process of re-epithelialization and

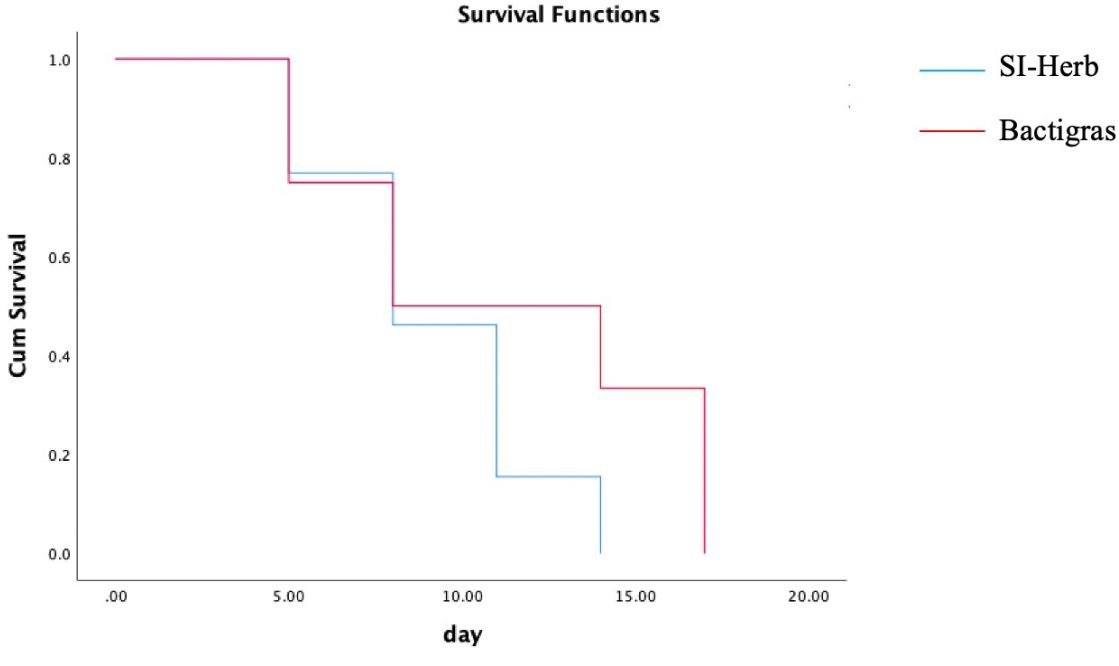

Fig 2. Time to complete wound epithelialization (Log-rank test (Mantel-Cox); p-value = 0.088); Data are presented in day(s).

facilitate the acceleration of wound healing.[13-18] A recent meta-analysis and systematic review showed that these herbs facilitated a faster time of burn wound healing compared to other treatments, such as saline gel, silver sulfadiazine cream, and chlorhexidine gel.[15] Moreover, *Centella asiatica* enhanced wound healing through improved angiogenesis and a stimulating effect on type 1 collagen, fibroblast growth factor, vascular endothelial growth factor production, and its anti-inflammatory effect.[17] *Aloe vera* improves the wound healing process by inhibiting inflammatory reactions and through its regenerative properties, which eventually increase the production of collagen.[18] *Aloe vera* also has anti-viral and anti-bacterial properties, and it helps the skin retain moisture, which affects wound healing.[18] The aforementioned reason explains the shorter duration of burn wound healing observed in the use of herbal-coated lipidocolloid dressings.

Pain during wound dressing changes is a significant concern in pediatric patients due to its potential psychological impact and the risk of future medical procedure avoidance.[19] Pain experienced during wound dressing or dressing removal is notably higher in the first week, which is attributed to increased exudate and incomplete epithelialization. Consequently, we set a cutoff for the pain score and compared observations between the first week and the subsequent week. Nevertheless, our findings are consistent with previous research, showing that the use of herbal dressings was associated with lower pain scores during dressing changes.[11]

None of the patients included in this study experienced wound infection which necessitated additional antibiotic treatment. However, the risk of local or systemic infection remains a significant consideration in the overall management of pediatric burn patients. Early post-burn antibiotic prophylaxis has shown no efficacy in preventing burn wound infections in the general population.[20] Likewise, a meta-analysis investigating antibiotic prophylaxis in pediatric burn patients revealed no notable disparity in the prevalence of local or systemic infections between cohorts receiving antibiotics and those abstaining from them.[21] Additionally, complications exclusively associated with systemic infections did not exhibit variance between patients who were administered antibiotics and those who were untreated.[21]

This study demonstrates the efficacy of herbal-coated lipidocolloid dressings in pediatric patients, leading to significant reductions in pain scores, bleeding, and difficulty during dressing removal when applied between days 3 and 8 post-injury. The findings of this research hold implications for the development of protocols involving the utilization of innovative commercial dressings for managing partial-thickness skin burns in pediatric populations across various community or general hospitals in Thailand. The limitation of this study is that the study was conducted in one institute in one province, therefore limiting the generalizability of the results. Therefore, a multi-center or national-level study should be implemented. A study of the cost-effectiveness of the dressings should also be conducted in the future. Further study on the use of a herbal-coated lipidocolloid dressing in pediatric populations involving less frequent wound dressing should be undertaken.

In conclusion, the application of a herbal-coated lipidocolloid dressing in pediatric patients with partial-thickness burns covering equal to or greater than 10% of the total body surface area resulted in significantly accelerated complete epithelialization compared to application of a paraffin-based dressing. Although no disparities were observed in the duration of complete epithelialization among burn patients with less than 10% of the total body surface area involved, they experienced significant reductions in pain score, bleeding score, and difficulty during wound dressing.

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DECLARATION

Conflict of Interest

This project obtained study material (SI-Herb®) from the Specialty Innovation Co., LTD. (Bangkok Botanica Co., LTD., Thailand) for utilization in this investigation. The principal investigator declares no additional financial conflicts of interest.

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Author Contributions

NH: Investigation, Conceptualization, Methodology, Validation, Resource Management, Formal analysis, Data curation, Writing - Original Draft, Writing - Review & Editing

WM: Data curation, Writing - Original Draft.

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Socioeconomic Factors and Clinical Characteristics Associated with Age at Autism Spectrum Disorder Diagnosis

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ABSTRACT

Objective: Investigate factors influencing autism spectrum disorder (ASD) diagnosis in children under and over 36 months, and determine the average age for ASD diagnosis at Charoenkrung Pracharak Hospital, Bangkok, Thailand, after implementing ASD screening.

Materials and Methods: A retrospective cross-sectional study of 252 children with ASD aged 1-15 years from 2014 to 2023, classified into ≤36 months (n=104) and >36 months (n=148) at diagnosis. Demographic, clinical data and child/family factors were analyzed using multivariate regression analysis.

Results: Mean age at ASD diagnosis was 44.77 ± 19.91 months. Attending well-baby clinics (aOR 2.64, p=0.038), higher family income ≥ 814 US dollars per month (aOR 2.33, p=0.020), and higher parental education (aOR 3.43, p=0.011) were significantly associated with diagnosis before 36 months. Hyperactivity as the main complaint (aOR 0.07, p=0.001) and global developmental delay/intellectual disability (aOR 0.45, p=0.023) predicted later diagnosis. Child's gender, being an only child, sibling order, and parental age had no significant impact.

Conclusion: Over half of all ASD diagnoses occurred after age 3, with an average age around 44 months. Regular attendance in well-child clinics allowing ASD screening, and higher socioeconomic status and parental education facilitated earlier diagnosis. In contrast, concerns about hyperactivity and global developmental delay often lead to delayed ASD assessment. Enhancing awareness of ASD among families with limited resources can promote timely diagnosis and access to intervention.

Keywords: Autism spectrum disorder; age at diagnosis; early intervention; screening; socioeconomic factors (Siriraj Med J 2024; 76: 589-594)

INTRODUCTION

Autism Spectrum Disorder (ASD) is a complex neurodevelopmental condition characterized by persistent deficits in social communication and interaction, coupled with restricted, repetitive patterns of behavior, interests, or activities.[1] The prevalence of ASD has risen substantially in recent years, with the Centers for Disease Control and Prevention estimating 1 in 36 children identified with ASD in 2020, a notable increase from 1 in 68 children in 2010.[2] In Thailand, approximately 1 in 161 children under 5 years old are diagnosed with ASD, representing a 6-fold increase over the past decade.[3] As a lifelong condition, ASD poses significant challenges for public health systems, families, and economic resources.[1,4]

Early diagnosis and intervention for ASD during the first three years of life are crucial, as this period of

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peak brain plasticity provides the greatest potential for positive developmental outcomes.[4,5] Numerous studies have shown that timely interventions can substantially improve long-term prognosis and mitigate financial and societal burdens associated with ASD.[4,6] While the average age of diagnosis has decreased from 10 years in the 1960s-1990s to around 4-5 years more recently[7], diagnostic delays persist due to the heterogeneous nature of ASD and variable clinical presentations.[8]

Understanding the factors influencing the timing of ASD diagnosis is critical to facilitating early identification and access to interventions. Previous research has linked certain characteristics of children, such as the severity of symptoms, intellectual disabilities, language delays, and regression, with earlier diagnosis.[6,9,10] Family factors such as socioeconomic status, levels of parental education, and having siblings with ASD have also been associated with age of diagnosis, although the findings remain inconsistent.[11-16]

Limited data exists on factors impacting the timing of ASD diagnosis in Thailand. Furthermore, Thailand currently lacks a comprehensive national policy for implementing ASD screening protocols. In 2014, the Charoenkrung Pracharak Hospital in Bangkok, Thailand, adopted the ASD screening protocols in a well-baby clinic recommended by the American Academy of Pediatrics.[17] The screening involved conducting the Modified Checklist for Autism in Toddlers (M-CHAT) during the 18 and 24-month well-child visits. The children who tested positive were referred for extensive evaluations by developmental-behavioral pediatricians who used DSM-5 criteria to diagnose ASD. This standardized screening enabled earlier identification of children requiring diagnostic assessments during routine well-child visits. Following the implementation of these ASD screening protocols, this study aimed to investigate child and family factors, including attendance at well-baby clinics with ASD screening protocols, that influenced the diagnosis of ASD in children under and over 36 months of age. Identifying factors associated with earlier versus later diagnosis can guide strategies to improve timely detection and intervention access for optimal outcomes.

MATERIALS AND METHODS

Study design and population

This study was conducted retrospectively to describe the characteristics of children aged 1-15 years diagnosed with ASD at the Autistic Child Center of Charoenkrung Pracharak Hospital between January 2014 and December 2023. Developmental-behavioral pediatricians diagnosed ASD according to the criteria specified in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5).[1]

Data collection

The medical records and evaluations performed by the attending physicians were used to collect demographic and clinical data for each participant. The following child factors were recorded: age at diagnosis of ASD, sex, chief complaint, comorbid conditions, number of siblings, birth order, history of siblings with ASD, and records of well-baby clinic visits to the hospital. In addition, the following family factors were recorded: parents' ages, parental education levels, and monthly family income, which determined the socioeconomic status.

Statistical analyses

This study employed descriptive statistics to describe the demographic characteristics of children with ASD and their family profiles by categorizing them into two groups based on their age at ASD diagnosis: before or after 36 months of age. The Chi-square test was used to establish the relationship between demographic characteristics and age at the time of diagnosis of ASD. The independent variables with statistical associations (p-value < 0.1) with age at the time of diagnosis of ASD were then selected for multivariate logistic regression analysis. Variables with an observed association of p-value < 0.05 in the multivariate logistic regression analysis were considered statistically significant. Data coding and entry were performed using Microsoft Excel. SPSS Statistics Program Version 26 was used for data analysis.

Ethical Considerations

The study was approved by the Human Research Ethics Committee of the Bangkok Metropolitan Administration (R006h / 64_EXP).

RESULTS

This study included a total of 252 participants, with a mean age at the time of diagnosis of 44.77 ± 19.91 months. Participants were classified into two groups: children older than 36 months (n=148) and those ≤36 months (n=104) at the time of diagnosis. The gender distribution was comparable between the two groups, with males representing 74.3% and 76.0% of the older and younger groups, respectively (Table 1).

As shown in Table 1, the chief complaints at the first visit differed significantly between the two groups. Delayed speech was more common among the younger group (83.7% vs 72.3%, p=0.037), while hyperactivity was more prevalent in the older group (23.0% vs 4.8%,

TABLE 1. Demographic characteristics of children with ASD before and after 36 months.

Demographic Characteristics	Total number of participants (n=252)	Descriptive results		p-value
		Younger age at diagnosis ≤ 36 months (n=104)	Older age at diagnosis > 36 months (n=148)	
Sex				0.768
Boy	189 (75.0)	79 (76.0)	110 (74.3)	
Girl	63 (25.0)	25 (24.0)	38 (25.7)	
Main Complaint at 1st Visit				
Delayed Speech	194 (76.9)	87 (83.7)	107 (72.3)	0.037*
Hyperactive	39 (15.5)	5 (4.8)	34 (23.0)	<0.001*
Others	20 (7.6)	12 (11.5)	8 (5.4)	0.101
Comorbidity				
ADHD	49 (19.4)	11 (10.6)	38 (25.7)	0.004*
GDD/ID	115 (45.6)	32 (31.1)	83 (56.5)	0.001*
Epilepsy	5 (1.9)	3 (2.9)	2 (1.4)	0.401
Well-baby clinic visits at the hospital				<0.001*
No	207 (82.1)	74 (71.2)	133 (89.9)	
Yes	45 (17.9)	30 (28.8)	15 (10.1)	
Number of children				0.073
Being an only child	130 (51.6)	61 (58.6)	69 (46.6)	
More than 1 child	122 (48.4)	43 (41.4)	79 (53.4)	
Birth order				0.155
Firstborn	158 (62.7)	71 (68.3)	87 (58.7)	
Other	94 (37.3)	33 (31.7)	61 (41.3)	
Positive siblings of ASD				0.811
No	238 (94.4)	99 (95.2)	139 (93.9)	
Yes	14 (5.6)	5 (4.8)	9 (6.1)	

Data presented as numbers (percentage)
Abbreviations: ADHD = Attention Deficit Hyperactivity Disorder, GDD = Global Developmental Delay, ID = Intellectual Disability
*Statistically significant with p-value ≤ 0.05

p<0.001). Furthermore, the older group had a higher prevalence of comorbid attention deficit hyperactivity disorder (ADHD) (25.7% vs 10.6%, p=0.004) and global developmental delay/intellectual disability (GDD/ID) (56.5% vs 31.1%, p=0.001). Well-baby clinic visits to the hospital were significantly more common among the younger group (28.8% vs 10.1%, p<0.001). Further exploration revealed that out of those who attended well-baby clinic visits, 14 (31.1%) screened positive on the ASD screening protocol, and all of them received an ASD diagnosis before 36 months of age. However, the number of children and the order of birth did not differ significantly between the groups.

As shown in Table 2, a higher proportion of children in the younger group had a family income ≥ 814 US dollars (74.1% vs. 55.4%, p=0.001) and a primary caregiver with compulsory education or higher (86.5% vs. 75.0%, p=0.019).

In Table 3, multivariate logistic regression analysis revealed that attending well-child clinics (adjusted odds ratio [aOR] 2.64, 95% CI 1.06-6.62, p=0.038), higher family income ≥814 US dollar (aOR 2.33, 95% CI 1.14-4.73, p=0.020), and higher levels of parental education (aOR 3.43, 95% CI 1.32-8.91, p=0.011) were significantly associated with an earlier diagnosis of ASD (≤36 months). On the contrary, hyperactivity as the main complaint

TABLE 2. Family profiles of children with ASD before and after 36 months.

Demographic Characteristics	Total number of participants (n=252)	Descriptive results Younger age at diagnosis ≤ 36 months (n=104)	Older age at diagnosis > 36 months (n=148)	p-value
Paternal age at child's birth				0.217
<35-year-old	97 (38.4)	47 (45.2)	50 (33.8)	
≥35-year-old	155 (61.6)	57 (54.8)	98 (66.2)	
Maternal age at child's birth				0.998
<35-year-old	137 (54.3)	58 (55.8)	79 (53.4)	
≥35-year-old	115 (45.7)	46 (44.2)	69 (46.6)	
Monthly family income				0.001*
<814 US dollars+	93 (36.9)	27 (25.9)	66 (44.6)	
≥814 US dollars+	159 (63.1)	77 (74.1)	82 (55.4)	
Parents' marital status				0.125
Married	189 (75.0)	83 (79.8)	106 (71.6)	
Divorce	63 (25.0)	21 (20.2)	42 (28.4)	
Primary Caregiver's educational level				0.019*
Below compulsory Education	51 (20.2)	14 (13.5)	37 (25.0)	
Compulsory education and higher	201 (79.8)	90 (86.5)	111 (75.0)	

Data presented as number (percentage)
+1 US dollar = 36.87 bahts

TABLE 3. Multivariate logistic regression analysis for the association between demographic characteristics and younger age at the time of ASD (≤ 36 months).

Demographic characteristics	Adjusted Odd Ratios	95% Confidence interval	p-value
Main Complaint at 1st Visit			
Delayed Speech	0.41	0.13, 1.28	0.125
Hyperactive	0.07	0.01, 0.35	0.001*
Comorbidity			
ADHD	0.65	0.25, 1.70	0.383
GDD/ID	0.45	0.23, 0.90	0.023*
Well-baby clinic visits at the hospital	2.64	1.06, 6.62	0.038*
Higher monthly family income (≥814 US dollars+)	2.33	1.14, 4.73	0.020*
Higher level of education (Compulsory education and higher) of the primary caregiver	3.43	1.32, 8.91	0.011*

Abbreviations: ADHD = Attention Deficit Hyperactivity Disorder, GDD = Global Developmental Delay, ID = Intellectual Disability
+1 US dollar = 36.87 bahts
*Statistically significant with p-value ≤ 0.05

(aOR 0.07, 95% CI 0.01-0.35, p=0.001) and the presence of GDD/ID (aOR 0.45, 95% CI 0.23-0.90, p=0.023) predicted a later diagnosis of ASD (>36 months).

DISCUSSION

The mean age at the time of ASD diagnosis in our study was 44.77 ± 19.91 months, which aligns with recent reports indicating that children are often diagnosed around 4 years of age.[2,18] Despite the early emergence of ASD symptoms within the first two years of life, diagnostic delays persist due to various factors, including limited awareness of developmental milestones, insufficient access to health services, and delays between initial referrals and specialist evaluations.

Our findings highlight the critical role of regular well-baby clinic visits in facilitating early ASD detection through standardized ASD screening protocols like the M-CHAT. This underscores the importance of implementing comprehensive developmental surveillance and ASD-specific screenings, as recommended by the American Academy of Pediatrics, to identify developmental delays and ASD at the earliest stages possible.[17,19]

Children with GDD / IDD may experience a delayed diagnosis of ASD. Early developmental delays can mask the social communication deficits and restricted/repetitive behaviors of ASD, leading to delayed recognition.[20] Healthcare providers need to be better trained to recognize the potential co-occurrence of ASD in children with GDD/ID and initiate timely diagnostic evaluations.

Hyperactivity as the main presenting concern was also associated with a later diagnosis of ASD, possibly due to the overlap of symptoms with ADHD.[21,22] This diagnostic challenge underscores the importance of considering ASD in young children with hyperactive behaviors, as early intervention is crucial for optimal outcomes.

Consistent with previous studies,[15,16] our findings indicate that higher socioeconomic status and parental education levels facilitated an earlier diagnosis of ASD. This may be attributed to increased awareness of ASD symptoms, better access to medical information and healthcare services, and greater advocacy for comprehensive evaluations. In contrast, families with limited resources and lower educational attainment can face barriers to the timely identification and diagnosis of ASD. Targeted efforts to enhance ASD awareness and improve access to screening and diagnostic services are essential to address these disparities.

Although previous research has suggested associations between factors such as having siblings with ASD, birth order, and age at diagnosis,[13,14,16] our study did not find significant relationships with these variables. These discrepancies may be attributable to differences in study populations, sample sizes, and methodologies employed.

It is important to acknowledge the limitations of our retrospective study design, which relied on medical record reviews and may have been subject to incomplete or missing data. Furthermore, the COVID-19 pandemic likely affected families' ability to seek medical attention, which could contribute to diagnostic delays during the study period.

These findings in our study underscore the importance of implementing comprehensive developmental surveillance and ASD screening protocols in well-baby clinics to facilitate early identification. Furthermore, increasing awareness of ASD and improving access to diagnostic services, particularly among families with limited resources, are crucial to promote timely diagnosis and intervention for children with ASD.

Future research should explore strategies to address socioeconomic disparities in ASD diagnosis and focus on developing educational initiatives and community-based programs to improve the recognition of ASD symptoms in diverse populations. Furthermore, longitudinal studies that examine the long-term outcomes of children diagnosed at different ages would provide valuable insights into the impact of early intervention on development and quality of life.

CONCLUSION

The average age of ASD diagnosis in this study was 44 months, with language delay serving as a common initial concern among parents. Regular attendance in well-child clinics that offer ASD screening, higher family income, and higher levels of parental education were associated with earlier ASD diagnosis. In contrast, concerns regarding hyperactivity and the presence of GDD/ID often led to delayed ASD assessments.

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Conflict of Interest

The authors declare that they have no conflict of interest.

Author Contributions

All authors approved the final article. The authors were involved with the study: SC: Conceptualization, Methodology, Investigation and data collection, Writing-Original draft. TA: Investigation and data collection. PW: Writing-Review and editing.

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The Correlation between Small Placental Volume Measured by Three-dimensional Ultrasonography and Adverse Pregnancy Outcomes: An Observational Study

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ABSTRACT

Objective: The placenta is a vital organ in the growth and development of fetuses within the uterus. The size of the placenta is positively associated with fetal well-being. The aim of this study was to investigate any potential correlation between placental volume and negative pregnancy outcomes.

Materials and Methods: This prospective cohort study was conducted at the department of obstetrics and gynecology, Bhumibol Adulyadej Hospital, Thailand between October 2023 and February 2024. Subjects were singleton pregnant women ever the age of 18 without underlying diseases, namely: diabetes mellitus, hypertension, and autoimmune diseases. Ultrasonography was performed between the gestational ages of 28 and 36 weeks. Placental volume was measured via 3-dimensional ultrasonography and analyzed with maternal and neonatal outcomes.

Results: A total of 132 participants were recruited. The mean age of participants was 28.6 years old. The abnormal (AV) and normal (NV) placental volume groups consisted of 14 and 118 cases, respectively. The AV group was older, with higher parity, cesarean delivery rate, and estimated blood loss. This group's newborns had lower Apgar scores rated at 1 and 5 minutes and more neonatal complications than the NV group (with statistical significance). Maternal age exceeding 34 years could also be used to predict abnormal placental volume with sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) at percentages of 57.1, 81.4, 26.7 and 94.1, respectively.

Conclusion: There is a correlation between placental volume abnormality and certainly adverse outcomes for newborns. Maternal age greater than 34 is associated with higher occurrence of placental volume abnormality.

Keywords: Placental volume; 3DUS; adverse pregnancy outcomes (Siriraj Med J 2024; 76: 595-603)

INTRODUCTION

The placenta is the most important organ of the fetus which undergoes significant changes throughout pregnancy.[1,2] It plays a major role in fetal growth and continuity of pregnancy by ways of nutrients and oxygen transferred through the placental circulation.[3,4] Any impairment in placental development and deficiency of its function can be an important cause of adverse pregnancy and fetal outcomes.[5] Low oxygen concentration in maternal circulation signals for the development of new vessels, and the enlargement of the placenta.[6] Placental growth and development are typically correlated with

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measures such as placental weight and volume. Many factors such as race, smoking, previous medical problems, pre-pregnancy body mass indexes (BMI), and total weight gain were associated with placental volumes.[7] The result of placental weight to newborn's birth weight ratio was defined as placental to birth weight ratio (PFR). It is widely recognized as an important indicator of placental function.[8]

Previous studies found that abnormal placental volume (PV) was linked to adverse pregnancy outcomes (APO) such as preeclampsia with severe features, fetal growth restriction (FGR), preterm delivery, abnormal fetal testing, respiratory distress syndrome, 5-min Apgar < 7, neonatal intensive care unit (NICU) admission, and stillbirth.[9,10] These negative outcomes were more likely in pregnant women with prior medical conditions, namely diabetes mellitus, chronic hypertension, certain infectious diseases, smoke, lower education and socioeconomic status.[11] The placental volume measurements have been incorporated into the assessment of pregnancy risk for APOs to improve specificity of prediction and reduced neonatal morbidity.[9]

Ultrasound is the prevalent imaging modality to study the placenta in clinical settings. It can be provided with low cost and broad availability.[12] There was a report of a weak association between two-dimensional ultrasonography (2DUS) and perinatal outcomes.[13] Quantitative evaluations of three-dimensional ultrasonography (3DUS) were used to evaluate placental volumes.[14] This practice has not yet been incorporated into routine clinical care. These new releases of 3DUS technology have been useful tools for enabling quality imaging to reach the prenatal prediction and future planning for obstetrician to follow antenatal care and for pediatricians to have high awareness of neonatal complications and post-delivery planning for each patient.[15,16]

There were limited reports on whether or not 3DUS placental volumes, in association with neonatal complications, might be used to determine appropriate the risk modification through changes in antenatal care (ANC).[17,18] This study aimed to examine the correlation between placental volume measured by 3DUS and perinatal outcomes in pregnant women who came for routine ultrasound protocol at the gestational age between 28 and 36 weeks. For helping obstetricians and pediatricians to predict the perinatal outcomes and to improve antenatal care.

MATERIALS AND METHODS

This investigation was conducted as a prospective cohort study. The Ethics Committee of Bhumibol Adulyadej Hospital (BAH) institutional review board (IRB72/66) approved the study. The associated registration number can be found on the Thai clinical trial website (www.thaiclinicaltrials.org): TCTR20230908005.

Enrollment

Pregnant women who attended ultrasound sessions at the Department of Obstetrics and Gynecology, BAH, Bangkok Thailand in their third trimester antenatal care between October 2023 and February 2024 were recruited. Inclusion criteria were singleton pregnant women, aged 18 and older, who attended antenatal care at BAH, 28 to 36 weeks of gestation, and no underlying medical conditions, including Human Immunodeficiency Virus (HIV) infection, pregestational hypertension, pregestational diabetes mellitus, and systemic lupus erythematosus (SLE). Exclusion criteria included subjects who received no antenatal care (ANC), inability to communicate in Thai language, and incomplete medical data. All participants received briefings about the investigation and signed the informed consent. Demographic data collected from each participant including maternal age, body mass index (BMI), prior medical conditions (e.g., hypertensive disorders, thalassemia, SLE, pregestational diabetes), parity, gestational weight gain, gestational age at the day of delivery, route of delivery, estimated blood loss, other maternal and neonatal complications. The flow chart of the study is presented in Fig 1.

3DUS measurement

Participants came for their ultrasonography at antenatal care during the third trimester. During the routine ultrasound session for monitoring fetal growth, experienced MFM fellows and obstetric staff also measured placental dimensions using three-dimensional ultrasound probes and recorded images of the placenta. The ultrasound device used in this current study was the Voluson E10 ultrasound machine (GE Healthcare, WI, USA). The three-dimensional probe was equipped with a 4- to 8-MHz transducer. The measurement procedure was done in two steps, to collect placental images and to calculate placental volumes. Inter- and intra-observer agreement were calibrated and reported reliability at level of 0.9 and 0.95, respectively.

We used 2DUS to identify the longest view of the placenta and adjusted the volume box to scan the placental volume.[10] However, the placental images that could not be seen entirely were excluded. The 3D placental sonography was then transferred to a computer graphics program using the ViewPoint 6 (3-dimensional Sonoview, GE Healthcare, WI, USA) configuration program. First,

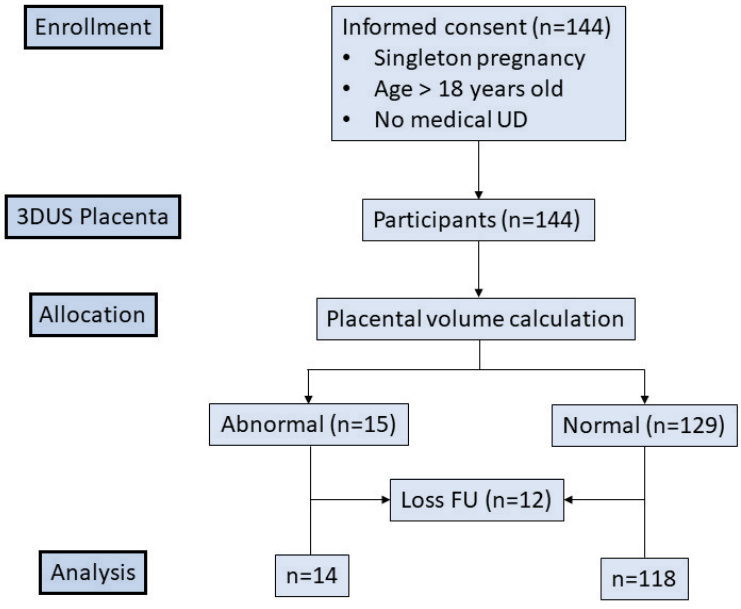

Fig 1. Flow chart of study.
Abbreviations: UD: underlying diseases, 3DUS: 3-dimensional ultrasonography, Abnormal: abnormal placental volume (<10 percentile), Normal: normal placental volume (between 10 and 90 percentile)

the reference image was chosen on the three orthogonal sections on the A plane. Second, the image that we used as a reference, which consists of outlining repeated contours of the placenta, was rotated six times by 30 degrees. These measurements were then analyzed using the VOCAL software (3-dimensional Sonoview; GE Healthcare, WI, USA), employing a rational technique to obtain accurate placental dimensions. After finishing the completed rotation, the total placental volume was automatically calculated as presented in Fig 2. For each participant, the single operator measured the placental dimension two times and the mean volume was calculated. The operator was blinded from the other measurements to ensure unbiased and accurate results. The placental dimension from both sonographs was calculated to placental volume and recorded. Abnormal placental volume was defined

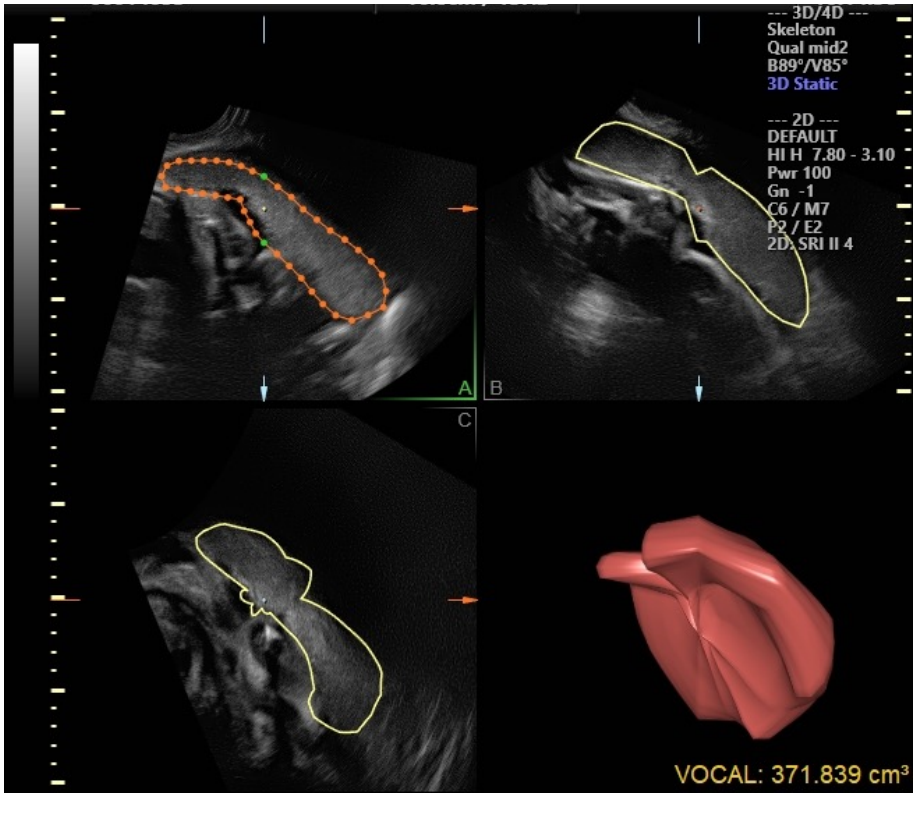

Fig 2. An example of placental volume measurement obtained using the virtual organ computer-aided analysis (VOCAL) method. The rendered image of the volume is shown in the right lower panel.

as the placental volume that less than 10 percentiles of normal range. After all subjects' newborns had been delivered either naturally or by obstetric indication, maternal and neonatal data were collected. It included GA at delivery (in weeks), absolute gestational weight gain, neonatal birth weight and the presence of some complications during maternal intrapartum and adverse perinatal outcomes.

Statistical analysis

The data was processed by using the SPSS version 18.0 (SPSS Inc, Chicago, IL, USA) programs. Continuous and category variables were analyzed and expressed as mean and standard deviation. Independent t-test or Chi-square tests were used for analyzing the category variables. The univariate logistic regression was used to evaluate the correlation between placental volume and clinical factors. Receiver operating characteristic (ROC) curve was used for evaluating the maternal age of the appropriate cut-off point. The correlation between placental volume measured by 3DUS and adverse pregnancy outcomes was considered. A p-value less than 0.05 was classified statistically significant.

RESULTS

A total of 132 participants were recruited during the period of study. There were 14 and 118 cases in abnormal (AV) and normal (NV) placental volume groups, respectively. The AV group refers to a group where members' placental volume was below the 10th percentile for their gestational age at the measured day as assessed by 3DUS.[2]

The mean age of participants was around 28.6 years old. Subjects in the AV group were statistically older than the NV group (32.6 and 28.1 years old). One-third (43/132) of subjects were nulliparous. Most subjects (120/132) delivered at GA for more than 37 weeks. Two-thirds (85/132) gave birth by vaginal delivery. The AV group had higher parity, higher cesarean delivery rate, higher estimated blood loss, babies with lower Apgar scores rated at one and five minutes, and higher neonatal complications than the NV group with statistical significance as shown in Table 1. Both groups had comparable weight gain, pre-pregnancy BMI, maternal consequences, NICU admission, low Apgar score rate, respiratory distress syndrome, fetal growth restriction, and oligohydramnios rate.

The ROC curve of maternal age was generated to predict an abnormal placental volume as shown in Fig 3. It gave sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) at percentages of 57.1, 81.4, 26.7, and 94.1, respectively. For the secondary outcome, the univariate logistical regression and multivariate analysis of abnormal placental volumes and clinical factors (maternal and neonatal) was presented in Table 2. A maternal age exceeding 34 years was the only significant maternal factor for abnormal placental volumes.

According to Table 2, those with a maternal age greater than 34 years old, cesarean delivery, or blood loss of more than 0.5 liters significantly had a 5.82-, 3.79-, and 3.46- times chance of placental volume abnormality versus others in the same categories. Participants below the age of 34 and those with babies with low Apgar score at 1 min with respiratory complications had 9.67- and 65-times higher risk of placental volume abnormality than the control groups respectively. Parity, gestational age at birth, total weight gain, pre-pregnancy BMI, maternal underlying disease, FGR, and NICU admission showed no association with abnormal placental volume.

DISCUSSION

Placental volume indicates intrauterine fetal health.[19] Measurement of placental thickness and calculated volume using 2DUS requires more experienced sonographers. This technology 3DUS has enabled the quantification of placental volume measurement more precisely. The computerized aids helped entirely level sonographers to perform accurate measurements for general obstetrician hands.[13]

The current study was conducted in singleton pregnancy during the early third trimester (28-36 weeks). The previous studies (according to Table 3) of PV measurements were performed during 7 and 14 weeks.[1,3,5,10,11] There were many changes from several factors throughout pregnancy. PV measurements in the first trimester might be too long a waiting period to be used for predicting obstetric outcomes in the next 6 months. For these reasons, we conducted this investigation to evaluate placental volumes at near-term.

Naturally, placental volumes vary by gestational age.[2] Abnormal placental volume in the current study occurred in older participants and had higher parity than those in the normal placental volume group. Around two-thirds of subjects from Reijnders', Soongsatitanon's, González's, and Farina's reports were nulliparous, and the mean maternal age of their study ranged from 30.4 to 32.8 years old. While one-third of Quant's and the present study were nulliparous. The mean age of Quant's and the present study were 31 and 28.6 years old, respectively. Maternal consequences (GDM, GHT) of participants in Quant's and the present were around 20 percent. Subjects

TABLE 1. Demographic character of singleton pregnancy with normal (n=118) and abnormal (n=14) placental volume.

	Placental volume			*p*-value
	Total	Abnormal	Normal	
Age (years) **	28.6 ± 5.9	32.6 ± 4.9	28.1 ± 5.8	*0.005*
Nulliparity *	43 (32.6)	1 (7.1)	42 (35.6)	*0.032*
Term at birth *	120 (90.9)	13 (92.9)	107 (90.7)	*0.316*
Normal delivery *	85 (64.4)	5 (35.7)	80 (67.8)	*0.018*
EBL (ml) **	317.8 ± 186	421.4 ± 184.7	305.5 ± 183	*0.027*
Normal TWG *	54 (40.9)	5 (35.7)	49 (41.5)	*0.676*
PrP BMI *				*0.059*
Underweight	23 (17.4)	0 (0)	23 (19.5)	
Normal	62 (47)	7 (50)	55 (46.6)	
Overweight	33 (25)	4 (28.6)	29 (24.6)	
Obesity	14 (10.6)	3 (21.4)	11 (9.3)	
MC *				*0.056*
No	102 (77.3)	8 (57.2)	94 (79.7)	
GDM	20 (15.2)	3 (21.4)	17 (14.4)	
GHT	8 (6.1)	3 (21.4)	5 (4.2)	
Others	2 (1.5)	0 (0)	2 (1.7)	
NICU *	7 (5.3)	1 (7.1)	6 (5.1)	*0.745*
Low Apgar *				
1 min	4 (3)	2 (14.3)	2 (1.7)	*0.009*
5 min	1 (0.8)	1 (7.1)	0 (0)	*0.004*
RDS *	6 (4.5)	5 (35.7)	1 (0.8)	*<0.001*
FGR *	7 (5.3)	1 (7.1)	6 (5.1)	*0.745*
Oligo *	10 (7.6)	1 (7.1)	9 (7.6)	*0.948*

*: n (%), **: mean ± standard deviation

Abbreviations: GA: gestational age, EBL: estimated blood loss, TWG: total weight gain, PrP BMI: pre-pregnancy body mass index (kg/m^2), Underweight: BMI < 18.5 kg/m^2, Normal: BMI 18.5–24.9 kg/m^2, Overweight: BMI 25-29.9 kg/m^2, Obesity: BMI ≥30 kg/m^2), MC: maternal consequence, GDM: gestational diabetes mellitus, GHT: gestational hypertension, Others: infectious disease, NICU: neonatal intensive care unit, RDS: respiratory distress syndrome, FGR: fetal growth restriction, Oligo: oligohydramnios

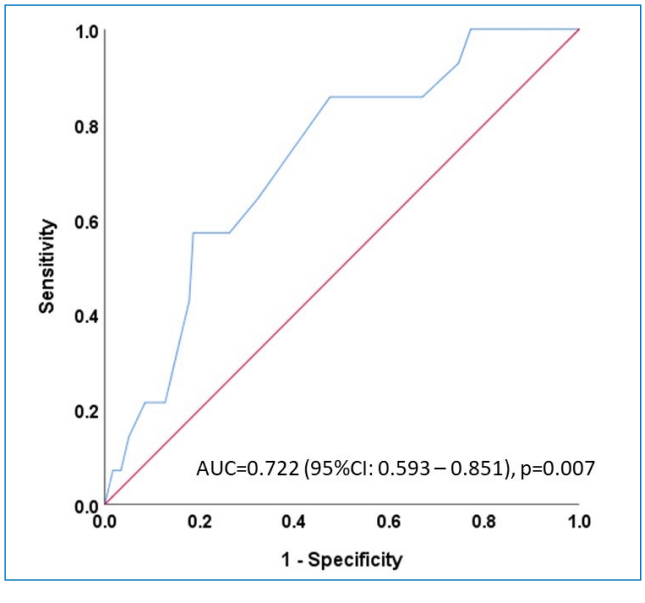

Fig 3. Receiver operating characteristic (ROC) curve of maternal age for prediction of abnormal placental volume (PV).
Abbreviations: AUC: area under curve, CI: confidence interval

TABLE 2. Univariate and multivariate logistic regression for placenta volume abnormality.

	Univariate		Multivariate	
	OR (95%CI)	*p*-value	OR (95%CI)	*p*-value
Ages				
< 34	Ref	*1*		
≥ 34	5.82 (1.83, 18.48)	*0.003*	5.96 (1.35, 26.36)	*0.019*
Gravida				
Primi	Ref	*1*		
Multi	7.18 (0.91, 56.85)	*0.062*		
GA at birth (weeks)				
≥ 37	Ref	*1*		
< 37	1.34 (0.16, 11.21)	*0.789*		
Route				
Vagina	Ref	*1*		
Cesarean	3.79 (1.19, 12.08)	*0.024*	4.31 (0.74, 25.16)	*0.104*
EBL (ml)				
< 500	Ref			
≥ 500	3.46 (1.09,11.04)	*0.036*	1.15 (0.2, 6.67)	*0.878*
Oligo	0.93 (0.11, 7.95)	*0.948*		
TWG				
Normal	Ref	*1*		
Abnormal	1.28 (0.4, 4.05)	*0.676*		
PrP BMI				
Normal	Ref	*1*		
Overweight	1.08 (0.29, 4.01)	*0.904*		
Obesity	2.14 (0.48, 9.6)	*0.319*		
MC				
No	Ref	*1*		
GDM	2.07 (0.5, 8.61)	*0.315*	1.94 (0.35, 10.75)	*0.45*
GHT	7.05 (1.42, 35.03)	*0.017*	1.26 (0.07, 23.81)	*0.877*
FGR	1.44 (0.16, 12.88)	*0.746*		
NICU	1.44 (0.16, 12.88)	*0.746*		
Low Apgar 1 min	9.67 (1.25, 74.95)	*0.03*	0 (0, 1.1)	*0.999*
RDS	65 (6.84, 617.65)	*<0.001*	1.01 (0, 1.1)	*0.999*

Abbreviations: OR: odd ratio, GA: gestational age. EBL: estimated blood loss, Oligo: oligohydramnios, TWG: total weight gain, PrP BMI: pre-pregnancy body mass index (kg/m^2), Underweight: BMI < 18.5 kg/m^2, Normal: BMI 18.5–24.9 kg/m^2, Overweight: BMI 25-29.9 kg/m^2, Obesity: BMI ≥30 kg/m^2, MC: maternal consequence, GDM: gestational diabetes mellitus, GHT: gestational hypertension, Others: infectious disease, FGR: fetal growth restriction, NICU: neonatal intensive care unit, RDS: respiratory distress syndrome

TABLE 3. Comparison adverse pregnancy outcome related to placental volume measuring by 3DUS from various studies

Authors	Present	Schwartz	Reijnders	Soongsatitanon	González	Quant	Farina
Years	2024	2022	2021	2019	2017	2016	2016
Country	Thailand	USA	Netherlands	Thailand	Spain	USA	Italy
Cases (n)	132	422	214	360	988	373	5019
Nulliparity	32.6	17.9	53.7	63.1	63.7	35.8	52.3
GA (weeks)	28-36	11-14	7-11	11-14	11-14	18-24	11-14
Age (years)*	28.6	30.5	32.1	32.8	30.4	31	30.6
BMI (kg/m^2) *	23.4	26.7	24.9	21.5	26.4	22.9	
MC							
No	77.3						
GDM	15.2	2.3			1.6		
GHT	6.1	6.3	4.2		2.6	21.6	
Others	1.4		25.7***				
Prediction	AE	SGA	AE	PrE, FGR	FGR	PrE, SGA	SGA
AE**							
NICU	5.3						
LA1min	3			1.4			
LA5min	0.8			1.1	8.79*		
RDS	4.5			1.1			
FGR	5.3	12.5	7.0	4.7	19.5	10.7	6.23
Preterm	9.1		10.7	35.3	271.5		
PrE**			3.3	2.8		7.2	
Oligo**	7.6						
C/S**	35.6			58.8	21.8		
EBL (ml)*	317.8						

*mean, **n (%), ***Any placental-related complications

Abbreviations: GA: gestational age, 2D: two dimension, 3D: three dimension, GA: gestational age, BMI: body mass index (kg/m2), MC: maternal consequence, Others: infectious disease and others specified as any placenta-related complication, GDM: gestational diabetes mellitus, GHT: gestational hypertension, AE: adverse neonatal event, PrE: preeclampsia, NICU: neonatal intensive care unit, LA1min: low Apgar <7 at 1 min, LA5min: low Apgar <7 at 5 min, RDS: respiratory distress syndrome, FGR: fetal growth restriction, Oligo: Oligohydramnios, C/S: cesarean delivery, EBL: estimate blood loss (ml)

in Reijnders from the Netherlands reported other placental-related pregnancy complications and hypertension were 25.7 and 4.2 percent, respectively. Participants in the current study, Reijnders, and Quant showed 20 percent of complications that affected placental vasculatures. These diseases, namely DM and HT, diminish blood supply to the placenta, leading to decrease in placental size.[20] Low placental volume was strongly correlated to FGR.[1,5,10,11]

Results of the current study supported reports from Schwartz, Reijnders, Soongsatitanon, González, Quant and Farina that small placental volume could be used to predict for small gestational age (SGA) at delivery.[21] Additionally, the study of Soongsatitanon had reported the low placental volume correlated with low Apgar scores at 1 and 5 minutes and neonatal respiratory complications. From the current study, the placental size

which consisted of abnormal placental volumes (<10th percentile of normal range) could be used to predict adverse events (AE), namely FGR, NICU admission, low Apgar scores at 1 and 5 minutes, and obstetric complications (route of delivery and blood loss). We supported that small placental volumes could be used to predict AE, neonatal respiratory, and obstetric complications.

The present study found that the placental volume measurement using 3DUS in the third trimester was a reliable predictor of neonatal birth weight and neonatal outcomes such as low Apgar and respiratory complications. Compared to previous works of Reijnders, Soongsatitanon, and Quant that were conducted during the first and second trimesters, small placental volume was found in which trimester could be used to predict only SGA or preeclampsia. Nevertheless, there were no preeclampsia cases among all participants in our investigation. The reason might be an effect of the prophylaxis prescription of preeclampsia (low-dose aspirin) given to all our participants.[22] The absence of preeclampsia cases led to the inability of the current study to suggest preeclampsia prediction.

In Conclusion, placental volume measurement by 3DUS during the third trimester could be used to predict low Apgar scores and neonatal respiratory complications at delivery period. Abnormal placental volume (<10th percentile of normal range) might be the important warning for obstetricians and pediatricians to be awareness of neonatal complications (birth asphyxia and RDS).

3DUS measurements in the third trimester by experienced MFM fellows and obstetric staff were the strength of this study. The loss of participants to follow up and insufficient equipment were unavoidable and possible limitations of this study. However, placental volume measurement might be interfered by placental site and fetal position. This might be another limitation of the current study. We recommend to perform additional placental volume measurements (3DUS) during the third trimester in all subjects, especially participants who are more than 34 years old for predicting and preparing the possibly adverse events at the time of delivery.

CONCLUSION

Placental volume abnormality increased risk of low Apgar score (OR 9.7) and neonatal respiratory complication (OR 65). Maternal age over 34 years old was associated with placental volume abnormality.

What is already known on this topic?

The placenta is a vital organ for intrauterine development of the fetus. Placental growth and development are typically represented by its weight and volume. Abnormal PV has been linked to obstetric, neonatal and intrapartum complications. Traditionally placental volume is measured using 2DUS during the first and second trimesters of pregnancy. However, with the introduction of 3DUS technology and advanced calculation software, this method has been significantly improved. The shift from 2DUS to 3DUS in measuring placental volume represents a significant advancement in prenatal care.

What does this study add?

Placental volume measurement by 3DUS in the third trimester could predict RDS and birth asphyxia. We recommended the placental volume measurement by 3DUS, especially in parturients older than 34 in the third trimester.

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Conflict of Interest

The author declares no conflict of interest.

Institutional Review Board Statement

This retrospective review has been approved by the local Institutional Review board (reference number: 72/66).

Informed Consent Statement

Permission of all figures was obtained from the patients.

Author Contributions

P.T. conceived of the presented idea and developed the material and methods. K.S. ensured and verified the analytical methods. P.T. and S.M. wrote the manuscript with support from K.B. to investigate formal writing language. N.O. supervised the findings of this work. All authors discussed the results and contributed to the final manuscript.

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Perception and Attitude towards Electronic Cigarettes among Rural Thai Young Adults

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ABSTRACT

Objective: This study examined perceptions and attitudes toward electronic cigarettes (e-cigarettes) among young adults aged 15-20 years in Samut Songkhram Province, Thailand, and their relationship.

Materials and Methods: A descriptive cross-sectional study was conducted between July and October 2023. The study included 328 young adults aged 15-20 selected from an educational institution in Samut Songkhram Province using simple random sampling. Data were collected using a self-administered questionnaire and analyzed using descriptive statistics and Pearson's correlation coefficient.

Results: The participants had a good level of knowledge about e-cigarettes. They exhibited a positive attitude towards electronic cigarettes regarding health aspects (M=3.05, SD=0.97) and a positive attitude towards the legal dimensions of e-cigarettes (M=3.12, SD=0.80). However, no statistically significant correlation was found between the perception of e-cigarettes and health-related attitudes toward them (r=0.013, p=0.820). On the other hand, there was a statistically significant positive correlation between the perception of e-cigarettes and legally oriented attitudes (r=0.192, p<0.001). Furthermore, a borderline positive correlation emerged between the perception of electronic cigarettes and the general attitudes toward them (r=0.102, p=0.065).

Conclusion: Young adults in rural Thailand have a good knowledge of e-cigarettes. However, they exhibit positive attitudes towards the health aspects and legal dimensions of e-cigarettes. Moreover, no significant relationship exists between perceptions and health-related attitudes. These insights emphasize the need for targeted strategies to address misperceptions and raise awareness about the health risks of e-cigarette use among rural youth.

Keywords: Attitude; electronic cigarette; perception; young adults (Siriraj Med J 2024; 76: 604-610)

INTRODUCTION

Electronic cigarettes (e-cigarettes) pose significant health risks and can have undesirable consequences, particularly among adolescents. Classified as a new form of electronic tobacco product, e-cigarettes have gained widespread popularity in the last decade.[1] Currently, there is an alarming upward trend in e-cigarette usage among youth in North America and Europe. In the United States, the prevalence of e-cigarette use within the past 30 days among high school students has risen from 1.5% in 2011 to a staggering 20.8% in 2018.[2] The situation is equally concerning in Mexico, where the prevalence of e-cigarette use reached a high of 22% in a sample of middle school students. According to US statistics, the number of e-cigarette consumers has doubled annually since 2008, reflecting the product's sustained popularity as a trendy device promoted for smoking cessation, often as an alternative to traditional nicotine replacement therapies such as snuff and patches.[3] Thailand has also witnessed a concerning rise, with university students exhibiting a 22.2% prevalence of e-cigarette use.[4]

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In Thailand, e-cigarettes have gained widespread popularity, particularly among adolescents, fueled by the misconception that they are nicotine-free, harmless to users and bystanders, and non-addictive. According to a 2021 report by the Tobacco Control Research and Knowledge Management Center (TRC), the number of Thai users of electronic cigarettes grew to 78,742, representing 0.14% of the population aged 15 and over, out of a total of 57 million people in this age group. Of these users, 40,724 smoked e-cigarettes daily, while 38,018 used them intermittently. Alarmingly, 24,050 users of e-cigarettes were between the ages of 15-24, with the majority concentrated in Bangkok and the central region (47,753 users).[4,5] Surprisingly, while 26.7% of Thais who knew about e-cigarettes believed they were more hazardous than conventional cigarettes, 11.3% considered them less dangerous, and 62.0% perceived both products as equally harmful. These figures are derived from the 2021 Health Behavior Survey, which collected data from 73,654 households nationwide, encompassing a sample of 164,406 individuals.[5]

To shed light on this alarming trend, the 2021 Thai Youth Survey in Educational Institutions investigated e-cigarette use among the high-risk age group of 15-24 years in various educational levels, surveying 12,948 participants throughout the country. The findings revealed significant regional variations, with the northern region showing the highest prevalence of 4.6%, followed by Bangkok and its vicinity (4.1%), the northeastern region (3.6%), the central region (2.3%), and the southern region (2.2%). When stratified by education level, university students exhibited the highest prevalence (4.6%), followed by vocational education students (4.2%), while high school students had a lower rate (1.6%).[5,6] In particular, the proportion of women using e-cigarettes increased by a concerning 3.6-fold compared to previous levels. A significant risk factor identified was frequent exposure to social media content that promotes the use of e-cigarettes, with those who access this content almost daily having a 3.7% probability of using e-cigarettes themselves, a remarkable 7.7 times higher probability than non-viewers.[6] Personal factors, perceptions and attitudes toward cigarettes, access to cigarettes, and legal knowledge were found to have an impact on smoking behavior.[7]

The report summarizing the performance of the Department of Disease Control revealed that Nakhon Pathom Province had an e-cigarette use rate of 11.24%, Ratchaburi Province had a rate of 9.61%, and Samut Songkhram Province had a rate of 7.76% among the public health office provinces in region 5. Focusing specifically on Samut Songkhram Province, which is the area of this study, 2020 statistics highlighted an overall prevalence of smoking of 7.76% among people aged 15 and over, with the highest rate of 16.03% observed in Muang Samut Songkhram District.[8] The increasing prevalence of e-cigarette use among Thai youth, particularly in the central region where Samut Songkhram Province is located, together with conflicting beliefs about their role in smoking cessation, underscores the need for further research. Therefore, this study aims to examine perceptions and attitudes toward electronic cigarettes among young adults in the rural community of Samut Songkhram province and to explore the relationship between these factors.

MATERIALS AND METHODS

Study design and population

This descriptive cross-sectional study investigated perceptions and attitudes toward electronic cigarettes among young adults in Samut Songkhram Province. Data collection was carried out between July and October 2023.

The study population consisted of young adults studying at an educational institution in Samut Songkhram Province, totaling 2,602 individuals. The sample size was determined using Krejcie and Morgan's formula[10], resulting in a required sample of 328 participants. Simple random sampling was used for participant recruitment. The inclusion criteria were young adults aged 15-20 years, currently enrolled in the selected educational institution in Samut Songkhram province, capable of communicating and completing the questionnaire comprehensively and providing informed assent/consent. Parental consent was also obtained for participants under 18 years old. The exclusion criteria were individuals who felt uncomfortable or distressed when answering the questionnaire and those with mental health issues.

Data collection

Data were collected using a self-administered questionnaire distributed through Google Form between July and October 2023. The researchers conducted briefing sessions with participants to explain the questionnaire completion process, provide details on response methods, and obtain informed consent. Participants were given 20-30 minutes to complete the questionnaire, and researchers ensured that the required sample size was achieved.

Measurements

The questionnaire was developed based on a review of the literature on young adults' perceptions and attitudes towards e-cigarettes. It comprised three sections:

1. General information: This section included questions about personal details such as sex, age, educational level, smoking status of the e-cigarette, and the status of parental use of e-cigarettes.

2. Perception of e-cigarettes: The perception of e-cigarettes refers to the beliefs, awareness, and understanding of the effects and risks associated with e-cigarette use. The perception of e-cigarettes was evaluated through a closed-ended 10-item questionnaire adapted from previous studies.[11] Respondents used a 5-point Likert scale, ranging from 'strongly agree' to 'strongly disagree', to indicate their level of agreement with statements related to the dangers, addictiveness, health impacts and other properties of e-cigarettes. A higher score indicates a more accurate and comprehensive perception aligning with established facts about the harms of e-cigarettes. The mean scores were classified as follows: 4.21-5.00 = highest perception, 3.41-4.20 = high perception, 2.61-3.40 = moderate perception, 1.81-2.60 = low perception, and 1.00-1.80 = lowest perception. These perception levels were further grouped into good (arithmetic mean 3.41-5.00), moderate (arithmetic mean 2.61-3.40), and low (arithmetic mean 1.00-2.60) for analysis purposes. The validity of the content of this questionnaire was verified by three e-cigarette research experts, resulting in an Item Objective Congruence (IOC) score of 0.93. A pilot test with 20 individuals similar to the sample group evaluated the reliability of the questionnaire, yielding a Cronbach alpha value of 0.91.

3. Attitudes toward e-cigarettes: Attitude refers to the favorable or unfavorable evaluations, feelings, and tendencies towards e-cigarettes. This questionnaire, adapted from previous research[7,11], consisted of 10 closed-ended questions rated on a 5-point Likert scale from "strongly agree" to "strongly disagree." The questions were divided into two domains:

Legal (5 questions, e.g., "I find it inappropriate that possessing and using e-cigarettes in Thailand is illegal") – this measures attitudes towards the legal status and regulations around e-cigarettes. A higher score indicates a more positive attitude towards making e-cigarettes legally accessible.

Health (5 questions, e.g., "I believe e-cigarettes allow control over nicotine concentration, making them less harmful to health") – this measures attitudes towards the perceived health impacts of e-cigarettes. A higher score suggests a more positive attitude towards e-cigarettes being less harmful than combustible cigarettes.

The arithmetic mean scores were interpreted as follows: 4.21-5.00 = the most positive attitude, 3.41-4.20 = positive attitude, 2.61-3.40 = neutral attitude, 1.81-2.60 = negative attitude, and 1.00-1.80 = most negative attitude. The attitudes were further classified into positive (arithmetic mean 2.61-5.00) and negative (arithmetic mean 1.00-2.60). The content validity was evaluated by three experts in e-cigarette research, achieving an index of item objective congruence (IOC) score of 0.86. A pilot test was conducted with 20 individuals similar to the sample group and reliability was tested using Cronbach's alpha, yielding a value of 0.94.

Statistical analyses

Data analysis was performed using SPSS software. Descriptive statistics, including frequency, percentage, median, arithmetic mean (M), and standard deviation (SD), were used to analyze the general characteristics of the sample. Pearson's product-moment correlation coefficient was employed to examine the relationship between perceptions and attitudes toward e-cigarettes among young adults.

Ethical Considerations

This study received ethical approval from the Research and Development Institute of Suan Sunandha Rajabhat University (COA.1-34/2023).

RESULTS

The sample consisted of 328 young adults residing in Samut Songkhram Province. The majority were male (68.9%), with a mean age of 17 (SD = 1.38). Most of the participants (64.6%) studied at the vocational certificate level. The majority (81.4%) did not smoke e-cigarettes, and most (80.8%) reported that family members did not smoke e-cigarettes. However, 69.5% had friends who smoked e-cigarettes (Table 1).

Regarding perceptions of e-cigarettes, the overall level of perception between the sample was good (M = 3.63, SD 0.73). The specific ratings for each perception item are shown in Table 2.

Regarding attitudes towards e-cigarettes, the sample exhibited a positive attitude toward the health aspects of e-cigarettes (M = 3.05, SD 0.97) and a positive attitude towards the legal aspects of e-cigarettes (M = 3.12, SD 0.80) (Table 3).

Analysis of young adults' perceptions and attitudes toward electronic cigarettes revealed no statistically significant negative correlation between perceptions of electronic cigarettes and health-related attitudes ($r = 0.013$, $p = 0.820$). However, there was a significant positive correlation between perceptions of electronic cigarettes and attitudes about legality ($r = 0.192$, $p < 0.001$). In general, although there was a positive correlation

TABLE 1. Demographic variables of the participants. (n=328).

Demographic Variables	N (%)
Gender	
Male	226(68.9)
Female	102 (31.1)
Age (years) [Mean±SD]	17.69±1.38
Education	
Vocational Certificate	212 (64.6)
Diploma/High vocational Certificate	110 (33.5)
Bachelor's degree	6(1.9)
Smoking electronic cigarettes	
Smoking	61(18.6)
Stop smoking	267 (81.4)
There is someone in the family who smokes electronic cigarettes.	
Yes	63(19.2)
No	265(80.8)
I have a friend who smokes electronic cigarettes.	
Yes	228(69.5)
No	100(30.5)

TABLE 2. Level of Perception towards e-cigarette in participants (n=328).

Variables	Mean	S.D.	Level
E-cigarettes are considered a new type of drug and contain toxins that are more dangerous than cigarettes	3.68	1.08	Good
E-cigarettes are as dangerous as heroin and cocaine	3.33	1.17	Moderate
E-cigarette smoke is harmful to people around you and can cause heart disease and blood pressure	3.75	1.05	Good
E-cigarettes can cause serious diseases such as cancer, emphysema, heart disease, etc	3.81	1.09	Good
E-cigarettes are causing more problems for new young smokers	4.21	0.93	Good
Smoking an e-cigarette is equivalent to smoking 15 regular cigarettes and contains more nicotine than traditional cigarettes	3.44	1.09	Good
E-cigarettes contain ingredients that are harmful to the body, such as heavy metals and arsenic	3.48	1.07	Good
The long-term effects of rolled cigarettes are more dangerous than e-cigarettes	3.82	0.97	Good
Nicotine is a substance that promotes relaxation	3.61	0.99	Good
Smoking e-cigarettes does not lead to cancer	3.12	1.26	Moderate
Overall Perception towards e-cigarette	3.63	0.73	Good

TABLE 3. Level of attitudes towards e-cigarettes in participants (n=328).

Variables	Mean	S.D.	Level
Overall attitudes towards e-cigarettes	3.08	0.82	Positive attitude
Health attitudes towards e-cigarettes	3.05	0.97	Positive attitude
Legal attitude towards e-cigarettes	3.12	0.80	Positive attitude

between perceptions and attitudes about e-cigarettes, it did not reach statistical significance (r = 0.102, p = 0.065) (Table 4).

DISCUSSION

The finding that participants exhibited a good overall level of perception (M = 3.63, SD = 0.73) about e-cigarettes suggests they have an accurate understanding and awareness of the facts surrounding the dangers and health risks of e-cigarette use. This aligns with the increased dissemination of information about e-cigarette harms from governmental sources and health campaigns accessible to youth through various media channels, such as social media platforms like Facebook, TikTok, Line, and YouTube.[12] The behavioral pattern of mobile phone use among young adults also influences their perceptions of e-cigarettes.[12] This finding is consistent with previous research[11] suggesting that perception comprises three components: 1) selective attention, where individuals selectively attend to stimuli that align with their needs and attitudes; 2) organization, where individuals organize information from various sources into a coherent whole for better understanding and appropriate response; and 3) interpretation, the individual process of assigning meaning through thoughts, speech, and expression.[13] The most crucial principle of perceptual organization is that individuals interpret stimuli based on their beliefs, attitudes, and experiences, which shape their thoughts, speech, and behavior.[14]

However, this positive perception did not translate into negative attitudes towards e-cigarettes, as the participants exhibited a positive attitude towards both the health aspects (M=3.05, SD=0.97) and legal dimensions (M=3.12, SD=0.80) of e-cigarettes. This discrepancy between perception and attitude could be attributed to the influence of various communication technologies and information sources that promote positive attitudes towards e-cigarettes, including scientifically credible evidence and unsubstantiated opinions from certain groups.[13] Additionally, government dissemination methods may not be attractive enough to effectively communicate the dangers of e-cigarettes to late adolescents and young adults.[15] Furthermore, adolescence is characterized by a quest for peer acceptance and experimentation despite knowing the risks of smoking, which can contribute to more positive attitudes towards e-cigarettes.[16,17]

The lack of a statistically significant correlation between perceptions of e-cigarettes and general attitudes

TABLE 4. Relationship between perception and attitude towards electronic cigarettes in participants (n=328).

Variables	Perception toward electronic cigarette	
	Pearson Correlation (r)	p-value
Health attitudes towards e-cigarettes	0.013	0.820
Legal attitude towards e-cigarettes	0.192	<0.001*
Overall attitudes towards e-cigarettes	0.102	0.065

*p-value < .05

towards them (r = 0.102, p=0.065) aligns with previous research.[12,18] This can be explained by the varying individual perceptions and interpretations of stimuli, which contribute to diverse attitudes towards e-cigarettes.[12,19] Despite understanding potential health risks, adolescents may not immediately prioritize or perceive these consequences as concerning.[20]

However, the positive correlation between perceptions of e-cigarettes and legally oriented attitudes (r=0.192, p<0.001) suggests that individuals with a better understanding of e-cigarettes tend to have more positive attitudes toward their legal accessibility. This finding highlights the need for robust legal frameworks and enforcement mechanisms to regulate e-cigarette use, particularly among vulnerable populations like rural youth.

Our results indicate an urgent need for multifaceted initiatives to educate rural Thai youth and reshape their positive attitudes toward e-cigarette health aspects and legality. Suggestions include developing engaging multimedia educational campaigns via youth's preferred channels, incorporating interactive peer-to-peer elements to counter misinformation, integrating e-cigarette education into school curricula with teacher/mentor involvement, and involving youth representatives in program design for sustained relevance. Coupling these initiatives with stricter regulations restricting youth e-cigarette access and marketing can create a coherent environment reinforcing negative attitudes. Periodic evaluations are crucial to adapt strategies based on evolving youth attitudes and behaviors.

A notable strength of this study is the use of validated questionnaires with good content validity and reliability to assess perceptions and attitudes toward e-cigarettes among the target population of rural Thai youth. Additionally, the decent sample size of 328 participants enhances the generalizability of the findings to similar rural settings. However, certain limitations should be acknowledged. First, the cross-sectional design precludes causal inferences about the relationships between perceptions, attitudes, and e-cigarette use behaviors over time. Longitudinal studies are warranted to establish temporality. Second, the study relied on self-reported data, which may be subject to social desirability or recall bias. Finally, the findings may have limited generalizability beyond the study's rural setting and age range of 15-20 years.

CONCLUSION

While young adults in rural Thailand have a good overall perception of the dangers of e-cigarettes, they exhibit positive attitudes towards both the health aspects and legal dimensions of e-cigarettes. In addition, there was no significant correlation between their perceptions of e-cigarette risks and health-related attitudes. These findings emphasize the need for a multifaceted strategy to address misperceptions, change attitudes, and prevent e-cigarette use among this vulnerable rural youth population.

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Conflict of Interest

The authors declare that they have no conflict of interest.

Author Contributions

All authors approved the final article. The authors were involved with the study: N S: Conceptualization, Methodology, Investigation and data collection, Writing-Original draft. P W: Conceptualization, Writing-Original draft, Writing-Review and editing. P L: Methodology, Investigation and data collection. WD: Methodology, Investigation and data collection. W K: Methodology, Investigation and data collection. S S: Methodology, Investigation and data collection. K S: Methodology, Investigation and data collection.

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The Performance of Peroral Endoscopic Myotomy in Sigmoid-Type Achalasia

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ABSTRACT

Objective: Sigmoid-type achalasia represents an advanced stage of achalasia characterized by significant dilation and tortuosity of the esophageal lumen. Considering the demonstrated efficacy of peroral endoscopic myotomy (POEM) in treating early-stage achalasia, this procedure may offer an alternative therapeutic approach for sigmoid-type achalasia. This study aimed to assess POEM's feasibility and short-term efficacy in patients with sigmoid-type achalasia.

Materials and Methods: We enrolled 16 consecutive patients with sigmoid-type achalasia (eight with type 1 and eight with type 2). The anticipated outcomes were symptom relief during the 12-month follow-up period (evaluated through a reduction in Eckardt symptom scores), an acceptable incidence of procedure-related adverse events, and a decrease in esophageal diameter and barium height.

Results: POEM was successfully performed in all cases, with a median operative time of 118.50 minutes (range: 52–206 minutes). No serious complications associated with POEM were observed. During the 12-month follow-up period, the median Eckardt symptom score decreased from 6 (2-10) preoperatively to 1 (0-3) ($P = 0.008$). Complications were mucosal injuries (31.25% of cases), pneumoperitoneum (12.5%), and minor bleeding (6.25%), although no interventions were needed.

Conclusion: POEM procedure has exhibited favorable treatment outcomes, showcasing a high clinical success rate in addressing sigmoid-type achalasia. Despite the occurrence of acceptable adverse events, the procedure remains a viable alternative treatment or bridging therapy for sigmoid-type achalasia. Nonetheless, it is crucial to acknowledge that this procedure presents greater challenges in comparison to the treatment of typical achalasia.

Keywords: POEM; achalasia; sigmoid achalasia (Siriraj Med J 2024; 76: 611-619)

INTRODUCTION

Achalasia, a primary esophageal motility disorder, is prevalent worldwide.[1] Sir Thomas Willis first described it in 1674, and Dr. Hertz formally named it in 1915.[2] Histologically, achalasia is characterized by the absence of Auerbach's nerve plexus, resulting in impaired esophageal peristalsis or insufficient lower esophageal sphincter relaxation. Although the etiology remains unclear, recent evidence suggests potential viral infection, autoimmune, and genetic causes.[3] The management of achalasia involves a spectrum of therapeutic modalities. Pharmacological interventions are utilized for patients deemed high-risk, who are unable to undergo procedural interventions. Endoscopic procedures, including botulinum toxin injection or pneumatic balloon dilatation, are offered to patients unable to tolerate the adverse effects of medications

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or general anesthesia. Nevertheless, these interventions often exhibit a notable incidence of early symptom recurrence, thus necessitating surgical intervention as a final recourse. Laparoscopic Heller myotomy with fundoplication stands as the definitive treatment for all presentations and severities of achalasia, contingent upon the patient's ability to withstand the procedural and anesthetic demands.[4] In 2010, Inoue introduced peroral endoscopic myotomy (POEM) for achalasia[5]; this procedure has since gained popularity worldwide due to its favorable outcomes code. In Thailand , POEM was initiated in 2013 supported by Thai Association for Gastrointestinal Endoscopy (TAGE).[6] Sigmoid-type achalasia signifies an advanced stage of the disease typically observed in cases with prolonged durations, often exceeding 10 years. Historically, esophagectomy has been a recourse for this condition; however, it is accompanied by notable morbidity and mortality rates. Presently, Heller myotomy stands as the established standard treatment, albeit recurrent symptoms remain common. POEM has demonstrated favorable outcomes in non-sigmoid achalasia, its efficacy in sigmoid-type achalasia is less substantiated due to limited data. Nevertheless, POEM presents a potential alternative therapeutic approach for sigmoid-type. This study aims to elucidate the treatment outcomes and associated complications of utilizing POEM as an alternative procedure for sigmoid-type achalasia.

MATERIALS AND METHODS

There are no absolute contraindications for POEM in patients diagnosed with achalasia, as it can be performed for all types of the condition. Sigmoid achalasia is diagnosed clinically with the aid of high-resolution manometry (HRM) or imaging studies. The study initially commenced as a retrospective investigation, involving the review of medical record data between 2014 and 2017. Subsequently, it transitioned into a prospective cohort study, continuing until 2022 under Institutional Review Board (IRB) approval, with strict adherence to the initial protocol. The enrollment criteria for patients were as follows: (1) being aged 18 years or older; (2) Having received a confirmed diagnosis of achalasia, which was based on clinical symptoms and further supported by diagnostic procedures such as EGD, BE, or HRM; (3) possessing a tortuous-shaped esophagus with or without a diameter exceeding 6 cm, as determined by an esophagogram or CT scan[7,8]; and (4) having undergone the POEM procedure between January 2014 and July 2022. Furthermore, patients with severe comorbidities rendering them unsuitable for peroral endoscopic myotomy (POEM) or anesthesia, those with malignant diseases, pseudo-achalasia, uncorrected coagulopathy, or those lacking adequate data for review, were excluded from the analysis.

The data were collected and analyzed in an anonymous format. Due to the cohort study nature of data collection and the impossibility of personal identification, signed patient consent forms were not necessary. This research received approval from the Siriraj Institutional Review Board (IRB) under protocol no. 394/2560(EC2), COAno. Si 599/2017.

Preoperative evaluations

The preoperative evaluations primarily employed 3 procedures: the Eckardt symptom scoring system[9], timed barium esophagography, and or high-resolution manometry. A CT scan served as an optional fourth method for select patients, as detailed below.

Eckardt symptom score

The Eckardt symptom scoring system was used to subjectively evaluate achalasia symptoms. This system measured 4 items: weight loss, dysphagia frequency, regurgitation frequency, and chest pain occurrence. Each item was assessed on a scale of 0–3, resulting in a total possible score of 12; higher overall scores indicated more severe disease.

Timed barium esophagography (TBE)

TBE helps predict treatment outcomes and recurrence rates.[10] TBE is similar to the barium swallow test but includes specific modifications. Notably, multiple sequential films are taken at predetermined intervals following a single swallow of a fixed volume of a barium suspension with a particular density. In our study, TBE was performed using a 200-ml oral bolus of low-density barium, with radiographs captured at 1, 2, and 5 minutes post-swallowing. Sigmoid-type achalasia was classified based on the degree of tortuosity of the esophageal lumen (revealed by the barium swallow), the diameter of the dilation, and the height of the esophagus.

High Resolution Manometry (HRM)

HRM using ManoScan™ (Medtronic company) was conducted using a standard technique, and the results were interpreted according to the Chicago Classification version 4.0 of esophageal pressure topography.[11] HRM is considered the gold standard for diagnosing achalasia cardia. However, the dilation and tortuosity of a sigmoid esophagus are readily demonstrated on an esophagogram or esophagogastroscopy. Manometry typically reveals incomplete or absent lower esophageal sphincter relaxation

in response to swallowing, a high median integrated relaxing pressure (> 15 mmHg), and an aperistalsis pattern. Achalasia type was also classified under HRM as Chicago classification.

Computerized Tomography scan (CT)

This study exclusively employed computed tomography (CT) scans for cases manifesting a notably tortuous esophagus, necessitating a comprehensive evaluation of its structure. CT scans quantified the extent of esophageal dilation and tortuosity, the latter assessed via the positioning of the lumen in axial CT images. Sigmoid-type achalasia was categorized into two subtypes following the classification system proposed by Inoue et al.[5] In sigmoid type 1 (S1), the esophagus exhibited marked dilation and tortuosity, featuring a single visible lumen on any CT slice. Conversely, sigmoid type 2 (S2) entailed highly dilated and tortuous esophagus, occasionally displaying a double lumen on CT slices or BE. [Fig 5]. CT scans also facilitated the assessment of adjacent anatomical structures, aiding in the exclusion of other pathologies and providing orientation information

POEM equipment and procedure

All procedures in each patient were performed by the same endoscopist, who is an expert in peroral endoscopic myotomy (POEM), having completed more than the established learning curve threshold of >20 cases.[12] The procedure of this study was performed in the same manner as the *standard POEM equipment and procedure* described previously by Phalanusitthepha et al.[12], which included the following details: The operation began with the patient lying in the supine position with the abdomen exposed under general anesthesia. A forward-viewing endoscope with an outer diameter of 9.8 mm, designed for routine upper gastrointestinal screening, was used with a transparent distal cap attachment (DH-28GR, Fujifilm). The procedure was performed under low-flow carbon dioxide insufflation to prevent air embolism. A mucosal incision was made with a triangular-tip knife after mucosal injection using a mixture of 0.9% normal saline with 0.3% indigo carmine dye. Submucosal tunneling was performed with the same knife until the achieved gastric area, about 2-3 cm below the EGJ, was reached for complete submucosal tunneling creation, and the length of the submucosal tunnel was created just slightly longer than the myotomy length. Next, the myotomy was performed only on the circular muscle, and the longitudinal muscle was spared; the length of the myotomy was performed with the standard POEM. Depending on the severe tortuosity of the esophagus, the myotomy location (anterior or posterior) was selected depending on the anatomy of sigmoid achalasia, which varied in each patient. While the procedure was performed, coagulating forceps (Coagrasper, FD-411QR; Olympus) connected to an electrosurgical energy generator, specifically a VIO 300D electrogenerator (ERBE), were used for hemostasis and to coagulate large vessels. For the final closure of the mucosal entry site, hemostatic clips (EZ-CLIP, HX-110QR; DF Olympus) were applied to avoid the leakage of esophageal content into the mediastinum.

Postoperative care

During the immediate postoperative period, chest X-rays and plain abdominal X-rays were conducted to ensure the detection of any possible complications, such as nonclinical pneumomediastinum, pneumothorax, and pneumoperitoneum, even in asymptomatic patients. Patients were also fasted for at least 16 hours, with intravenous antibiotic infusions and appropriate pain relief administered as needed.

Outcome measurements

The primary endpoint of the study was clinical success, defined as achieving an Eckardt score of less than 3 at one month post-procedure. Secondary outcomes encompassed achieving technical success, defined as the completion of gastric and esophageal myotomy within a single-stage procedure, along with the evaluation of operative details and perioperative complications. Eckardt scores were assessed before and after the POEM procedure at 1, 3, 6, and 12 months. Recurrent symptoms were defined as Eckardt scores exceeding 3. Additionally, esophageal diameter and barium height were measured pre- and post-POEM via BE or TBE; in the case of TBE, the value used for comparison is the 5-minute value. Post-procedure gastroesophageal reflux disease (GERD) symptoms were also thoroughly evaluated.

Follow-up

Medical records were reviewed to assess patient follow-up at intervals of 1, 3, 6, and 12 months, focusing on the evaluation of clinical symptoms and Eckardt symptom scores. A timed barium esophagogram was conducted at the 1-month mark. Esophagogastroduodenoscopy and high-resolution manometry (HRM) were carried out during the 12-month sessions.

Statistical analysis

Data with and without normal distribution were presented as mean ± SD or median (range), respectively. Wilcoxon's signed-rank test was used to compare non-

normal varaibles between pre- and post-treatment. Friedman's test was employed to test the change in non-normal variables among 5 different time points with Bonferroni's correction for pairwise comparisons. Fisher's exact test was applied to determine factors related to advrerse event. Two-sided p-values less than 0.05 were considered statistical significance. IBM SPSS 29.0 (Chicago, IL, USA) was employed.

RESULTS

The data were collected between January 2014 (when POEM was first performed at Siriraj Hospital) and July 2022. The study recruited 16 patients; their demographic data are detailed in Table 1. There were 8 men and 8 women, with a mean age of 43.13 ± 14.15 years old. Their disease courses varied from 9.31 ± 3.42 years. Eight patients had been diagnosed with S1 achalasia; the remaining eight had S2 achalasia. Among these 16 patients, 5 individuals had previously undergone other procedures. Specifically, one patient had undergone a biopsy in the EGJ area, one had received pneumatic dilation treatment, two had undergone Heller myotomy, and one had received both pneumatic dilation and Heller myotomy treatments. All cases underwent HRM examination, but due to the significant tortuosity of the esophageal tube, a complete examination could only be successfully performed in 2 cases, allowing for accurate interpretation. Among these cases, one was classified as Chicago type I, and the other as type II. The median Eckardt score was 6, and the average esophageal diameter was approximately 6.49 cm. The average height of the barium column at 5 min of TBE was 7.15 cm (Table 1).

All 16 patients underwent POEM successfully. The median operative time was 118.50 (52-206) minutes, while the average myotomy length was 9.19 ± 2.5 cm. The median length of hospital stay was 3 days (Table 2). The lengths of the esophagogastric junction and the myotomy were measured using incisors as a landmark. After the procedure, four patients developed GERD symptoms, all of whom had mild symptoms that resolved with medication; however, in the EGD follow-up, reflux esophagitis was not found. The technical success rate was 100%, consistent with the clinical success rate at 1 month. However, at 12 months, one patient (6.25%) experienced recurrent symptoms. (Table 3).

Several adverse event were noted, ranging from mild to moderate according to the ASGE severity guideline.[13] In 5 cases (31.25%), mucosal injuries were caused by the tip of the esophagogastroscope cap and dual knife; one injury occurred in the fundus and esophagogastric junction zone, while the others were in the esophagogastric junction zone. However, the mucosal defects were securely closed using endoscopic hemoclips , and there was no need for further intervention. No cases of pneumothorax occurred. One patient (6.25%) experienced minor bleeding at the posterior pharynx, which stopped spontaneously without the need for additional intervention. Pneumoperitoneum occurred in 2 patients (12.50%). In these cases, the air in the peritoneal cavity was released intraoperatively via a 20-gauge needle puncture. There were no reoperations or mortality postoperatively, and none of the patients required any intervention related to achalasia (Table 5).

The median preoperative Eckardt symptom score was 6 (2-10). By the 1, 3, 6 and 12-month follow-ups, the symptom scores had dropped to 1(0-3), 1(0-2), 1(0-4) and 1(0-3), respectively (P = 0.008) (Table 4) (Fig 1). Pairwsie comparisons showed significant difference in Eckardt score between pre and post 1, 3 month. Before the POEM procedure, the maximal dilatation of the esophagus was 6.49 cm on average, but 1 months afterward, the means were 4.4 cm (P = 0.003) (Table 4) (Fig 2). While esophageal height at 5 min of TBE was 7.15 cm before the procedure, the height decreased to 5 cm at the 1-month follow-ups (Table 4) (Fig 3).

The adverse event was found in S1(4) and S2 (4) cases equally (Table 5). The patient who had previous procedures tend to have complications more than those with no previous procedure, but not statically significant (P=0.282). In the S1 group, adverse event tended to develop in patients who had undergone previous procedures. However, in the S2 group, patients experienced adverse events at a consistent rate, rateregardless of their history of previous procedures, but the difference was not statically significant (P=0.143) (Table 5).

The association between operative time and adverse events. Although no statistically significant correlation was found, it is worth noting that adverse events tended to occur more frequently with longer operative times (Table 5).

DISCUSSION

For sigmoid-type achalasia, Faccani et al.[14] recommended using transhiatal esophagectomy as the standard treatment for patients aged less than 55 years who have severe mucosal inflammation or moderate to severe dysplasia. However, esophagectomy for achalasia has a morbidity rate of 50% and a mortality rate of 3%.[15] By comparison, in a study by Panchanatheeswaran et al.[16] involving 8 patients with sigmoid-shaped esophagus who underwent laparoscopic Heller myotomies, all patients experienced improvements in their dysphagia and regurgitation symptoms. Thus, laparoscopic Heller myotomy remains

TABLE 1. Demographic data of 16 patients.

Sex, Male/ Female : n	8/8
Age (years)	
Mean ± SD	43.13 ± 14.15
Median (range)	40 (23-70)
Disease course (years) : mean ± SD	9.31 ± 3.42
Type of sigmoid achalasia	
S1	8
S2	8
Previous intervention : n (%)	5 (31.25%)
Biopsy	1 (6.25%)
Endoscopic pneumatic dilatation	1 (6.25%)
Heller myotomy	2 (12.50%)
Endoscopic pneumatic dilatation and Heller myotomy	1 (6.25%)
Chicago classification : n (%)	
Type I	1 (6.25%)
Type II	1 (6.25%)
Type III	0
Cannot be evaluated due to severe tortuous	14 (87.50%)
Eckardt symptom scores: median (range)	6 (2-10)
Esophageal dilatation, mean ± SD (cm)	6.49 ± 2.43
Barium height, mean ± SD (cm)	7.15 ± 3.76

TABLE 2. Operative details of POEM procedure and complications.

Operative data	
Operation time, median (range), mins	118.5 (52-206)
Myotomy length mean ± SD, cm	9.19 ± 2.50
Length of hospital stay median (range), days	3 (2-10)

TABLE 3. Treatment outcome.

	Number (%)
GERD symptom	4 (25)
Reflux esophagitis (EDG at 12 month)	0
Technical success	16 (100)
Clinical success at 1 month	16 (100)
Recurrent symptom at 12 month	1 (6.3)

TABLE 4. Pre-POEM and post-POEM Eckardt symptom scores, esophageal dilatations, and Barium height.

	Pre	Post 1 month	Post 3 month	Post-6 month	Post 12 month	*p*-value
Eckardt symptom scores#	6 (2-10)	1 (0-3)	1(0-2)	1 (0-4)	1 (0-3)	*0.008*
Esophageal dilatation, cm*	6.49 ± 2.43	4.4 ± 1.46	-	-	-	*0.003*
Barium height, cm*	7.15 ± 3.76	5 ± 3.52	-	-	-	*0.066*

#Median (range), *Mean ± SD

TABLE 5. Complication and Factor related to adverse event.

(a) Complications	Number (%)
Mucosal injury	5 (31.25)
Mild*	4
Moderated*	1
Pneumoperitoneum	
Mild*	2 (12.50)
Bleeding	
Moderated*	1 (6.2)

(b) Factor related to adverse event		n	AE: Number (%)	*P*-value
Type	**Previous procedure**			
S1	Yes	3	3	
	No	5	1	*0.143*
S2	Yes	2	1	
	No	6	3	
Previous procedure				
Yes		5	4	*0.282*
No		11	4	
Operative time (min)				
≤120		8	2 (25%)	*0.132*
>120		8	6 (75%)	

* ASGE severity grading system

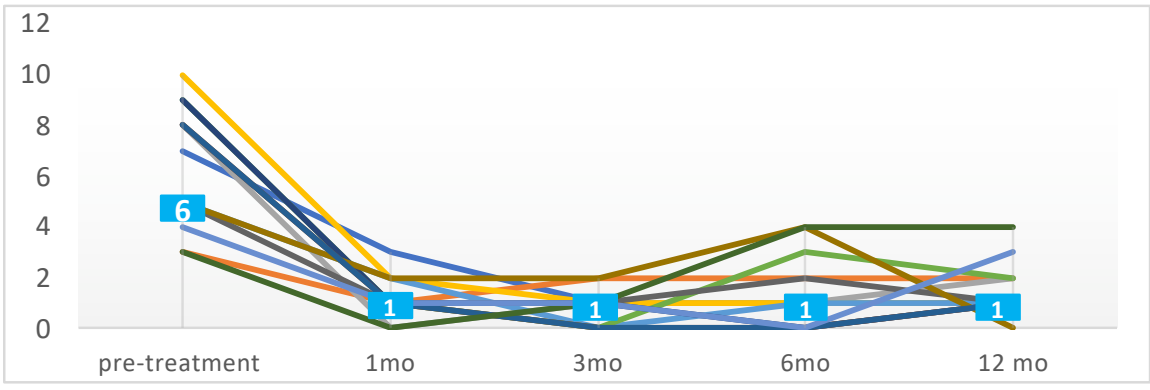

Fig 1. The median of the Eckardt score at pre and post POEM, each point of follow up (1, 3, 6, 12 month)

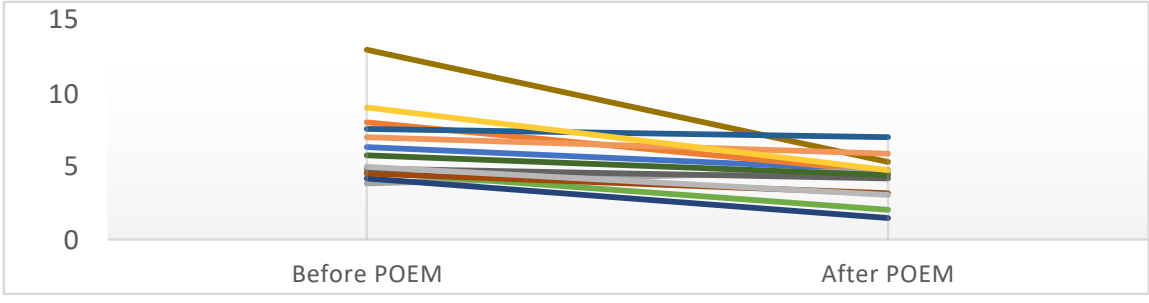

Fig 2. The mean of esophageal diameter before and after POEM 1 month follow-up

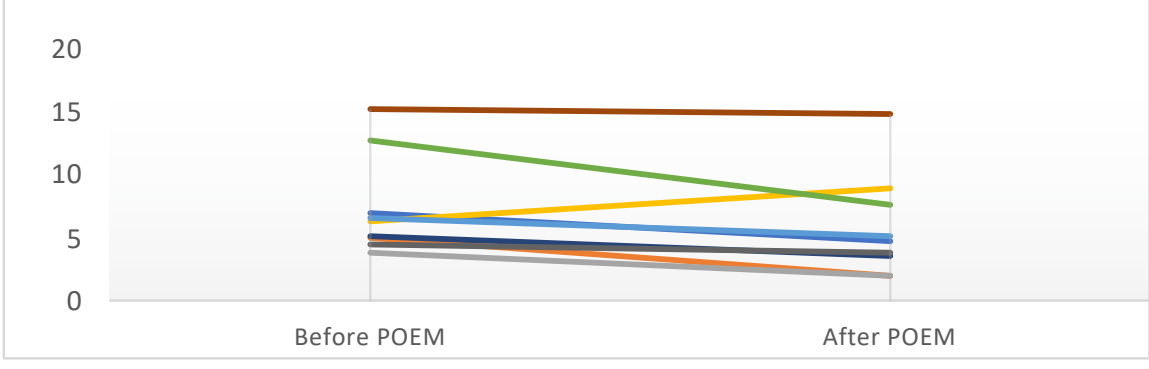

Fig 3. The mean of barium height before and after POEM 1 month follow-up

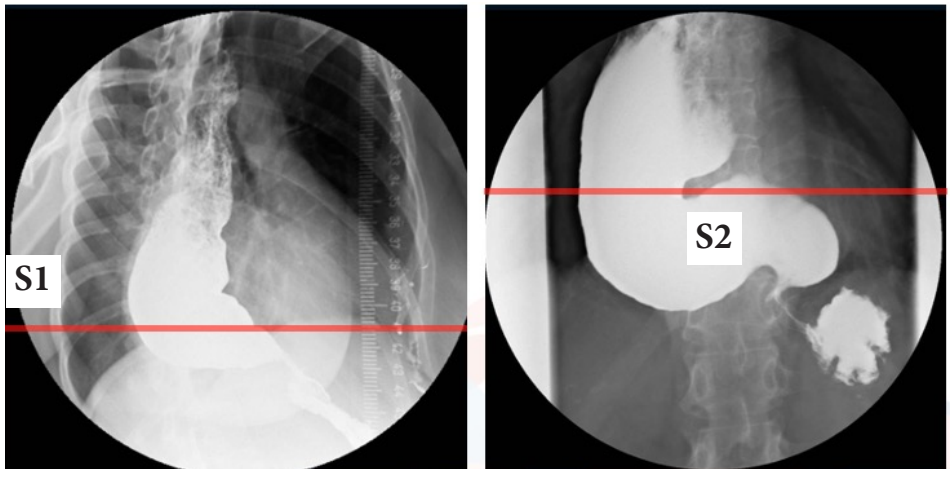

Fig 5. sigmoid type (S1, S2)

the standard operative treatment for achalasia, and it can be performed for sigmoid-type achalasia.

POEM involves minimally invasive surgery to treat achalasia, and its effectiveness has been supported by numerous studies.[5,17,18] In cases of sigmoid-type achalasia, the objective of using the POEM treatment is to reduce morbidity and mortality. Unlike its role with non-sigmoid types of achalasia, POEM for sigmoid-type achalasia focuses on relieving the outflow tract obstruction caused by aperistalsis of the esophagus. A sigmoid-shaped esophagus has tortuous acute angulations and is highly dilated, making it difficult for an endoscopist to control the scope. Before the POEM procedure is executed, retained food particles in the esophagus must be removed. Mucosal inflammation is typically generalized from the proximal site of the esophagus to the esophagogastric junction due to the stasis of food particles and the presence of candida esophagitis. The fibrosis found in the submucosal space makes it challenging to create a submucosal tunnel and can cause mucosal perforations. If a patient exhibits evidence of esophageal candidiasis, an antifungal drug should be administered. When the submucosal tunnel is created near the esophagogastric junction, the angulation of the esophagus and inflammation can result in a false submucosal tract. The endoscopist must therefore exercise caution to avoid mucosal injuries, or else the scope might enter the peritoneal cavity; this is especially the case with S2 achalasia, when even greater care is needed.

A recent review by Jin Xu et al.[19] demonstrated an overall clinical success rate of 90.4%. Additionally, several studies reported adverse events ranging from 3% to 13%[19,20], a range similar to our findings. Our study also showed a high clinical success rate (100%), which may be attributed to the technical success leading to clinical success. Hence, this result may suggest that POEM yields a favorable outcome comparable to that observed in non-sigmoid-type achalasia. However, it is imperative to note that POEM for the treatment of sigmoid-type achalasia presents significantly greater technical challenges than in non-sigmoid achalasia. In the 12-month follow-up, only one case of recurrent symptoms was identified. The factors contributing to recurrent symptoms were not clearly discerned, representing a limitation of this study. This limitation arises due to the small sample size, precluding definitive conclusions regarding this factor.

The POEM procedure took 118.50 minutes (52–206), longer than the typical operative time for non-sigmoid types of achalasia.[21] In our study, mucosal injuries occurred in 5 patients (31.25%), higher than the frequency observed for non-sigmoid types[22], this might be attributed to the severe tortuosity and significant dilation of the esophagus, which are inherent characteristics of the disease, resulting in a more challenging surgical procedure compared to the non-sigmoid type. This study suggests a propensity for perioperative adverse events in S2 and previous procedure cases. However, statistical significance was not attained, and due to the restricted number of cases, definitive conclusions on this matter cannot be reached. Nonetheless, in consideration of the outcomes, despite persistent esophageal lumen dilation, the mean esophageal diameter decreased by 4 cm twelve months postoperatively. Improvement in dysphagia symptoms was evident through lower Eckardt symptom scores, with a mean reduction of 3. As the morphological changes to the esophagus may be irreversible, symptom relief, weight gain, and manometry outcomes should be the main criteria to evaluate the clinical success of treatment with POEM.

In addition to other limitations of this study, it is important to acknowledge that the lower esophageal sphincter was not assessed in all patients due to the severely tortuous esophagus, which hindered the appropriate placement of the probe.[23] Regarding the adverse events observed in this study, the analysis suggests that cases more likely to experience adverse events are those with S2-type achalasia, in which the esophagus exhibits severe tortuosity and significant dilation, as well as cases with prior interventions leading to fibrosis, making the surgical plane difficult and challenging. The data show that the adverse event of POEM in sigmoid-type achalasia is more than in non-sigmoid type achalasia, which is the same reason as previously described.[19,20] However, due to the limited statistical significance of the numerical data, the small sample size, and the short-term follow-up, the impact may not be statistically significant. Notably, this disease is extremely rare, and this series may represent the largest compilation to date. Gathering more patient data is crucial for further understanding.

CONCLUSION

The POEM procedure is feasible for treating sigmoid-type achalasia, with a high rate of clinical success, even in the presence of acceptable adverse events. Therefore, it can be considered as a viable alternative treatment or bridging therapy for patients with sigmoid-type achalasia. However, it is important to note that POEM is technically more challenging than the treatment of typical achalasia. Nevertheless, esophagectomy may remain the only option for many patients with a sigmoid esophagus or for those in whom myotomy or other treatment modalities have failed. There is a need for a large, multicenter study, possibly a randomized controlled trial, to provide definitive data

on the roles of various treatment options for managing this condition.

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Conflicts of Interest

There is no conflict of interest in publishing this article.

DISCLOSURE

A portion of the results from the current study was presented at the academic conference International Digestive Endoscopy Network(IDEN), which took place on June 8-10, 2023 in Korea, and the abstract was published in the proceedings.

Author Contributions

Conceptualization : C.P. ; Datacollection : S.M., J.W. ; Formal analysis : T.S., S.M. ; Funding acquisition : none ; Investigation : C.P., M.M., S.L., T.S. ; Methodology : C.P., M.M., S.L., ; Project admistration : C.P., S.M. ; Resources : C.P. ; Supervision : V.C., T.A., A.M. ; Visualization : V.C., T.A., A.M. ; Writing- original draft : J.W., S.M. ; Writing-review &editing : S.M., T.S. All authors have read and agreed to the final version of the manuscript.

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Development and Evaluation of the DMIND Questionnaire: Preparing for AI Integration into an Effective Depression Screening Tool

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ABSTRACT

Objective: Thailand's mental health crisis is exacerbated by high demand and a shortage of mental health professionals. The research objective was to develop and validate the Detection and Monitoring Intelligence Network for Depression (DMIND) questionnaire, designed to be culturally relevant and easily administered in clinical settings. Crafted with expert input, items specifically conducive to artificial intelligence (AI) analysis were selected to facilitate the future development of an AI-assisted depression scoring model. This approach underscores the tool's dual utility in both human-led and technology-enhanced diagnostics.

Materials and Methods: We enrolled 81 participants from psychiatric and tertiary care hospitals in Bangkok. Participants were assessed using the DMIND questionnaire, followed by the Hamilton Depression Rating Scale (HDRS-17). Statistical analyses included the content validity index (CVI), Cronbach's alpha, Pearson's correlation coefficient, Cohen's kappa, and receiver operating characteristic (ROC) analysis. The Liu method, Youden index, and nearest neighbor method were used to determine the optimal cut-off point

Results: The DMIND questionnaire showed strong validity, with an item-level CVI (I-CVI) and scale-level CVI (S-CVI) exceeding 1.0, indicating strong consensus on its relevance and utility. The tool also demonstrated high internal consistency (Cronbach's alpha = 0.96). ROC analysis showed an AUC of 0.88, indicating high accuracy in depression screening. An optimal cut-off score of 11.5 was identified, balancing predictive value and sensitivity.

Conclusion: The DMIND questionnaire represents a significant advancement in innovative mental health diagnostics, addressing unmet clinical needs by providing accurate and efficient assessments capable of AI integration for further enhancing mental health service delivery in Thailand.

Keywords: Depression; depression screening; mental health; artificial intelligence (Siriraj Med J 2024; 76: 620-629)

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INTRODUCTION

Thailand is grappling with a mounting mental health crisis, characterized by a surge in depression rates that increasingly overwhelm the available healthcare resources. This scenario necessitates the rapid detection and management of depression to ensure effective intervention and mitigate risks such as suicide.[1] Unfortunately, current diagnostic practices are severely limited by the scarcity of professionals trained to employ complex tools like the Hamilton Depression Rating Scale (HDRS), the Beck Depression Inventory (BDI), and the Montgomery-Åsberg Depression Rating Scale (MADRS). These tools, while rigorous, require significant expertise and time to administer, which is unfeasible in many Thai healthcare settings.[2-4]

Considering these challenges, there is an urgent need to develop new, more accessible diagnostic tools. These tools should ideally align with clinical standards akin to those of the HDRS[2,3] but with greater ease of use, capable of capturing the delicate expressions of depression. Simplicity and sensitivity are vital for artificial intelligence (AI)-driven systems, enhancing the systems' ability to detect depression from emotional text effectively. Utilizing AI in this context expedites the diagnosis of depression and strengthens assessment precision[4-6], thereby enabling quicker and more effective treatment decisions in Thai healthcare settings.

Moreover, unlike the simple adaptation of existing tools, questionnaire development requires a comprehensive understanding of both the clinical landscape and AI technology.[5] This dual focus ensures that the new tool is clinically effective and optimized for AI applications, potentially revolutionizing diagnostic practices by improving accuracy and operational efficiency.[6-8]

Taken together, the study's objective was to construct and validate the Detection and Monitoring Intelligence Network for Depression (DMIND) questionnaire, aiming for it to be culturally relevant, easily administered in clinical settings, and seamlessly integrated with AI systems in the future.

MATERIALS AND METHODS

Study participants and eligibility

Participants aged 18-60 were recruited using quota sampling from outpatient departments at two hospitals in Bangkok, Thailand: The Somdet Chaopraya Institute of Psychiatry and King Chulalongkorn Memorial Hospital. This method ensured a balanced representation of normal controls and patients diagnosed with depression. Inclusion criteria comprised proficiency in Thai, absence of intellectual disability, and consent to video and audio recording. Exclusion criteria consisted of communication difficulties, facial expression issues, or any schizophrenia spectrum disorder or substance use disorder. Data collection occurred between September and December 2023. All participants provided informed consent before data collection. Clinical depression was diagnosed by an HDRS score ≥ 8, whereas normal controls scored 7 or less.

A total of 81 participants were enrolled: 39 were diagnosed with depression, and 42 were non-depressed controls. The sample size calculation followed the method by Li and Fine[6], utilizing HDRS sensitivity as the gold standard (sensitivity = 0.85). The target sensitivity was 0.65, reflecting the standard sensitivity range of 0.6-0.9 commonly used in depression screening tests. The sample size was calculated to be 72 using the sample size for comparing the sensitivity (or specificity) of two diagnostic test.

DMIND questionnaire development

The DMIND questionnaire was developed for depression screening by adapting items from the 17-item HDRS (HDRS-17)[7,8] and the Patient Health Questionnaire-9 (PHQ-9).[9,10] While HDRS-17 offers a comprehensive assessment of depression severity, PHQ-9 focuses on specific depression symptoms.[11] Two expert psychiatrists reviewed both scales and selected questions deemed appropriate for the study population and suitable for AI-based scoring. Two items from PHQ-9 (loss of interest, depressed mood) and four from HDRS-17 (depressed mood, loss of interest, inability to work, suicidal ideation) were selected due to their potential to evoke strong emotional responses, making them ideal for AI systems to capture nuanced linguistic and behavioral cues. These six selected items from PHQ-9 and HDRS-17 were adapted and further expanded into additional questions guiding the user/patient to provide more information and induce more emotional responses. Following pilot testing conducted in July and September 2023, the final version comprised nine items (six scored and three unscored). The DMIND questionnaire was then adapted into an audio version, integrated into an application (known as the DMIND application), and administered via an avatar resembling a psychiatrist. This digital interface enables standardized assessment and AI analysis of video responses.

Research procedure

Participants were interviewed at their respective hospitals, either following their doctor's appointment or at their convenience. They first completed the DMIND questionnaire using the application, followed by assessment

with the HDRS-17. Both assessments were administered by a trained psychiatric nurse/psychologist on the same day in quiet, distraction-free rooms. Evaluators for each assessment were blinded to the results of the other. Subsequently, a licensed psychiatrist reviewed and scored the responses on the DMIND application.

Assessments

Our DMIND questionnaire comprises nine items rated on a 4-point scale, including six scored items and three additional open-ended questions that are not scored. Higher scores indicate higher levels of depression, with a maximum value of 36 points. The following is an example questionnaire item: "คุณยังอดทนหรือฝืนทำหน้าที่หลักนั้นได้อยู่ไหม" (translation: "Can you still endure or resist carrying out your main duty?"). Response videos were rated by a trained psychiatrist with many years of experience.

The HDRS-17, developed by Max Hamilton in the late 1950s, is widely used in clinical trials to measure depression severity. It assesses depressive symptoms over the preceding 14 days, including depressed mood, feelings of guilt, suicide ideation, insomnia, work and activity level, retardation, agitation, psychic and somatic anxiety, gastrointestinal and general somatic symptoms, genital symptoms, hypochondriasis, weight loss, and insight. Responses are rated on a 5-point scale (0-4), with higher scores indicating greater severity. With a maximum score of 56, interpretation of scores ranges from 0-7 (normal), 8-16 (mild depression), 17-23 (moderate depression), to 24 or higher (severe depression).

Statistical analysis

Results were summarised using descriptive statistics. The content validity of the developed questionnaire was evaluated using the content validity index (CVI) where four independent experts graded each item for relevance and clarity. Internal consistency was evaluated using Cronbach's alpha. The relationship between the DMIND and HDRS-17 scores was determined using Pearson's correlation coefficient. Cohen's kappa coefficient was used to examine the agreement between the two tools, ensuring the questionnaire's reliability and accuracy. ROC analysis helped determine the area under the ROC curve (AUC), while the optimal cut-off point was evaluated using the Liu method[12], Youden's index (YI)[13], and the nearest neighbor method. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were also calculated. All analyses were conducted using STATA software release 15.1.

RESULTS

Participant demographics

The study included 81 participants (19 males and 62 females), comprising 42 normal controls and 39 patients with depression. The mean age was 33.91±10.53 years. Among the participants, 17.28% were married and 62.97% were employed. Most participants had completed a bachelor's degree or higher (75.31%), whereas the rest had completed either secondary (17.28%) or elementary education (6.17%). Detailed demographic information is provided in Table 1.

The average total HDRS-17 and DMIND score among all participants was 15.20±8.12 points and 10.28±6.12 points, respectively (Table 2).

Participants diagnosed with depression had a mean HDRS-17 score of 22.15±4.46 points and a mean DMIND score of 15.28±3.43 points. Conversely, the normal control group had a mean score of 8.74±4.64 points and 5.64±4.05 points on the HDRS-17 scale and DMIND questionnaire, respectively.

Validity and reliability

Regarding the content validity of the DMIND questionnaire, our study found an item-level CVI (I-CVI) and a scale-level CVI (S-CVI) value of 1.0. This value indicates excellent expert consensus on each item's relevance in measuring the intended objectives, thus demonstrating strong content validity across the questionnaire.

Regarding reliability, the DMIND questionnaire had a Cronbach's alpha coefficient of 0.957 for the total score (Table 3). The high coefficient value represents acceptable internal consistency, implying that the items within the questionnaire are sufficiently correlated and provide a consistent measure of the construct it is intended to assess.

The Pearson's correlation coefficient between the DMIND and HDRS-17 total score was 0.833 ($p < 0.001$), signifying a strong positive correlation between the two measures. Furthermore, each item in the DMIND questionnaire had a statistically significantly high correlation with its respective HDRS-17 item. These findings support the concurrent validity of the DMIND questionnaire.

ROC analysis and optimal cut-off point

From the ROC analysis and the nearest neighbor method, the optimal cut-off point was 11.5 points, with an AUC of 0.88 (95% CI = 0.80-0.95). At this optimal value, the sensitivity was 87.2% (95% CI = 72.6%-95.7%), the specificity was 88.1% (95% CI = 74.4%-96.0%), the

TABLE 1. Demographic characteristics.

Variable	Total (n=81)	HDRS-17		DMIND Questionnaire with a 11.5 cut-off point	
		Normal (n=42)	Depressed (n=39)	Normal (n=42)	Depressed (n=39)
Age (years)					
Mean ± SD	33.91±10.53	34.00±11.69	35.31±12.17	33.60±10.39	35.74±13.33
Median (IQR)	31 (16)	31.50 (15)	33 (19)	31.50 (17)	33 (19)
Min-Max	18-65	19-65	18-61	18-60	18-65
Gender, n (%)					
Male	19 (23.46)	11 (26.19)	8 (20.51)	10 (23.81)	9 (23.08)
Female	62 (76.54)	31 (73.81)	31 (79.49)	32 (76.19)	30 (76.92)
Religion					
Buddhist	70 (86.42)	37 (88.10)	33 (84.62)	36 (85.71)	34 (87.18)
Christian	4 (4.94)	4 (9.52)	0 (0.00)	4 (9.52)	0 (0.00)
Muslim	1 (1.23)	0 (0.00)	1 (2.56)	0 (0.00)	1 (2.56)
Others	6 (7.41)	1 (2.38)	5 (12.82)	2 (4.76)	4 (10.26)
Birthplace Region					
Central	55 (67.90)	25 (59.52)	30 (76.92)	28 (66.67)	27 (69.23)
North	2 (2.47)	1 (2.38)	1 (2.56)	1 (2.38)	1 (2.56)
Northeast	12 (14.81)	6 (14.29)	6 (15.38)	5 (11.90)	7 (17.95)
South	7 (8.64)	6 (14.29)	1 (2.56)	5 (11.90)	2 (5.13)
East	4 (4.94)	3 (7.14)	1 (2.56)	3 (7.14)	1 (2.56)
West	1 (1.23)	1 (2.38)	0 (0.00)	0 (0.00)	1 (2.56)
Marital status, n (%)					
Unmarried	57 (70.37)	31 (73.81)	26 (66.67)	30 (71.43)	27 (69.23)
Married	14 (17.28)	6 (14.29)	8 (20.51)	6 (14.29)	8 (20.51)
Divorced	10 (12.35)	5 (11.90)	5 (12.82)	6 (14.29)	4 (10.26)
Education level, n (%)					
None	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Elementary	5 (6.17)	2 (4.76)	3 (7.69)	1 (2.38)	4 (10.26)
Junior Secondary	1 (1.23)	1 (2.38)	0 (0.00)	1 (2.38)	0 (0.00)
Senior Secondary	13 (16.05)	5 (11.90)	8 (20.51)	6 (14.29)	7 (17.95)
Bachelor's degree	52 (64.20)	29 (69.05)	23 (58.97)	28 (66.67)	24 (61.54)
Higher than bachelor's degree	9 (11.11)	5 (11.90)	4 (10.26)	6 (14.29)	3 (7.69)
Missing data	1 (1.23)	0 (0.00)	1 (2.56)	0 (0.00)	1 (2.56)
Occupation, n (%)					
Student	14 (17.28)	6 (14.29)	8 (20.51)	8 (19.05)	6 (15.38)
Government officer	5 (6.17)	4 (9.52)	1 (2.56)	5 (11.90)	0 (0.00)
Contractor/Freelance	12 (14.81)	7 (16.67)	5 (12.82)	6 (14.29)	6 (15.38)
Employee of a private company	23 (28.40)	12 (28.57)	11 (28.21)	13 (30.95)	10 (25.64)
Self-owned business	8 (9.88)	6 (14.29)	2 (5.13)	6 (14.29)	2 (5.13)
Online merchants	1 (1.23)	1 (2.38)	0 (0.00)	1 (2.38)	0 (0.00)
Unemployed	16 (19.75)	6 (14.29)	10 (25.64)	3 (7.14)	13 (33.33)
Other	2 (2.47)	0 (0.00)	2 (5.13)	0 (0.00)	2 (5.13)

TABLE 1. Demographic characteristics. (Continue)

Variable	Total (n=81)	HDRS-17		DMIND Questionnaire with a 11.5 cut-off point	
		Normal (n=42)	Depressed (n=39)	Normal (n=42)	Depressed (n=39)
Income, n (%)					
<10,000	5 (6.17)	1 (2.38)	4 (10.26)	2 (4.76)	3 (7.69)
10,000-20,000	14 (17.28)	8 (19.05)	6 (15.38)	6 (14.29)	8 (20.51)
>20,000-30,000	17 (20.99)	10 (23.81)	7 (17.95)	9 (21.43)	8 (20.51)
>30,000-40,000	40 (49.38)	23 (54.76)	17 (43.59)	25 (59.52)	15 (38.46)
>40,000	2 (2.47)	0 (0.00)	2 (5.13)	0 (0.00)	2 (5.13)
Missing data	3 (3.70)	0 (0.00)	3 (7.69)	0 (0.00)	3 (7.69)
Medical History, n (%)					
No	58 (71.60)	35 (83.33)	23 (58.97)	33 (78.57)	25 (64.10)
Yes	23 (28.40)	7 (16.67)	16 (41.03)	9 (21.43)	14 (35.90)
NCDs	6 (26.09)	1 (14.29)	5 (31.25)	2 (22.22)	4 (28.57)
Neuro	5 (21.74)	1 (14.29)	4 (25.00)	2 (22.22)	3 (21.43)
Endocrine	2 (8.70)	1 (14.29)	1 (6.25)	1 (11.11)	1 (7.14)
GI	3 (13.04)	2 (28.57)	1 (6.25)	2 (22.22)	1 (7.14)
Gynecology	2 (8.70)	1 (14.29)	1 (6.25)	1 (11.11)	1 (7.14)
Psychiatric History, n (%)					
No	10 (12.35)	6 (14.29)	4 (10.26)	4 (9.52)	6 (15.38)
Yes	71 (87.65)	36 (85.71)	35 (89.74)	38 (90.48)	33 (84.62)
Substance Use History, n (%)					
No	77 (95.06)	41 (97.62)	36 (92.31)	41 (97.62)	36 (92.31)
Yes	4 (4.94)	1 (2.38)	3 (7.69)	1 (2.38)	3 (7.69)
Family Psychiatric History, n (%)					
No	66 (81.48)	34 (80.95)	32 (82.05)	33 (78.57)	33 (84.62)
Yes	15 (18.52)	8 (19.05)	7 (17.95)	9 (21.43)	6 (15.38)

Abbreviations: HDRS-17: 17-item Hamilton Depression Rating Scale; DMIND Questionnaire: Detection and Monitoring Intelligence Network for Depression questionnaire; SD: Standard deviation; IQR: Interquartile range; NCDs – Noncommunicable diseases; Neuro - Neurological disease; GI – Gastrointestinal issues.

TABLE 2. Participant scores for each assessment.

Variable	Total (n=81)	HDRS-17 Depression Diagnosis	
		Normal (n=42)	Depressed (n=39)
HDRS-17 score			
Mean ± SD	15.20±8.12	8.74±4.64	22.15±4.46
Median (IQR)	15 (11)	9 (8)	21 (7)
Min-Max	0-33	0-16	17-33
DMIND questionnaire score			
Mean ± SD	10.28±6.12	5.64±4.05	15.28±3.43
Median (IQR)	11 (10)	5.50 (6)	15 (4)
Min-Max	0-21	0-13	7-21

Abbreviations: HDRS-17: 17-item Hamilton Depression Rating Scale; DMIND Questionnaire: Detection and Monitoring Intelligence Network for Depression questionnaire; SD: Standard deviation; IQR: Interquartile range.

TABLE 3. The internal consistency of the HDRS-17 and DMIND.

HDRS-17	Mean ± SD	Cronbach's Alpha	DMIND	Mean ± SD	Alpha
Q1 (0-4)	1.72±1.19	0.649 Q2 (0-3)	Q1 (0-3) 1.54±0.90	1.80±1.04 0.950	0.949
Q7 (0-4)	1.83±1.31	0.688 Q5 (0-3)	Q3 (0-3) 1.44±0.89	1.77±1.02 0.951	0.950
Q3 (0-4)	1.06±1.33	0.705 Q7 (0-3) Q9 (0-3)	Q6 (0-3) 1.03±1.02 1.41±0.99	1.38±1.05 0.955 0.950	0.949
Total score (0 to 12)	4.60±3.15	**0.762**	**Total score (0 to 21)**	**10.28 ± 6.12**	**0.957**

Abbreviations: HDRS-17: 17-item Hamilton Depression Rating Scale; DMIND: Detection and Monitoring Intelligence Network for Depression questionnaire; SD: Standard deviation.

PPV was 87.2% (95% CI = 72.6%-95.7%), and the NPV was 88.1% (95% CI = 74.4%-96.0%) (Table 5). This AUC value indicates that the DMIND questionnaire performs well in identifying patients with depression, demonstrating high sensitivity (Fig 1).

Using the Liu method and Youden index, the optimal cut-off score was 13.5 points with an AUC of 0.88 (95% CI = 0.82-0.95). At this value, the sensitivity was 76.9% (95% CI = 60.7%-88.9%), the specificity was 100% (95% CI = 91.6%-100%), the PPV was 100% (95% CI = 88.4%-100%), and the NPV was 82.4% (95% CI = 69.1%-91.6%).

Agreement Between the DMIND questionnaire and the HDRS-17

The Cohen's kappa statistic was calculated for both optimal cut-off scores determined in the previous analysis. When the cut-off score was 11.5 points, the percentage agreement was 87.65 percent and the Kappa value (κ) was 0.75, suggesting substantial agreement ($p < 0.001$) between the two tools. Similarly, for a cut-off score of 13.5 points, the percentage agreement was 88.89 percent and κ = 0.78, indicating substantial agreement ($p < 0.001$) between the tools.

TABLE 4. Correlation between DMIND and HDRS-17 total scores.

HDRS-17	DMIND	Pearson's Correlation Coefficient	*p*-value
Q1	Q1 Q2	0.662 0.536	<0.001 <0.001
Q7	Q3 Q5	0.682 0.664	<0.001 <0.001
Q3	Q6 Q7 Q9	0.689 0.606	<0.001 <0.001
Total score		**0.833**	**<0.001**

Abbreviations: Q: Question; HDRS-17: 17-item Hamilton Depression Rating Scale; DMIND: Detection and Monitoring Intelligence Network for Depression questionnaire.

TABLE 5. Analysis of different cut-off points using the ROC analysis.

Cut point	Sensitivity	Specificity	Correctly Classified	LR+	LR-
≥ 0	100.00%	0.00%	48.15%	1.00	
≥ 1	100.00%	16.67%	56.79%	1.20	0.00
≥ 2	100.00%	19.05%	58.02%	1.24	0.00
≥ 3	100.00%	26.19%	61.73%	1.35	0.00
≥ 4	100.00%	30.95%	64.20%	1.45	0.00
≥ 5	100.00%	42.86%	70.37%	1.75	0.00
≥ 6	100.00%	50.00%	74.07%	2.00	0.00
≥ 7	100.00%	57.14%	77.78%	2.33	0.00
≥ 8	97.44%	69.05%	82.72%	3.15	0.04
≥ 9	94.87%	78.57%	86.42%	4.43	0.07
≥ 10	94.87%	80.95%	87.65%	4.98	0.06
≥ 11	89.74%	80.95%	85.19%	4.71	0.13
≥ 12*	87.18%	88.10%	87.65%	7.32	0.15
≥ 13	76.92%	95.24%	86.42%	16.15	0.24
≥ 14**	76.92%	100.00%	88.89%		0.23
≥ 15	64.10%	100.00%	82.72%		0.36
≥ 16	48.72%	100.00%	75.31%		0.51
≥ 17	30.77%	100.00%	66.67%		0.69
≥ 18	28.21%	100.00%	65.43%		0.72
≥ 19	23.08%	100.00%	62.96%		0.77
≥ 20	12.82%	100.00%	58.02%		0.87
≥ 21	2.56%	100.00%	53.09%		0.97
> 21	0.00%	100.00%	51.85%		1

* Optimal cut-off point using the nearest neighbor method was 11.5 points

** Optimal cut-off point using the Liu method and Youden index was 13.5 points

Abbreviations: ROC: Receiver operating characteristic; LR+: Positive likelihood ratios; LR-: Negative likelihood ratios.

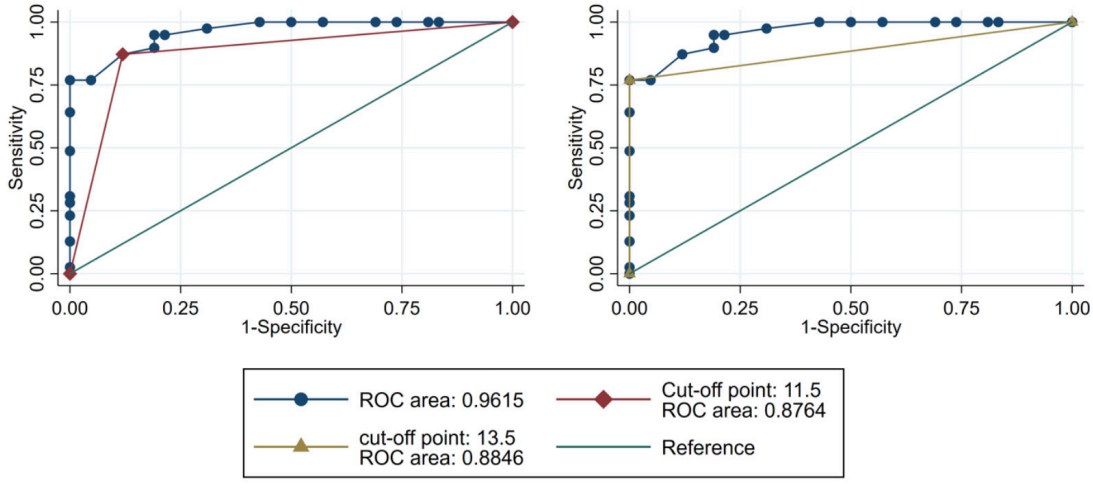

Fig 1. Receiver operating characteristic (ROC) analysis and optimal cut-off point using the nearest neighbor method, Liu method, and Youden index

These findings further support the reliability of the DMIND questionnaire, signifying strong alignment between the DMIND questionnaire and HDRS-17 categories.

DISCUSSION

The DMIND questionnaire is a valid tool for depression pre-screening

The DMIND questionnaire demonstrates high reliability for depression pre-screening, as indicated by a Cronbach's alpha coefficient of 0.957, signifying strong internal consistency. This reliability is comparable to other assessments, such as the Thai HDRS-17.[16] Key items like depressed mood and suicidal thoughts in the DMIND questionnaire were intentionally developed to yield higher scores, aiming to ensure timely intervention and minimize false negatives. Furthermore, the ROC curve analysis revealed a promising AUC of 0.88, placing our tool in a favorable position among existing tools like the MADRS, which has an AUC of 0.78.[14-19] These findings indicate that the DMIND questionnaire effectively distinguishes between depressed and non-depressed individuals.

An optimal cut-off score of 11.5 points resulted in a sensitivity of 87.2% and specificity of 88.1%, effectively balancing true positives and negatives. Although another optimal cut-off point was identified at 13.5 points, we selected the 11.5 cut-off score to prioritize high sensitivity, which ensures suitability for future AI integration and prevents urgent cases from being overlooked.

Looking at existing depression detection models, a study by Mudasir[14] proposed an advanced deep learning model utilizing Word2Vec (a technique in natural language processing) and term frequency-inverse document frequency (TF-IDF). These methods were employed to train convolutional neural network (CNN) and long short-term memory (LSTM) models for early depression detection, targeting sensitive cues indicative of serious issues like self-harm or suicidal thoughts, which current depression detection models often fail to accurately detect. The study collected data from Facebook, Twitter, and YouTube using advanced crawling strategies to ensure a unique, diverse dataset with various indicators of depression. The authors reported that the Word2Vec LSTM and Word2Vec (CNN + LSTM) models achieved accuracies of 99.02% and 99.01%, respectively, outperforming existing methods in recall, precision, accuracy, and F1-score. Word2Vec features were particularly effective, achieving accuracies of 95.02% (CNN) and 98.15% (CNN + LSTM) on Facebook and YouTube data. In another study, sensitivity analysis results from Guohou, Lina, and Dongsong[15] revealed that problem-related questions were the most influential in depression detection. More specifically, questions about depression, emotions, and unresolved life problems significantly impacted detection accuracy when multimodal features were utilized. Additionally, Amanat et al.[16] proposed a productive model by implementing the LSTM and recurrent neural network (RNN) model to predict depression from text, semantics, and written content derived from interviews with 99.0% accuracy, thereby proving beneficial in protecting suicidal individuals. Together, these approaches support our current perspective of the DMIND questionnaire, where we hope to collect detailed video responses and apply AI techniques to optimize depression detection.

Practical uses of the DMIND questionnaire for future AI application

The DMIND questionnaire presents a promising tool for routine depression screening across various healthcare settings and online channels. Avatar-based interviews within our DMIND application eliminate the necessity for human involvement, reducing the workload on healthcare personnel and helping users/patients feel more comfortable expressing their true feelings and opinions. This interface enables healthcare providers to gain more in-depth information and more accurately diagnose patients. With future AI integration, the DMIND questionnaire and application have the potential to enhance depression detection from emotional text, boosting diagnostic precision and expediting treatment decisions. This fusion of clinical insight and AI technology optimizes diagnostic practices, transforming and streamlining healthcare delivery.

Strengths and weaknesses

The DMIND questionnaire boasts several notable strengths. Questionnaire items were selected from well-established tools, and the assessor of each tool in this study was blinded to the results of the other assessment. The questionnaire demonstrated high internal consistency and strong diagnostic performance, showing high sensitivity (87.2%) and specificity (88.1%). Additionally, the questionnaire's user-friendly design, featuring an audio interface and psychiatrist avatar, increases user engagement and comfort, potentially improving the accuracy and detail of responses compared to conventional methods. Furthermore, its potential for AI integration allows for future automated emotional text analysis, improving diagnostic precision and efficiency.

The study's limitations include a relatively small sample size of 81 participants recruited from only two

locations. Consequently, our research findings may not be generalizable to the broader Thai population. Potential bias from relying on expert review for validation could affect objectivity, highlighting the need for additional validation methods. Moreover, the questionnaire focused on a limited number of high-impact questions, which could cause other relevant symptoms to be overlooked, potentially reducing the assessment's comprehensiveness.

Future research

Future research should aim to develop and integrate an AI-assisted scoring model to confirm the questionnaire's suitability for AI integration and verify that the use of AI will effectively improve depression diagnosis precision and efficiency. Additionally, further research should be conducted to enhance the DMIND application to increase user acceptance and user-friendliness. Large-scale testing with a more diverse pool of participants is essential to validate these improvements.

CONCLUSION

In conclusion, the authors successfully developed the DMIND questionnaire, a 9-item depression pre-screening tool. The developed tool exhibits strong internal consistency, discriminatory ability, and practical attributes, making it reliable for depression screening and future AI integration. Further studies will focus on developing and integrating an AI depression scoring model.

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Ethics Statement

All subjects gave their informed consent before participating in the study. This study was conducted in accordance with the World Medical Association Declaration of Helsinki and was approved by the Ethical Review Board of the Somdet Chaopraya Institute of Psychiatry (008/2566) and the Faculty of Medicine Chulalongkorn University (COA No. 1266/2023).

Author Contributions

SH was responsible for the conceptualization and study design, as well as the initial drafting of the manuscript. KL contributed to the data collection and curation. PP performed the statistical analysis. KS, CK, KC, and PJ assisted in project administration. PV, TA, and NN provided supervision and guidance throughout the project. SH, NH, AA, and RY reviewed and edited the manuscript. All authors participated in the methodology design, contributed to the data interpretation, and approved the final manuscript.

Conflict of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have influenced the work reported.

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Prevalence and Association of Congenital Heart Disease with Hirschsprung's Disease

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ABSTRACT

Objective: Neurocristopathies play a role as pathogenesis of Hirschsprung's disease and congenital heart diseases (CHDs). This study seeks to identify concomitant deformities, syndromes, and/or associations associated with Hirschsprung's disease warrant evaluation for CHDs through echocardiography.

Materials and Methods: A retrospective analysis was conducted on Hirschsprung's disease patients at Siriraj Hospital between January 2006 and December 2022. Echocardiograms were performed when clinical symptoms, abnormal chest X-rays (CXR), desaturation, heart murmurs raised suspicions of cardiovascular anomalies.

Results: Among 299 Hirschsprung's disease patients, 43 (14.4%) exhibited CHDs. The sensitivity of CXR (n=268) and echocardiograms (n=51) in diagnosing CHDs was 48.8% and 100%, respectively. Predominant CHD presentations included patent ductus arteriosus (n=29), atrial septal defects (n=18), and ventricular septal defects (n=15). The presence of concomitant deformities, syndromes and/or associations associated with Hirschsprung's disease significantly heightened the likelihood of concurrent CHDs (Odds ratio = 23.56, $p < 0.001$). Patients with Hirschsprung's disease and concomitant deformities (n=28) (excluding syndromic or chromosomal abnormalities) had 1.73 times the odds of CHDs ($p = 0.262$) compared to those without concomitant deformities. Patients with Hirschsprung's disease and Down syndrome (n=34) exhibited 77.78 times higher odds of CHDs ($p < 0.001$), while those with other syndromes and/or associations (n=6) had 13.03 times higher odds of CHDs ($p = 0.005$) compared to patients lacking these conditions.

Conclusion: CHDs were identified in 14.4% of Hirschsprung's disease patients. Echocardiograms should be selectively employed in Hirschsprung's disease associated with Down syndrome, other syndromes, or concomitant deformities.

Keywords: Hirschsprung; cardiac screening; neurocristopathy; echocardiography (Siriraj Med J 2024; 76: 630-637)

INTRODUCTION

The pathogenesis of Hirschsprung's disease involves the absence of ganglion cells over a variable length of the distal gut, starting from the internal sphincter and extending proximally. This results in absent peristalsis in the affected bowel. The root cause of Hirschsprung's disease is insufficient cranio-caudal migration, proliferation and differentiation of neural crest cells within the hindgut.[1-5] Besides Hirschsprung's disease's association with neural crest differentiation, cardiac neural crest cells, a smaller distinct subset of neural crest cells, also play a crucial role in proper cardiovascular formation, including development of smooth muscles, septation of the cardiac outflow tract, valves, aortic arch artery, cardiac aortopulmonary septum,[6-10] and arterial truncus.[11,12] Studies have shown a wide-ranging prevalence of between 1.4%-17%[7-9, 13-16] of CHD in individuals with Hirschsprung's disease.

There is a controversial debate over whether all patients diagnosed with Hirschsprung's disease should undergo a heart evaluation via an echocardiogram[8,17] or if this should be limited to those presenting additional deformities, syndromes, and/or chromosomal abnormalities.[13] Despite

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reports of a high incidence of CHD in some patients with Hirschsprung's disease, the Division of Pediatric Surgery, Department of Surgery, Faculty of Medicine, Siriraj Hospital, Mahidol University does not perform routine echocardiograms for all patients with this condition.

The objectives of this study were to define the prevalence of associated CHDs in patients with Hirschsprung's disease and to evaluate which specific concomitant deformities, syndromes, and/or associations requiring further examination of associated CHDs through echocardiography. Moreover, the diagnostic index including sensitivity, specificity, positive predictive valve (PPV), and negative predictive value (NPV) of either CXR or echocardiograms in detecting associated CHD was also studied.

MATERIALS AND METHODS

This study was approved by the Institutional Review Board of Siriraj (COA no. Si 843/2022). All patients with Hirschsprung's disease who were admitted for further evaluation and/or surgical treatment at Siriraj University Hospital, Mahidol University between January 2006 and December 2022 were retrospectively reviewed. Patients with Hirschsprung's disease who lacked comprehensive heart examination records (i.e., cardiac physical examination, CXR, electrocardiography and/or echocardiogram) and patients who had undergone cardiac surgery for CHD at another hospital were excluded.

In this study, CHD was defined as "a gross structural abnormality of the heart or intrathoracic great vessels potentially or actually affecting function," as defined by *Mitchell et al.*[18] This definition excludes persistent left superior vena cava, bicuspid aortic valves, mitral valve prolapse, Marfan syndrome, cardiomyopathies, and congenital arrhythmias without an associated structural heart defect (such as long Q-T syndrome). Conditions like atrial septal defects within the oval fossa, and patent foramen ovale and patent ductus arteriosus are not considered CHD within the first 14 days of life and are excluded as they are considered normal occurrences. CHDs that require percutaneous or surgical interventions are described as major.[8] Diagnosis often follows a physical examination, with further specialized tests based on clinical features. Echocardiography is used for detailed examination when a cardiovascular abnormality is suspected based on symptoms, an abnormal CXR, reduced pulse oximetry readings, or the presence of heart murmurs.

Definition of anomaly in this study

This study categorized "any associated anomalies" as instances of Hirschsprung's disease that also involved any other anomaly, either as part of a concomitant deformity, a syndrome and/or association, and/or a chromosomal abnormality. "Concomitant deformity" was defined as Hirschsprung's disease occurring alongside another congenital deformity, not including Down syndrome or any specific syndromes and/or associations or chromosomal abnormalities. A "syndrome and/or association" referred to Hirschsprung's disease coupled with a specific syndrome and/or association or any chromosomal abnormality, excluding Down syndrome which was categorized in another group.

Demographic and clinical data, including age, sex, transitional zones, CXR results, echocardiogram results, and other additional congenital anomalies were systematically collected. Quantitative data were presented as mean and standard deviation for normally distributed datasets, and as median with interquartile range for datasets not following normal distribution. The study utilized a Pearson's χ^2 test or Fisher's exact test to analyze qualitative data comparisons between the two groups, and the Mann-Whitney U test for comparing medians in quantitative data. The analysis included calculating odds ratios (OR) to assess the relationship between various exposures (anomalies, deformities, syndromes and/or associations) and the occurrence of CHD.

The diagnostic index including sensitivity, specificity, PPV, and NPV of either CXR or echocardiograms in detecting associated CHD was also studied.

Data analysis was conducted using the PASW Statistics program (SPSS for Windows, version 26.0, SPSS Inc., Chicago, Illinois, USA). A *p-value* below 0.05 was considered statistically significant.

RESULTS

In a cohort of 299 patients diagnosed with Hirschsprung's disease, 43 children (14.4%) had associated CHDs. Of these, 20 patients had major CHDs. The variety of CHD found in patients with Hirschsprung's disease is outlined in Table 1.

Chest X-rays (CXR) and echocardiograms were performed in 268 and 51 patients, respectively. The sensitivity, specificity, false positive rate, false negative rate, PPV, and NPV of both CXR and echocardiograms in detecting CHD are detailed in Table 2. The sensitivity of CXR and echocardiography in diagnosing associated CHD among patients with Hirschsprung's disease were 48.8% and 100%, respectively.

Demographic and clinical characteristics, such as age, sex, transitional zone levels, and operative

TABLE 1. Types of congenital heart disease in patients with Hirschsprung's disease.

Types of congenital heart diseases	N (%)
Acyanotic	
Left-to-right shunts;	
PDA	29 (9.7%)
ASD	18 (6.0%)
VSD	15 (5.0%)
Complete atrioventricular septal defect	1 (0.3%)
Obstructive lesions	0 (0%)
Cyanotic	
Right-to-left shunts;	
Pulmonary atresia	2 (0.7%)
Tetralogy of Fallot	1 (0.3%)
Tricuspid atresia	1 (0.3%)
Complex "mixing" lesions;	
Total anomalous pulmonary venous return	1 (0.3%)
Univentricular heart disease	1 (0.3%)
Obstructive lesions(right-sided);	
Pulmonary stenosis	4 (1.3%)
Others	
Interrupted aortic arch type B	1 (0.3%)

TABLE 2. The sensitivity, specificity, false positive, false negative, positive predictive valve (PPV), and negative predictive value (NPV) of CXR or echocardiograms in detecting associated congenital heart diseases.

	CXR (n = 268) 95% CI	Echocardiogram (n = 51) 95% CI
Sensitivity	21/43 (48.8%) (35% - 63%)	43/43 (100%) (92% - 100%)
Specificity	225/225 (100%) (98% - 100%)	6/8 (75%) (41% - 93%)
False positive	0/225 (0%) (0% - 2%)	2/8 (25%) (7% - 59%)
False negative	22/43 (51.2%) (37% - 65%)	0/43 (0%) (0% - 8%)
PPV	21/21 (100%) (85% - 100%)	43/45 (95.6%) (85% - 99%)
NPV	225/247 (91.1%) (87% -94%)	6/6 (100%) (61% - 100%)

techniques were compared between patients who did and did not have CHD, as shown in Table 3. The analysis showed no significant differences in the age at operation ($p = 0.51$), sex distribution ($p = 0.19$), transitional zone ($p = 0.37$), or the application of abdominal assisted transanal endorectal pull-through (TERPT) ($p = 0.97$) techniques between the two groups.

The prevalence of CHD detected by echocardiograms in patients with Hirschsprung's disease, alongside any concomitant deformities, syndromes and/or associations, were compared to those without any concomitant deformities, syndromes and/or associations and are shown in Table 4.

Among the 299 patients diagnosed with Hirschsprung's disease, 61 (20.4%) had associated anomalies, including

TABLE 3. Demographic data of all patients with Hirschsprung's disease, including age, sex, levels of transitional zone and operative techniques: A comparison of those with congenital heart disease and those without congenital heart disease.

Variables	All patients (n = 299)	Associated CHDs		*p* - value
		CHDs (n = 43)	No - CHDs (n = 256)	
Age of surgery (Months)				0.508
Median (Interquartile range)	3.35 (10.84)	3.68 (15.38)	3.10 (10.80)	
Sex, n (%)				0.190
Male	216 (72.2%)	27 (62.8%)	189 (73.8%)	
Female	83 (27.8%)	16 (37.2%)	67 (2.3%)	
Transitional zone, n (%)	276			0.367
Short segment	165 (55.2%)	27 (62.8%)	138 (53.9%)	
Long segment	111 (37.1%)	13 (30.3%)	98 (38.2%)	
Surgery, n (%)	296			0.974
TERPT	166 (55.5%)	24 (55.8%)	142 (55.5%)	
Abdo-assisted TERPT	86 (28.8%)	13 (30.2%)	73 (28.5%)	
Other pull-throughs	44 (14.7%)	6 (14%)	38 (14.8%)	

TABLE 4. The prevalence of congenital heart diseases detected by an echocardiogram in patients with Hirschsprung's disease who had concomitant deformities or syndromes and/or associations was compared against those without any concomitant deformities or syndromes and/or associations.

Anomalies	CHDs (n = 43) (%)	No - CHDs (n = 256) (%)	*p* - valve	Odd ratio (OR) (95% CI)
Any associated anomalies (n = 61)	33 (76.7%)	28 (10.9%)	< 0.001	23.56 (10.50 - 52.86)
Concomitant deformity (n = 28)	6 (14.0%)	22 (8.6%)	0.262	1.73 (0.66 - 4.54)
Down syndrome (n = 34)	28 (65.1%)	6 (2.3%)	< 0.001	77.78 (27.93 - 216.60)
Syndrome and/or association (n = 6)	4 (9.3%)	2 (0.8%)	0.005	13.03 (2.31 - 73.51)

concomitant deformities, syndromes and/or associations. Within this subgroup, 33 patients (54.1%) were identified having CHD. Patients with Hirschsprung's disease and associated anomalies were 23.56 times more likely to have CHD compared to those without such anomalies (76.7% vs 10.9%, OR 23.56, 95%CI 10.50 - 52.86; $p < 0.001$).

The presence of Hirschsprung's disease with concomitant deformities was noted in 28 cases, which included three cases of anorectal malformation, three of Meckel diverticulum, three of cleft lip and palate, two of central nervous system anomalies, two of gastroschisis, two of malrotation, two of hypospadias, two of limb anomalies, and one case each of microcephaly, macrocephaly, esophageal achalasia, annular pancreas, duodenal atresia, asplenia, ureteropelvic junction obstruction, bilateral undescended testis, sensorineural anomaly. Patients with Hirschsprung's patients and concomitant deformities had a 1.73-fold increase in the incidence of CHD compared to those without such deformities (14.0% vs 8.6%, OR 1.73, 95%CI 0.66 - 4.54; $p = 0.262$).

Down syndrome was identified as the most prevalent chromosomal abnormality ((34/299 (11.4%)) in patients with Hirschsprung's disease, and thus, it was classified into a distinct subgroup. Among patients with Hirschsprung's disease and Down syndrome, 28 (82.4%) had associated CHDs and 13 of these 28 patients (46.4%) had major CHDs. Patients with Hirschsprung's disease and Down syndrome were 77.78 times more likely to have CHD compared with those without Down syndrome (65.1% vs 2.3%, OR 77.78, 95%CI 27.93 - 216.60; $p < 0.001$).

Six patients with Hirschsprung's disease also had associated syndromes or associations, consisting of two cases of Mowat-Wilson syndrome, one case of DiGeorge syndrome, one case of Pierre Robin sequence, one case of Dandy-Walker syndrome and one case of Waardenberg syndrome. Patients with Hirschsprung's disease combined with these specific syndromes or associations were found to be 13.03 times more likely to have CHD compared to those without any syndromes and/or associations (9.3% vs 0.8%, OR 13.03, 95%CI 2.31 - 73.51; $p = 0.005$).

DISCUSSION

Cardiac neural crest cells contribute significantly to development of cardiac outflow tract, heart valves, aortic arch artery, cardiac aortopulmonary septum,[6-10] and the arterial truncus.[11,12] In our study, CHDs found in patients with Hirschsprung's disease aligned with the pathogenesis of cardiac neurocristopathies. Predominantly, these included acyanotic, left-to-right shunt CHD: patent ductus arteriosus (29 cases, 9.7%), atrial septal defects (18 cases, 6.0%), and ventricular septal defects (15 cases, 5.0%). Additionally, a case of hypoplastic left heart syndrome in a patient with Hirschsprung's disease was documented.[9]

Our study revealed that the sensitivities of CXR and echocardiography for diagnosing associated CHD in patients with Hirschsprung's disease were 48.8% and 100%, respectively. Echocardiography, with a 100% sensitivity, is the most effective screening tool for detecting asymptomatic CHDs, however, its precision for diagnosing specific types and conducting preoperative assessments of complex CHD is somewhat limited. While transthoracic echocardiography was efficient for diagnosing and evaluating simple CHDs, its accuracy in complex CHD cases was lower, at only 77.7%. Therefore, some patients may require additional investigations, such as computed tomography scans, cardiac magnetic resonance imaging and cardiac catheterization.[19]

The reported prevalence of CHD in patients with Hirschsprung's disease varies widely across studies, and ranges between 1.4% - 17%.[7-9,13-16] This variation has sparked debate on the appropriateness of using echocardiography to evaluate all patients with Hirschsprung's disease or for who have concomitant deformities or a syndrome or only those with chromosomal abnormality. Some research suggests that echocardiography can detect CHD in up to 45% of Hirschsprung's disease patients without cardiac symptoms, which has led to call advocating for universal echocardiographic screening in all patients with Hirschsprung's disease even if there is no concomitant deformities, syndromes or chromosomal abnormalities.[8,17] Conversely, some studies recommended echocardiography solely for patients with Hirschsprung's disease presenting with certain syndromes or other chromosomal abnormalities.[13] The discrepancies in incidence rates across studies can be attributed to differences in study methodologies and the severity of CHD.[20]

In prospective studies, mild forms of CHD, which are often asymptomatic and lack significant murmurs, tend to be detected. A prospective observational study reported an 8.3%[8] incidence of associated CHD, which is significantly higher than retrospective series or systematic literature reviews.[21-24] For instance, in the largest retrospective study[21], which examined 2,174 patients with Hirschsprung's disease, only 27 children (1.2%) were identified as having associated CHDs. The variance in reported prevalence of cardiac anomalies between prospective and retrospective studies can be attributed to that mild or absent of symptoms of associated CHDs in patients with Hirschsprung's disease could lead to misdiagnosis and/or a delayed diagnosis. Conotruncal anomalies such as transposition of the great arteries and double-outlet right ventricle, which are believed

to result from developmental issues tied to neural crest cells' critical embryological roles, were rare.[25,26]

In our retrospective study, we found that 43 out of 299 patients with Hirschsprung's disease (14.4%) also had associated CHD, indicating a higher incidence rate compared to other retrospective studies, even though echocardiograms were conducted on only 51 patients. This elevated incidence might be attributed to a higher prevalence of concomitant deformities, syndromes, and/or associations, along with a significant proportion of major CHDs (20/43 (46.5%)) in our study.

In our research, we observed that patients with Hirschsprung's disease with any associated anomalies (61/299 (20.4%)) who had either a concomitant deformity, a syndrome, and/or association, were 23.56 times more likely to have CHD compared to those without such anomalies ($p < 0.001$). These associated anomalies were categorized into three groups: 1) "concomitant deformity", defined as Hirschsprung's disease that co-occurs with another congenital deformity, excluding syndromes and/or association diseases or chromosomal abnormalities; 2) Down syndrome; and 3) a "syndrome and/or association" defined as Hirschsprung's disease with a specific syndrome and/or association or any chromosomal abnormality, excluding Down syndrome. Given these findings, it cannot be conclusively stated that all cases of Hirschsprung's disease with associated anomalies should automatically undergo echocardiographic screening for CHD without considering the distinct effects of these subgroups. Therefore, we conducted further analysis to determine whether each subgroup presents a higher risk of associated CHD and if it is suitable to perform routine echocardiographic screenings.

Hirschsprung's disease occurs as an isolated condition in approximately 70% of cases. In the remaining 30%, it is associated with various concomitant anomalies, such as gastrointestinal malformations, craniofacial and distal limb anomalies, sensorineural hearing loss, and abnormalities affecting the skin, central nervous system, genitalia, and kidneys.[6,13,27] Our study found that patients with Hirschsprung's disease who also had concomitant anomalies had a higher prevalence of CHD (6/28 (21.43%)) than patients with Hirschsprung's disease who had no concomitant anomalies (37/271(13.65%)). However, this difference in prevalence was not statistically significant ($p = 0.262$) and the odds ratio was 1.73.

Down syndrome is the most frequently occurring chromosomal abnormality associated with Hirschsprung's disease, appearing in 1% - 6% of patients.[8,28-30] Our findings show a higher prevalence of Down syndrome at 11.4% (34/299 patients), which is notably above the rate reported in, than other series. In our series, where 82.4% (28/34 patients) of patients with both Hirschsprung's disease and Down syndrome had CHD, had higher this incidence than other reported occurrences ranging between 36.1% - 62.5%.[8,13,28,31,32] The likelihood of encountering CHD in patients with Hirschsprung's disease and Down syndrome was 77.78 times higher than in those without Down syndrome ($p < 0.001$). Therefore, we recommend performing an echocardiogram for every patient with Hirschsprung's disease associated with Down syndrome. Moreover, our study suggests that a combination of Hirschsprung's disease and Down syndrome tends to present with more severe congenital heart abnormalities requiring surgical treatment compared to cases of Down syndrome alone.[8,33]

Hirschsprung's disease is linked with various syndromes and/or association,[7] such as Down syndrome (70%), Mowat-Wilson syndrome (24%), Cat eye syndrome (3%), Smith-Lemli-Opitz syndrome (2%), Turner syndrome (1%) and others such as central hypoventilation syndrome, and Goldberg-Shprintzen syndrome. The prevalence of CHD in cases of Hirschsprung's disease associated with a syndrome or chromosomal abnormality is reported at 51% (range 20% - 80%).[7] The prevalence of CHD associated with Hirschsprung's disease and each syndrome, or chromosomal abnormalities, varies[7], and is lowest in Mowat-Wilson syndrome and highest in Smith-Lemli-Opitz syndrome.[34] In our study, we observed six patients with Hirschsprung's disease and additional syndromes and/or associations: two with Mowat-Wilson syndrome, one with DiGeorge syndrome, one with Pierre Robin sequence, one with Dandy-Walker syndrome, and one with Waardenberg syndrome. Patients with Hirschsprung's disease and any associated syndrome and/or association were 13.03 times more likely to have CHD compared to those without such diseases ($p = 0.005$). Therefore, we recommend conducting an echocardiogram in each case of Hirschsprung's disease associated with a syndrome and/or association.

Limitations

1. The nature of retrospective study is the main limitation of this study which lead to selective bias whether indications and types of cardiac investigation should be conducted. A further prospective study should be performed.
2. In this study, the decision to perform echocardiographic examinations was triggered by clinical suspicions arising from symptoms, abnormal CXR, reduced pulse oximetry readings, or a heart murmur. This approach may lead to an underestimation of mild cardiac lesions.
3. The findings of this study reflect experiences of

a single institution, which serves a referral center for Hirschsprung's disease. The applicability of our results to other settings may be limited.

4. The absence of long-term cardiovascular follow-up data hindered our ability to identify mild CHDs that might manifest later in adolescence or adulthood.

CONCLUSION

In our study, Hirschsprung's disease was associated with CHDs in 14.4% of cases. CXR demonstrated a low sensitivity in diagnosing associated CHDs, indicating that echocardiograms should be considered as a more reliable diagnostic tool. However, it is not advisable to recommend echocardiograms for all patients indiscriminately.

Role of echocardiographic screenings should be applied in patients with Hirschsprung's disease associated with Down syndrome, other syndromes and/or associations, or concomitant deformities.

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Conflicts of interest

The authors have no conflicts of interest to declare.

Author Contribution

Conceptualization: RR. Methodology: RR, CT. Formal analysis: CT. Project administration: RR, CT. Visualization: RR, CT. Writing - original draft: RR. Writing- review and editing: RR. Approval of final manuscript: all authors.

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A Systematic Review and Illustrative Case of Post-Decompressive Craniectomy Syndrome Following Traumatic Brain Injury

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ABSTRACT

Post-decompressive craniectomy syndrome (PDCS) is a complication following decompressive craniectomy (DC). PDCS or also known as trephine or sunken skin flap syndrome has an indirect relationship with traumatic brain injury (TBI). The mechanism of PDCS is not yet fully understood and the clinical manifestations are diverse, causing PDCS to often be underdiagnosed. In this study, the authors aim to create a systematic review of PDCS following TBI including a discussion of incidence, clinical and radiological manifestations, management and outcome. This systematic review is conducted based on the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guideline. The literature search included electronic databases PubMed, Cochrane, JNS and EMBASE. All studies included were available in English and full-text format. In this research, 42 case reports were obtained. The population was predominantly male (72%) with a mean population age of 44.7 ± 17.3 years. The mean interval for onset and cranioplasty procedure was 80.17 ± 77.34 days and 92.05 ± 77.06, respectively. The most common clinical manifestations were sunken skin flap in the defect area (74%) and decreased consciousness (64%). Paradoxical herniation (74%) was the most common radiological manifestation. There was no connection between the occurrence of PDCS and the size of the defect. Cranioplasty remains the mainstay of management with clinical improvement in 96% of cases. PDCS should be suspected in every patient with symptoms of new neurological deficits after DC. Early management must be carried out to prevent further deterioration.

Keywords: Post-decompressive craniectomy syndrome, complication, decompressive craniectomy, cranioplasty
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INTRODUCTION

Post-decompressive craniectomy syndrome (PDCS) or trephine or sunken skin flap syndrome is a complication of decompressive craniectomy (DC) which describes new neurological deficits due to cortical dysfunction caused by brain compression in the defect area.[1–3] The incidence of this syndrome is estimated at 10% to 20% in patients after DC procedures.[4,5] Abnormalities in normal anatomy and physiology may cause a range of symptoms, including mental status abnormalities, hemodynamic disturbances, and neurological impairments.[6,7] The clinical and radiological characteristics presenting with PDCS are often atypical, making it important to consider these complications in each post-DC patient.[8,9]

One of the most common causes of increased intracranial pressure is traumatic brain injury (TBI).[10,11] Brain edema

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due to TBI causes intracranial hypertension.[12,13] DC is a procedure in the field of neurosurgery where skull bones are removed with the aim of reducing intracranial pressure.[14] The rationale for carrying out DC is the closed box concept of the intracranial cavity based on the Monro-Kellie doctrine.[15] DC provides the potential space of the cranial cavity and allows the expansion of the brain.[16]

DC has the effect of causing the cortex to become vulnerable to external pressure due to a skull defect.[17] Cranioplasty is a procedure to close cranial defects and is still considered the primary management to this day. Cranioplasty is performed to prevent or eliminate collapse of the brain parenchyma and the brain remains mechanically protected. Closure of bone defects is necessary to prevent differences in atmospheric pressure pressing on the cortex in the defect area.[18] Several concepts have been put up to attempt to explain the physiology of this disease, but the explanation is still elusive.[19,20]

The diverse manifestation of PDCS and its unclear mechanisms may contribute to its underdiagnosis and under-representation in the neurosurgical literature, resulting in a lack of awareness of this relatively common disorder within the neurosurgical community. Thus, we conducted a systematic review to discuss PDCS following TBI, which currently does not have much literature discussing this matter.

MATERIALS AND METHODS

Study design and literature search strategy

This systematic review aimed to review the incidence and complications of PDCS. The search strategy for journals was carried out referring to the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocol (PRISMA) guideline (Fig 1). Journal data was collected through several databases such as PubMed, Cochrane, JNS, EMBASE. The articles searched had no limitations on the year published and used the keywords "Trephine Syndrome" OR "Sunken skin flap syndrome" AND "Traumatic brain injury" AND "Craniectomy" AND "Cranioplasty". Authors reviewed the reference lists of all relevant studies including published studies. We excluded all unpublished studies or articles-in-press.

The definition of the syndrome was (1) a neurological deficit that usually appears after DC, (2) new complications that appear not as a sequel to the initial lesion, and (3) clinical improvement after cranioplasty. Subjects were patients who underwent a traumatic DC procedure with age >16 years. Exclusion criteria were subjects with age < 16 years and the cause of craniectomy other than trauma.

Data collection and synthesis process

Articles were accepted for this review if they were written in English or Indonesian and had no publication year restrictions. The data studied included sex, age, timing of first symptom and cranioplasty, sign and manifestation, defect area, outcome and bias. Statistical averages and percentages for all populations and characteristics were examined and described descriptively.

Illustrative case

A 35-year-old male patient presented with severe headache, came to our emergency department at Dr. Soetomo General Academic Hospital, Surabaya, Indonesia. He had a history of decompressive craniectomy procedure 3 months prior due to traumatic intracerebral haemorrhage and skull depressed fracture. His symptoms worsened 1 month before admission. Physical examination showed a visible sunken skin flap in the defect area. Brain computed tomography (CT) scan revealed paradoxical herniation in the defect area (Fig 2). The patient underwent cranioplasty. The patient had an uneventful postoperative course and was discharged with no headaches, emesis, or new neurological deficits.

RESULTS

The literature search yielded a total of 42 studies. The research flow diagram can be seen in Fig 1. The databases searched included PubMed, Cochrane, EMBASE, and JNS. The search was conducted in January 2024. After removing duplicates, we removed 489 articles in the abstract review and a further 288 articles in the full-text review. Of the remaining studies, we continued with a systematic review for 42 eligible studies with a total of 47 patients. All studies founded during the strategy process were either a case report or a case series. A case report or case series is a study that describes the course of a patient's condition descriptively. This is differentiated from a quantitative study in which analysis and comparisons are carried out between outcomes or treatments. Authors found no other quantitative studies such as cohort, case control or cross sectional studies.

Sex and age

The sex distribution is dominated by male (72%) compared to female (28%). The population's average age was 44.7 ± 17.3 years (Table 1).

Timing of onset and cranioplasty

The mean interval for symptoms to appear after the decompressive craniectomy procedure was 80.17 ± 77.34 days. The mean interval value for the cranioplasty

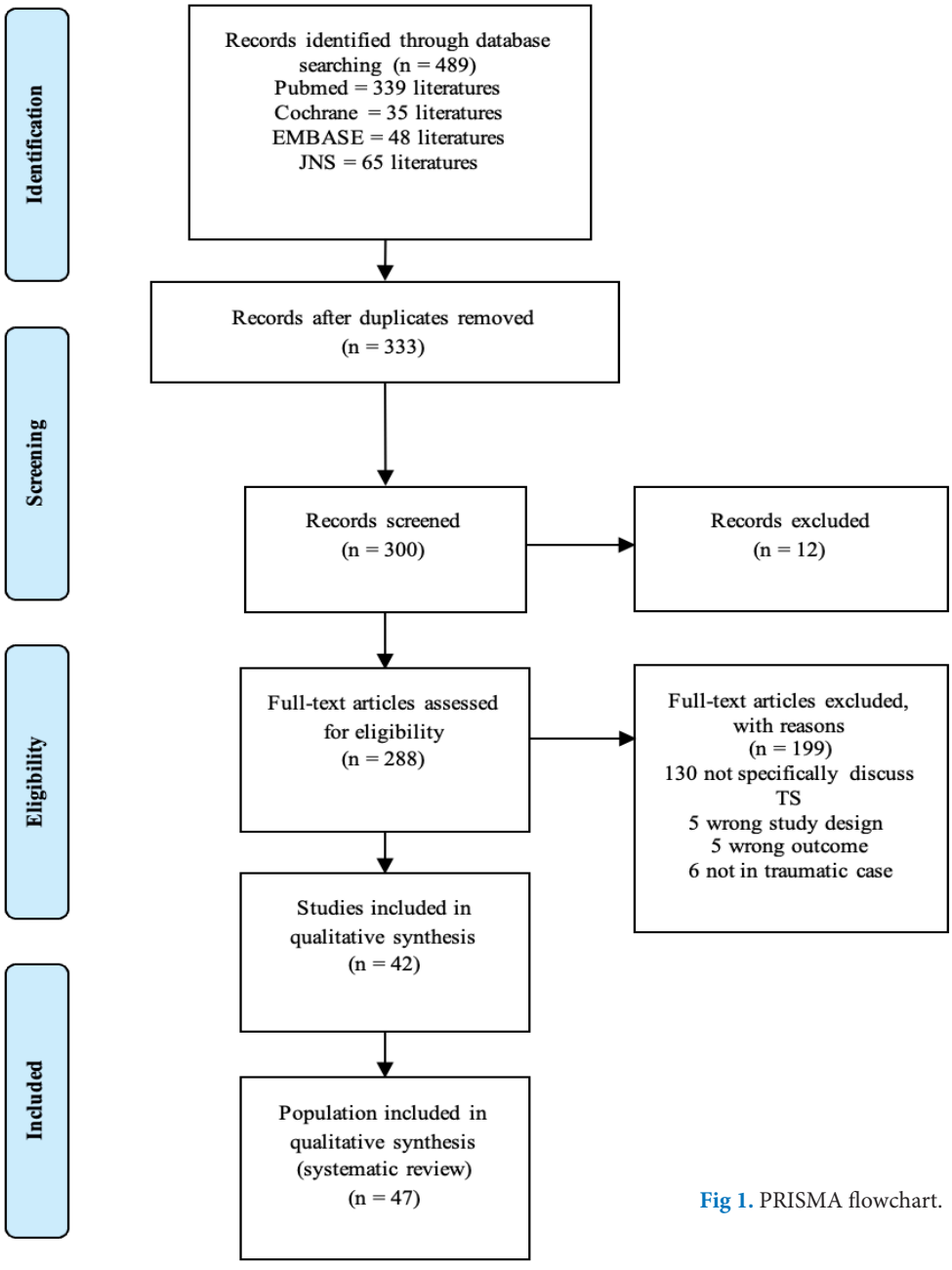

Fig 1. PRISMA flowchart.

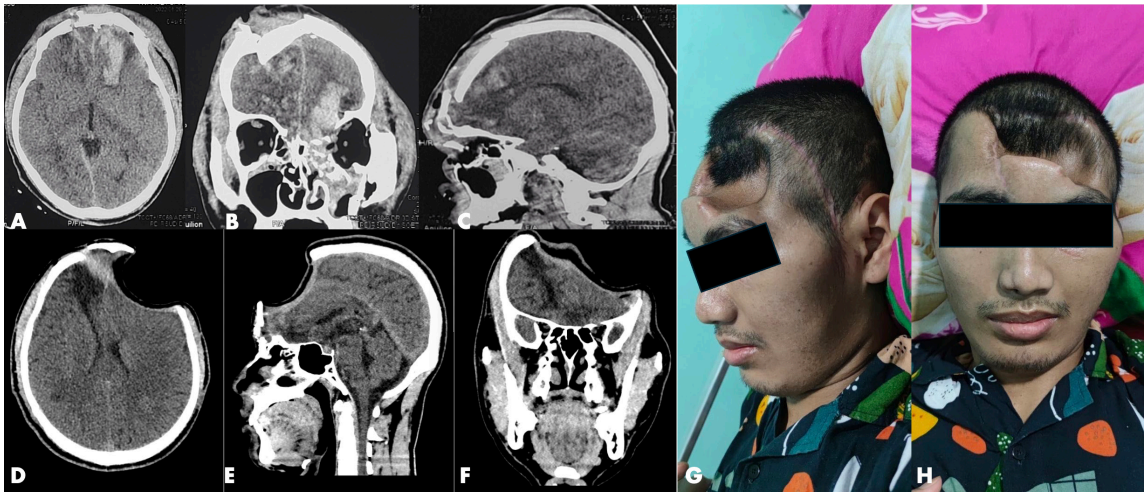

Fig 2. Preoperative CT revealed intracerebral haemorrhage and depressed fracture (A, B, and C). Radiological (D, E, and F) and clinical (G and H) images show features of the syndrome in the defect area after 3 months post-DC procedure.

TABLE 1. Demographic data.

Characteristic		No. (%) of Cases
Sex (n)	Male (%)	34 (72)
	Female (%)	13 (28)
Age (year)		44.7 ± 17.3
Timing from DC to onset (days)		80.17 ± 77.34
Timing from DC to cranioplasty (days)		92.05 ± 77.06

procedure was 92.05 ± 77.06 days after the decompressive craniectomy procedure (Table 1).

Clinical manifestation

The results of clinical manifestations in cases of TS after traumatic decompressive craniectomy are shown in Table 2. The most common clinical manifestations are sunken skin flap in the defect area (74%), and decreased consciousness (64%). Other symptoms include motor weakness (43%), headache (30%), language deficits (23%), worsening of positional symptoms (19%), cognitive deficits (13%), cranial nerve deficits (13%), seizures (10%), psychosomatic (4%), and sensory deficits (2%). Literature analysis reported no cases of mortality.

Radiographic image

The radiological features of the supporting examinations carried out are as shown in Table 3. Paradoxical herniation

TABLE 2. Clinical manifestation.

Clinical feature	No. of Cases	Percentage (%)
Sunken skin flap	35	74
Decreased consciousness	30	64
Motor weakness	20	43
Headache	14	30
Language deficits	11	23
Positional symptoms	9	19
Cognitive deficits	6	13
Cranial nerve deficits	6	13
Seizure	5	10
Psychosomatics	2	4
Sensory deficits	1	2
Mortality	0	0

TABLE 3. Radiographic image.

Radiological feature	No. of Cases	Percentage (%)
Paradoxical herniation	35	74
Hydrocephalus	11	23
Infarction	0	0

was the most common radiological presentation (74%), followed by hydrocephalus (23%). Literature analysis reported no features of infarction.

Defect area

Only 2 studies reported the size of the defect in a population of PDCS cases after traumatic craniectomy decompression, namely 43.6 cm^2 and 110 cm^2.

Outcome

In the majority of cases (n=45) there was clinical improvement after the cranioplasty procedure (96%).

Bias

An analysis was carried out to assess the risk of bias: confounding, selection, information, and reporting bias on 42 pieces of literature that underwent a systematic review. Details of the results of the risk of bias analysis can be seen in Fig 3. Authors assessed the bias based on the modified Cochrane Collaboration tool : Risk of Bias in Non-randomised Studies–of Interventions' (ROBINS-I).[20]

DISCUSSION

Epidemiology

Demographic factors such as age and gender may be risk factors that influence outcomes after craniectomy and cranioplasty. A study conducted by Santander et al., reported that in terms of age and gender, there was no difference between patients with or without PDCS.[21] The majority of the PDCS case population was male, which was also related to the fact that the predominance of the patient population undergoing DC following TBI occurred mostly in male patients.[22] Men were also predominant in this study. Demographic factors such as age and gender may be risk factors that influence outcomes after decompression and cranioplasty. In a cohort study by Sveikata et al in 2021, of the total of 40 patients studied, age and gender had a low p value on the risk of TS after decompression. These findings led to the conclusion that the incidence of PDCS following TBI was not significantly influenced by age or gender.[23]

Onset and clinical manifestation

The lack of established diagnostic criteria makes it difficult to diagnose PDCS patients early. Recent studies show that radiologically, 81% of patients with PDCS have sunken defect area, hydrocephalus, obliteration of ventricle, but the individual diagnostic yield is still low.[23,24] Approximately 50% of PDCS manifest without classic radiological signs such as sunken skin flaps, and more than 80% without paradoxical brain herniation. This study also showed that the majority of clinical manifestations included improvement after the cranioplasty procedure (96%), visible sunken skin flap (74%), and decreased consciousness (64%). Detailed physical and radiological examinations must be carried out to establish the diagnosis with such diverse manifestations.[23,25,26]

A study by Santander, reported that the majority of presentations were motor impairment (82%).[21] Therefore, some researchers recommend screening for cognitive deficits. Previous studies showed that 47% of patients with PDCS had cognitive impairment.[21,27] As the name of this syndrome suggests, sunken defect area was associated with PDCS in 57.14% cases.[30-31] Several studies also confirmed this, but it must also be taken into

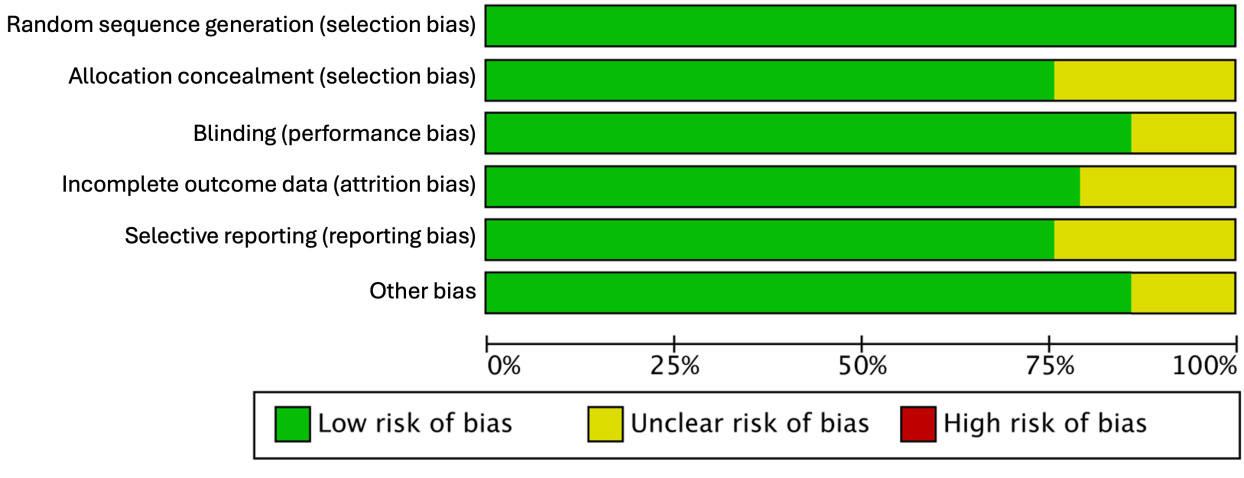

Fig 3. Bias analysis summary. The bias analysis was conducted based on the modified Cochrane Collaboration tool : Risk of Bias in Non-randomised Studies–of Interventions' (ROBINS-I).

account that some patients with sunken defect area had no neurological deficits.[28–30] Therefore, sunken defect areas are not cardinal symptoms of PDCS. This finding also corresponds to the definition used by several other studies, where true PDCS should be suspected when clinical presentation improve after cranioplasty.[31]

Radiological examination

Cerebrospinal fluid, atmospheric pressure, and cerebral blood flow are some of the variables that affect the PDCS occurrence. It is consistent that paradoxical herniation and hydrocephalus were the most common radiological signs in this study. Of these factors, atmospheric pressure is reported to be the main factor that causes compression and damage to cortical tissue in unprotected brain tissue in bone defects, which ultimately causes neurological deficits and then repair after cranioplasty.[32] Imaging with cranial F18-fluorodeoxyglucose positron emission tomography CT (F-18 FDG-PET/CT) is helpful for assessing brain metabolism. After TBI, molecular shifts and inflammation cause disruptions in glucose metabolism.[33]

Defect area

The size of the craniectomy has long been considered a factor in this syndrome. There is no correlation published in the literature, but craniectomies with an area >100 cm^2 may be associated with the incidence of PDCS.[22]

Tarr et al. showed that occurrence of PDCS increased with a craniectomy area of 50 cm^2 or more.[34] Although Sveikata et al showed that there no correlation between the extent of craniectomy in the PDCS and non- PDCS groups, wide craniectomy as an inclusion criterion in the study (mean area 112.8 ± 35.4 cm^2).[23] Our analysis is that PDCS will have a tendency to appear if it exceeds a certain area. So in patients who have extensive DC such as hemicraniectomy, the incidence of PDCS must be watched out for.[34]

Management and outcome

The initial management of PDCS that can be done is positioning from supination to a sitting position in the hope that intracranial pressure will decrease. Cranioplasty should be performed immediately when PDCS is suspected to prevent irreversible recovery of the functional outcome.[35] The incidence of cranioplasty-related complications (such as infection) or the inability to decompress it thoroughly should be monitored.[36]

Cranioplasty remains the primary management of PDCS.[36,37] Previous study reported that the earliest cranioplasty in patients with PDCS can be performed within 18 months after DC. The defect location factor (left, right, front, posterior or bilateral) did not have a significant correlation with the occurrence of PDCS.[29] Cranioplasty management in younger patients shows better postoperative outcomes.[38,39]

In another systematic review study, it was concluded that early cranioplasty (<3 months) does not have significant advantages when compared to late cranioplasty (>6 months). Early cranioplasty could reduce length of stay at hospital, but did not reduce the risk of complications.[40]

Research on cranioplasty after decompressive craniectomy by Safi et al in 2022, which used a sample of 132 patients, stated that the patient's initial level of awareness had a significant influence on post-cranioplasty outcomes.[41] This study analysed multiple logistic regression statistics to identify significant factors related to pre-cranioplasty Glasgow Outcome Scale (GOS), decompression indication, and cranioplasty waiting time. The study concluded that the best Glasgow Coma Scale (GCS) the patient had before the cranioplasty procedure had a significant influence on the outcome (p value 0.001). In 55 patients out of 132 samples who underwent cranioplasty after the decompression procedure had good outcomes with a pre-cranioplasty GOS score of 4-5 (good grade) and poor outcomes in patients with a pre-cranioplasty GOS score of 2-3 (poor grade).[29,34,41]

Limitation of the study

Authors didn't review ongoing trials because there were currently no ongoing trials with this study topic until this study conducted. The author didn't perform meta-analysis study due to two main reasons. First, there was no literature or research reports that randomly compare the effectiveness, outcomes and side events of PDCS. Second, the limited number of samples is due to the fact that all studies are either case reports or case series. The very small number of quantitative studies means that meta-analysis cannot be carried out.

CONCLUSION

The pathomechanism of PDCS is still unclear to date. The atypical clinical manifestations and delayed onset make PDCS difficult to recognize early. Clinicians should be aware of the possibility of PDCS in patients with new post-DC neurologic deficits. Cranioplasty should be planned as soon as the patient meets the criteria for defect closure to prevent further deterioration. Authors hope there will be more quantitative studies in the future so that meta-analysis and research related to PDCS can be carried out, so they will have higher level of evidence and more representative result.

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Author Contributions

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Conflict of Interest

None

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Prehabilitation in Clinical Practice: A Review of Concepts and Implementation in Enhancing Post-operative Outcomes

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ABSTRACT

In the presence of globalization and advancing clinical knowledge, there is a paradigm shift from a single patient care sector to a multidisciplinary-collaborated health care team. In pursuit of favorable postoperative outcomes, reduced length of hospital stay, minimized complications and morbidity, and accelerated recovery, prehabilitation strategies assume a prominent role following preoperative assessment. Fundamental to prehabilitation are physical activity, nutrition, and psychological interventions, aimed at enhancing preoperative functional reserve through expert-designed program sessions spanning various specialties. Enhanced Recovery After Surgery (ERAS) serves as an intra- and postoperative strategy to facilitate the smooth return of patients to their baseline status post-operation by mitigating surgical stress. Integrating prehabilitation into ERAS protocols holds promise for optimizing postoperative outcomes. Protocols for prehabilitation across diverse patient groups have been proposed, paving the way for the routine incorporation of prehabilitation into patient care.

Keywords: Prehabilitation; perioperative; postoperative outcomes; enhanced recovery after surgery (ERAS); multidisciplinary; multimodal (Siriraj Med J 2024; 76: 646-654)

INTRODUCTION

In the midst of globalization and the expanding global population, particularly in the context of an aging demographic, the demand for healthcare, including hospitalization, has surged.[1,2] This increase is further accompanied by the prevalence of non-communicable diseases, emerging conditions, and chronic comorbidities, necessitating both medical and surgical interventions. To address these challenges, evidence-based guidelines for intraoperative and immediate postoperative care have been established. These guidelines aim to facilitate rapid recovery and mitigate postoperative complications, such as prolonged hospital stays, hospital readmissions, escalated healthcare costs, and elevated mortality rates.[3-5]

Optimizing perioperative care necessitates a multidisciplinary approach that integrates surgical and anesthesia standpoints. Comprehensive medical management spans from preoperative assessment through to patient discharge. However, the pivotal factor determining favorable postoperative outcomes lies in the patient's preoperative functional capacity. Limited functional capacity has been consistently linked to increased risks of 30-day mortality and postoperative complications. Consequently, various strategies have been devised to enhance and optimize preoperative functional status, particularly among vulnerable populations such as the elderly, frail individuals, and those suffering from malnutrition.[4,6,7] The preoperative phase is widely acknowledged as a

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critical window for risk assessment, optimization, and meticulous patient preparation in anticipation of the physiological stress induced by surgical procedures.[8]

This review article underscores the significance of prehabilitation as a strategy for enhancing preoperative functional capacity by strengthening physiological and metabolic reserves in at-risk patients. It advocates for the integration of prehabilitation into routine anesthesia practice, emphasizing its potential benefits. The article also explores how prehabilitation can be integrated with Enhanced Recovery After Surgery (ERAS) within a framework of multidisciplinary collaboration, and introduces its implementation among various groups of specific patients.

Definition of prehabilitation

Prehabilitation, a term first proposed approximately two decades ago by Topp et al., pertains to a program aimed at enhancing functional capacity prior to admission to the intensive care unit (ICU).[9] Despite its original conceptualization, prehabilitation has undergone a paradigm shift, and is now viewed as a valuable strategic approach during preoperative preparation to mitigate surgery-induced stress.[10] The fundamental objective of prehabilitation is to minimize the risk of postoperative complications and expedite recovery through the proactive implementation of physical training, nutritional enhancement, and mental support, with the aim of reducing morbidity and mortality following surgery.

Optimizing the preoperative patient status necessitates a multidisciplinary collaboration involving perioperative clinicians, surgeons, anesthesiologists, geriatricians, nurses, physiotherapists, nutritionists, and various other pertinent healthcare professionals. This endeavor is often referred to as "pre-surgical conditioning", representing measures aimed at enhancing the functional and mental status of patients before surgery, improving disease manifestations, and preventing potential adverse events through the adoption of prehabilitation principles.[11]

Implementation of preoperative prehabilitation approaches

The effectiveness of treatment extends beyond the surgical procedure alone; it also relies on the speed of recovery and the restoration of pre-surgery functional capacities. Implementing carefully planned physical activity programs, initiated 4-6 weeks before scheduled surgery, has been shown to enhance fitness levels.[12] Additionally, as previously mentioned, integrating nutritional interventions, psychological support, and cessation of smoking and alcohol consumption is imperative and should be incorporated into the multimodal prehabilitation regimen.

Physical exercises

One of the core components of prehabilitation is physical exercise, which encompasses a variety of activities proven to enhance functional capacity. These include aerobic exercise, resistance training, muscle strengthening, balance training, and flexibility exercises. The design of physical exercise programs is tailored to align with patients' baseline physical abilities, as assessed by measures such as the 6-minute walk test (6MWT), oxygen consumption in the aerobic threshold (AT), and peak exercise capacity (VO_2 max).[11] Typically, the recommended total exercise duration is 2.5 hours per week, consisting of 2-3 sessions of 30-40 minutes of aerobic exercise per week. The target heart rate for each exercise session should range between 50-80% of the maximum age-related heart rate, calculated as 220 minus the individual's age in years. Strengthening exercises targeting daily-life muscles are recommended twice a week, alternating with sessions of flexibility and balance exercises.[4,13] To tailor an appropriate exercise program for each individual, common assessments of preoperative functional capacity[14-31] are conducted as outlined in Table 1.

Nutritional optimization

The concept of nutrition in prehabilitation extends beyond merely replenishing deficit calories. Nutritional support is envisioned proactively, encompassing both the preoperative and postoperative periods.[32] It is recommended that all patients, especially those with malnutrition and those undergoing gastrointestinal or cancer surgery, be encouraged to receive nutritional support. Enteral nutrition is prioritized for patients scheduled for major surgical interventions, with an intake of 1.2-1.5 g/kg of body weight of protein for approximately 7-14 days. Protein supplementation is suggested within 1 hour following physical activity to optimize muscle protein synthesis. Consumption of 140 g of carbohydrates around 3 hours prior to exercise is encouraged to enhance muscle and liver glycogen storage.[33-36]

Psychological wellness

Mental health holds equal significance to physical well-being, particularly in the context of surgery. Preoperative stressors such as fear, anger, depression, and anxiety, if left unaddressed, can accumulate and negatively impact recovery, treatment outcomes, and overall quality of life. Various strategies are proposed to alleviate psychological

TABLE 1. Preoperative functional capacity assessments[14-31]

Assessments	Details	Interpretation
Cardiopulmonary Exercise Testing (CPET)[14-18]	The gold standard for measuring functional capacity and the capability to achieve metabolic demands. Requires significant time and resources. Involves estimating cardiopulmonary function and cellular respiration by assessing physiological responses to exercise and cardiorespiratory performance. Includes the monitoring of electrocardiogram (EKG), minute ventilation, heart rate, O_2 uptake, and CO_2 output.	The scoring system ranges from 0 to 20, where scores of 0-5 indicate normal reference levels, while scores > 5 signify escalating risk factors. These include: a ratio between pulmonary ventilation and CO_2 production (VE/VCO_2) slope of ≥ 34 = 7 points; heart rate recovery (HRR) of ≤ 16 beats/min = 5 points; O_2 uptake efficiency slope (OUES) of ≤ 1.4 = 3 points; end tidal CO_2 partial pressure ($PETCO_2$) of < 33 = 3 points; and peak O2 consumption (VO_2 max) of ≤ 14 ml/kg/min = 2 points. Peak VO_2 < 15 ml/kg/min corresponds to metabolic equivalents (METS) < 4, resulting in postoperative complications. Peak VO_2 > 20 ml/kg/min indicates a low risk of postoperative mortality. The level of O_2 uptake at which lactate begins to increase in the circulation (anaerobic threshold, AT) < 9-11 ml/kg/min is related to postoperative complications and mortality.
The Duke Activity Status Index (DASI)[14,19-21]	Utilization of a 12-item questionnaire to determine the capacity of physical tasks performance. DASI score spans from 0 to 58.2 and possesses predictive capability for estimating the VO_2 max as expressed by the formula: VO_2 max = (0.43 x DASI score) + 0.96.	DASI > 34 indicates a predicted VO_2 max > 15 ml/kg/min. DASI < 34 is associated with an increased risk of 30-day mortality or experiencing moderate to severe postoperative complications among patients vulnerable to myocardial infarction or undergoing major surgery. DASI < 31.95 signifies low functional capacity among patients with preexisting stroke.
The 6-minute walk test (6MWT)[14,22-24]	A sub-maximal exercise assessment wherein a patient walks back and forth on a level surface between 2 designated markers. The final walking distance is reported in meters (m).	The 6MWT values of 427 m and 563 m indicate a low AT of < 11 ml/kg/min and a high AT of > 11 ml/kg/min, respectively. A 6MWT result of < 350 m is associated with an increased risk of 12-month disability following surgery. A 6MWT result of 400 m corresponds to New York Heart Association (NYHA) classification 2.

TABLE 1. Preoperative functional capacity assessments[14-31] (Continue)

Assessments	Details	Interpretation
The incremental shuttle walk test (ISWT)[14,25,26]	Walking on a flat surface between 2 points with acceleration. ISWT is associated with VO_2 max measurement. The final walking distance is reported in meters (m).	The ISWT result > 360 m corresponds with VO_2 max > 15 ml/kg/min and AT > 11 ml/kg/min.
Brain natriuretic peptide (BNP) and N-terminal pro-brain natriuretic peptide (NT-pro BNP)[14,27,28]	The preoperative plasma levels of BNP and NT-pro BNP may be relevant to both mortality and cardiac complications following non-cardiac surgery.	A BNP level ≥ 92 pg/ml and an NT-pro BNP level ≥ 300-450 pg/ml may serve as predictors of postoperative morbidity within 30 days.
High-sensitivity cardiac troponin T (hs-cTnT)[29,30]	The preoperative level of plasma hs-cTnT can aid in predicting peri-operative myocardial injury/infarction.	A cutoff of ≥ 14 pg/ml designates an abnormal level of hs-cTnT, which predicts perioperative coronary artery adverse events.
Growth differentiation factor-15 (GDF-15)[29,31]	The preoperative plasma level of GDF-15 can predict the risk of myocardial injury after non-cardiac surgery and also enhance cardiac risk evaluation by 30% compared to the Revised Cardiac Risk Index (RCRI) alone.	The risk of myocardial injury after non-cardiac surgery is 12% when the GDF-15 level is between 1,000-1,500 pg/ml, and 34% when > 3,000 pg/ml.

Abbreviations: 6MWT: The 6-minute walk test; AT: Anaerobic threshold; BNP: Brain natriuretic peptide; CO_2: Carbon dioxide; CPET: Cardiopulmonary exercise testing; DASI: The Duke Activity Status Index; EKG: Electrocardiogram; GDF-15: Growth differentiation factor-15; hs-cTnT: High-sensitivity cardiac troponin T; ISWT: The incremental shuttle walk test; kg: Kilogram; m: Meter; METS: Metabolic equivalents; min: Minute; ml: Milliliter; NT-pro BNP: N-terminal pro-brain natriuretic peptide; NYHA: New York Heart Association; O_2: Oxygen; OUES: Oxygen uptake efficiency slope; $PETCO_2$: End tidal carbon dioxide partial pressure; pg: Picogram; RCRI: Revised Cardiac Risk Index; VCO_2: Carbon dioxide production; VE: Pulmonary ventilation

stress, including deep breathing techniques, meditation, muscle relaxation, yoga, cognitive training, and potentially seeking consultation with a psychologist.[37] An integrated exercise and nutrition plan can be incorporated into the program to provide psychological relief, motivating and encouraging patients to engage in prompt mental and physical preparation before their planned surgery.

Preoperative education is advocated in conjunction with psychological interventions. Such education, encompassing information pertaining to surgery and anesthesia, perioperative management, and pain control, has been demonstrated to mitigate anxiety and enhance patient satisfaction.[38] The multimodal prehabilitation approaches[4,11,13,33-37] are outlined in Table 2.

Prehabilitation for specific groups of patients

Strengthening the functional reserve prior to surgery constitutes the core principle of prehabilitation. It is essential to note that while specific interventions primarily target patient cohorts vulnerable to surgical stress, certain individuals, particularly those identified as such, may require tailored prehabilitation interventions to optimize their surgical outcomes.

Frail surgical patients

Frailty denotes the age-related process encompassing both functional and cognitive decline, which subsequently elevates the risk of 30-day postoperative complications and 1-year mortality.[39] Despite the absence of a standardized universal prehabilitation regimen for frailty,[40] adopting a multimodal prehabilitation strategy could be beneficial. Such a program for frail patients may include[41]:

1. Moderate to intense aerobic exercise and resistance training targeting muscles essential for daily functioning, such as the upper and lower limbs, for 75-90 minutes, twice per week

TABLE 2. The multimodal prehabilitation approaches.[4,11,13,33-37]

Components of multimodal prehabilitation		
1) Physical exercise intervention		
Aerobic exercise: 30 min/day, 2-3 times/week, maintaining the target heart rate of 50-80% of age-adjusted maximal heart rate, such as: walking cycling running hiking swimming etc.	Resistance exercise: 8-15 repetitions/set for 1-2 sets, 2 times/week, targeting the strengthening of muscles essential for daily activities including arms, shoulders, chest, abdomen, back, and legs. Examples of exercises include: push-ups weight lifting abdominal curls etc.	Flexibility and balance: 2-3 times/week, holding each position for 20-30 sec, including: standing on one leg lateral thigh lift single-leg squat stretching yoga etc.
2) Nutritional intervention		**3) Psychological intervention**
Enteral nutrition is prioritized, with a protein intake of 1.2-1.5 g/kg supplemented by an additional 20-30 g of protein following aerobic exercise. An intake of 140 g of carbohydrates is recommended 3 hours before exercise to support glycogen storage in the muscles and liver. Arginine and omega-3 fatty acids are supplemented to enhance immune function.		A 60-min session with a psychological expert is recommended to reduce anxiety and negative mood effects. Psychological support also enhances patient motivation and compliance with the prehabilitation program. Examples of techniques for psychological support include: mindfulness meditation deep breathing muscle relaxation positive thinking etc.

Abbreviations: min: Minute; sec: Second

2. Dietary adjustments tailored to body weight and composition, aiming for an intake of 25-30 kcal/kg and protein intake of 1.5 g/kg, initiated 4 weeks prior to surgery and supplementation with arginine and omega-3 fatty acids to enhance immune function

3. Psychological prehabilitation coupled with patient education

Overall, the implementation of multimodal prehabilitation interventions in frail patients is strongly recommended (1B-1C recommendation) to enhance postsurgical outcomes.[40]

Cancer patients

Multimodal prehabilitation remains a mainstream practice, with recent systematic reviews focusing on exercise training programs for cancer patients. These programs typically include a warm-up period of 5-10 minutes, followed by a 30-minute session comprising aerobic and resistance exercises or aerobic training alone, concluding with a 5-10-minute cool-down period. Sessions are typically conducted 3-4 times per week over a span of 4 weeks. As a consequence of the limited number of studies and low sample size, the benefit of exercise prehabilitation in cancer patients is not apparent. However, there is a tendency towards the advantages of prehabilitation for reductions in the length of hospital stay and postoperative complications.[42]

Elderly patients

Among the elderly population aged over 65 years,

baseline health can be stratified into three groups: good health, pre-frail (experiencing normal aging), and frail (exhibiting pathological presentation). Regardless of initial health status, a decline in functional capacity is typically observed after surgery, with recovery to the baseline preoperative level often taking several months.[43] With the implementation of moderate to intense aerobic and resistance exercise aiming for 80% of the maximum heart rate, 1.2-1.5 g/kg/day of protein intake with the supplementation of 20-30 g whey protein after aerobic exercise, and an anxiety relief program, an increase in muscle strength, muscle power, and VO_2 max is observed.[44]

Prehabilitation and Enhanced Recovery After Surgery (ERAS)

ERAS has been recommended in the intraoperative care plan to promote early recovery and prevent adverse outcomes.[45-52] However, there are a limited number of studies investigating the beneficial association between prehabilitation and the ERAS protocol. While ERAS has the potential to independently mitigate surgical stress and optimize surgical outcomes, some research has demonstrated an expedited return to baseline functional status, referred to as surgical resilience, among patients who undergo preoperative prehabilitation followed by ERAS intervention. Patients undergoing a multimodal prehabilitation plan demonstrated superior preservation of muscle mass and walking capacity, as determined by the 6MWT after surgery, compared to those who received only the ERAS protocol.[53,54] Collectively, prehabilitation serves as a complement to ERAS by targeting the reduction of surgical stress through the enhancement of preoperative functional reserve. Nevertheless, the effectiveness of prehabilitation relies on both the baseline functional capacity and adherence to multimodal interventions.

The independent factors contributing to adverse postoperative outcomes include advanced age (≥ 75 years), smoking, hypertension, kidney disease requiring dialysis, body mass index (BMI) ≥ 30 kg/m², chronic steroid use, and American Society of Anesthesiologists (ASA) physical status classification ≥ 3.[55] These risks for adverse postoperative outcomes are largely attributed to old age and frailty, characterized by a decline in the functional capacity and performance of organ systems, as well as cognitive function. Therefore, the implementation of prehabilitation for elderly and frail patients, as previously discussed in this context, is required.

While prehabilitation is not novel in the fields of surgery and anesthesia, its integration into ERAS protocols for ensuring optimal recovery and reducing postoperative complications is not widely practiced in routine clinical settings, particularly in Thailand. A concise overview is provided in this article regarding prehabilitation and its interaction with personalized protocols tailored to individual patients, aiming to enhance clinical outcomes and mitigate adverse postoperative events. The integration scheme[4,53,54,56] of prehabilitation and ERAS targeting favorable postoperative outcomes is demonstrated in Fig 1.

Integrating prehabilitation into clinical practice through a multidisciplinary collaboration

Prehabilitation necessitates multifaceted collaboration among various healthcare professionals. Commencing with the mutual agreement between surgeons and patients regarding the forthcoming operation, the subsequent step involves preoperative screening for risk stratification and patient optimization, typically conducted in the preoperative clinic. The responsible team comprises clinicians from diverse specialties, nurses, and notably

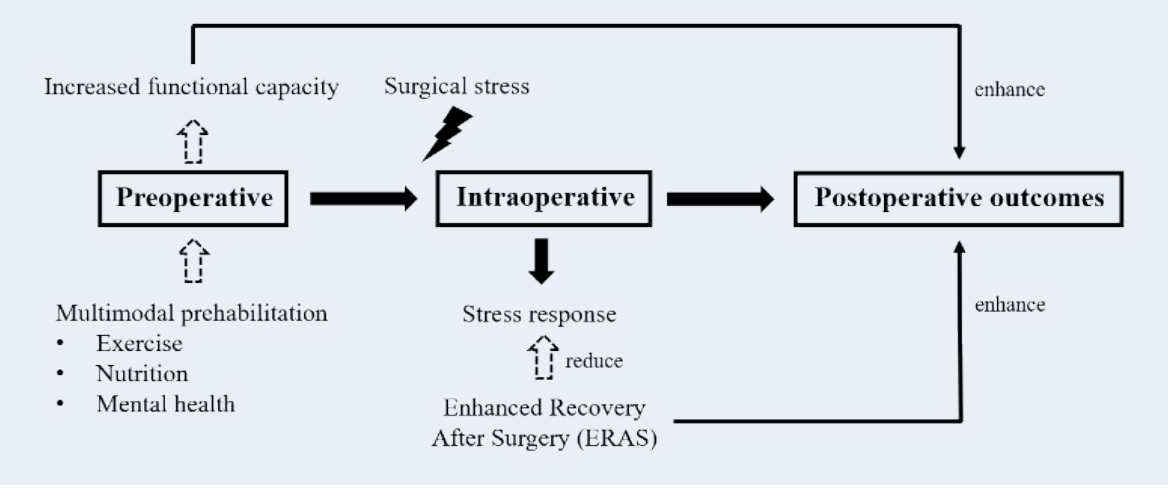

Fig 1. Integration of prehabilitation and ERAS in surgical care to improve postoperative outcomes[4,45,46,54]

anesthesiologists, who conduct preoperative evaluations in the preanesthetic clinic. After preoperative evaluation, the baseline functional assessments are determined by the prehabilitation team, which includes physiotherapists, exercise trainers, nutritionists, pharmacists, psychologists, smoking and alcohol cessation counselors, and other pertinent healthcare personnel. Prehabilitation interventions are implemented. This thorough preoperative evaluation and the subsequent prehabilitation program serve as a preparatory platform for elective surgery patients before their scheduled procedures.[4,57]

Future directions in prehabilitation

Several studies have investigated the implementation of prehabilitation programs for patients undergoing various surgical procedures. These multimodal interventions have shown promising results in enhancing patients' functional capacity and reducing postoperative complications.[18,40,42] However, despite the documented benefits of multimodal prehabilitation in improving functional capacity, there remains limited effectiveness among vulnerable patients with low baseline functional reserve and poor adherence to interventions. Previous studies on prehabilitation have shown variations in study design, sample size, and outcome measurement. Furthermore, adherence to prehabilitation protocols varies widely across studies, ranging from 16% to 97%.[58] Therefore, there is room for improvement in the form of prudent preoperative risk prediction, involving mutual decision-making among multidisciplinary care teams to tailor personalized prehabilitation interventions. Given the association of cognitive decline with aging, frailty, and malignancy, there is growing interest in integrating cognitive stimulation training into prehabilitation programs alongside exercise, nutrition, and psychological approaches, which are the cornerstones of the prehabilitation concept.[59,60]

CONCLUSION

Multimodal prehabilitation represents a preoperative strategy aimed at mitigating the stresses associated with subsequent surgery and anesthesia. Integrating prehabilitation with ERAS protocols can enhance functional capacity and fortify surgical resilience, thereby reducing complications during and after the operation. While exercise intervention plays a prominent role in the efficacy of prehabilitation, the significance of nutritional and psychological support is less apparent. A possible application to current perioperative practice is the integration of a preoperative prehabilitation program for indicated patients, emphasizing individualized care aimed at enhancing functional capacity in parallel with the intraoperative ERAS protocol. However, a knowledge gap exists that future research needs to address to refine interventions and establish clear outcome measures, thereby fully exploring the potential of prehabilitation as a multidisciplinary approach to improving postoperative outcomes.

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Author Contributions

PS was responsible for conceptualization, data curation, manuscript writing, and the review of the final manuscript. AJ contributed to data curation and the writing of the initial draft. NN managed data curation. All authors have read and approved the final manuscript.

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Conflicts of interest

The authors declare that there are no conflicts of interest.

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Food-Dependent Exercise-Induced Anaphylaxis: A Challenging Life-threatening Condition

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ABSTRACT

Food-dependent exercise-induced anaphylaxis (FDEIA) is an uncommon but potentially life-threatening condition characterized by allergic reactions triggered by the combination of specific food ingestion and physical exertion. Despite its rarity, FDEIA poses significant diagnostic and management challenges due to its complex pathophysiology and variable clinical presentation. Diagnosis relies on careful evaluation of clinical history, symptomatology, and laboratory tests, with inherent difficulties in distinguishing FDEIA from other related conditions. Management of FDEIA involves comprehensive strategies to minimize the risk of allergic reactions through measures such as allergen avoidance, patient education, and timely administration of epinephrine. While existing treatment approaches primarily target acute reactions, ongoing research endeavors are crucial for validating emerging diagnostic and therapeutic modalities. This review offers a comprehensive overview of FDEIA, encompassing its epidemiology, underlying pathophysiology, clinical presentations, diagnostic challenges, and management approaches.

Keywords: Anaphylaxis; exercise; food allergy; food-dependent exercise-induced anaphylaxis; gluten; challenge test (Siriraj Med J 2024; 76: 655-660)

INTRODUCTION

Food-dependent exercise-induced anaphylaxis (FDEIA), first described in the 1970s, is a rare but potentially life-threatening condition characterized by allergic symptoms triggered by the combination of specific food ingestion and physical exertion.[1,2] Evidence indicates that FDEIA constitutes a subset of food-induced anaphylactic reactions.[3] Despite its relatively low incidence, FDEIA can lead to significant morbidity and mortality if not promptly recognized and managed.[3] While exercise-induced and food-induced anaphylaxis are well-documented individually, their confluence in FDEIA presents unique diagnostic challenges for clinicians.[4] FDEIA's complex pathophysiology and variable clinical presentation complicate its diagnosis and management.[3] Recent research has focused on understanding the role of mast cells, immunoglobulin E (IgE)-mediated reactions, and exercise-induced immune responses in FDEIA. Advances in diagnostic criteria, including oral food challenges with exercise provocation, have enhanced diagnostic accuracy and informed more targeted management strategies.

This review provides a comprehensive overview of FDEIA, including its epidemiology, pathogenesis and pathophysiology, causative food, augmenting factors, clinical manifestations, diagnostic criteria, and management approaches. Relevant articles on FDEIA published in the MEDLINE database from inception to March 2024 were evaluated and summarized. Our search strategy included keywords such as "food-dependent exercise-induced anaphylaxis," "exercise-induced anaphylaxis," and "food allergy." We included peer-reviewed articles that provided significant insights into the epidemiology,

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pathogenesis, clinical manifestations, diagnosis, and management of FDEIA. Exclusion criteria included non-English articles, abstracts without full-text availability, and studies unrelated to FDEIA. Data extraction focused on summarizing key findings and identifying gaps in the current understanding of FDEIA.

Epidemiology

Estimating the precise prevalence and incidence of FDEIA remains challenging due to its rarity. A questionnaire survey conducted among 11,647 Japanese children reported FDEIA incidences of 0% in kindergartens. 0.06% in elementary schools and 0.21% in junior high schools.[5] Subsequent surveys in Japanese schools found FDEIA prevalence rates of 0.017% among 76,229 junior high school students and 0.0047% among 170,146 elementary school students.[6,7] In Korea, registry data of 558 participants across 16 centers focusing on anaphylaxis revealed that persons under 18 years accounted for 60% of registered patients, with FDEIA prevalence at 1.2% among children and 3.1% among adults.[8] Notably, FDEIA represents 30% to 50% of exercise-induced anaphylaxis cases.[6,9] Previously reported prevalence documented FDEIA diagnosis using questionnaire-based surveys and not confirmed by laboratory tests or food challenges.[5-8] Most documented cases are associated with wheat and seafood ingestion.[5-7] Although FDEIA predominantly affects adolescents and young adults, it has been reported across various age groups.[7] The prevalence of FDEIA is likely to vary among different populations due to differences in dietary patterns, exercise habits, and geographic exposure to allergens.

Pathogenesis and pathophysiology

The pathogenesis and pathophysiology of FDEIA involve complex interactions between allergenic proteins from ingested foods, exercise, and immune responses (Fig 1).[10] Food allergens implicated in FDEIA vary among individuals, with common triggers, including wheat, shellfish, celery, and legumes.[11] Moreover, a broader spectrum of food categories such as meat, vegetables, fruit, seeds, and cereals, has been associated with FDEIA.[11,12] Omega-5 gliadin, a component of wheat, is a notable allergen in FDEIA.[13-15] Its molecular structure, rich in glutamine and proline, forms stable, immunogenic epitopes resistant to gastrointestinal digestion.[13-15,16] These proteins can penetrate the intestinal mucosa and reach the systemic circulation, particularly when exercise increases intestinal permeability.[17,18] Studies have shown that reducing omega-5 gliadins in mutant wheat cultivars significantly decreases allergenicity in patients with FDEIA, suggesting potential safe alternatives for these individuals.[19] Understanding the molecular composition and reactivity of omega-5 gliadin is essential for developing targeted diagnostic and therapeutic strategies for FDEIA.

Physical exercise is an augmenting factor in FDEIA pathophysiology by increasing the permeability of blood vessels. Both strenuous and light exercise can trigger

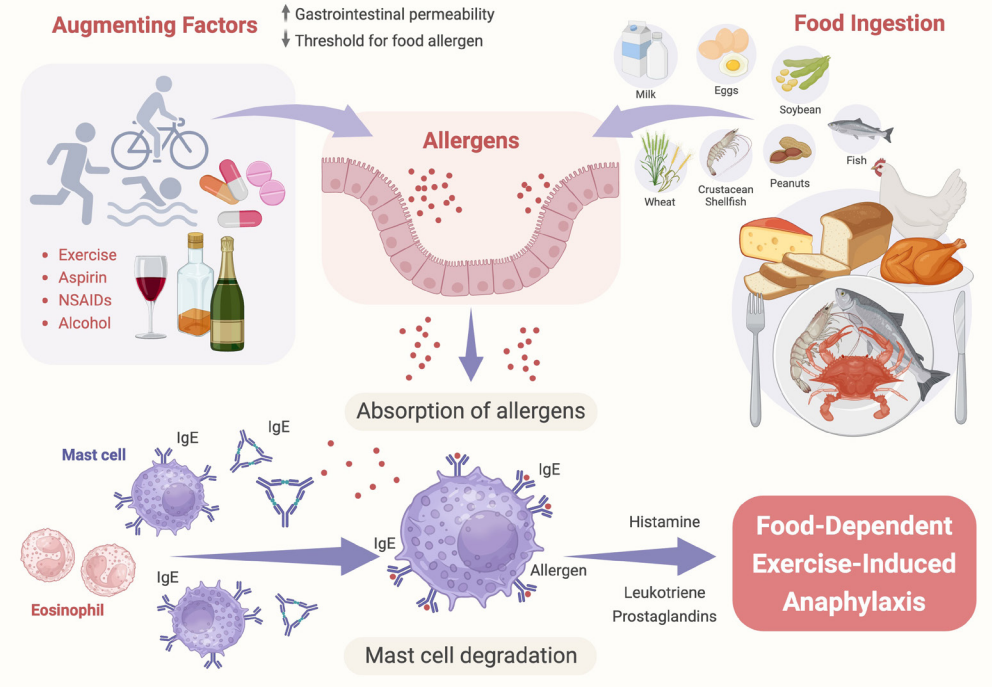

Fig 1. The pathogenesis and pathophysiology of food-dependent exercise-induced anaphylaxis. This diagram provides a visual representation of the sequential events leading to the development of FDEIA, highlighting the critical role of food allergen ingestion, exercise as an augmenting factor, and mast cell activation in the pathophysiology. Upon ingesting the culprit food, the food-allergenic proteins bind to specific immunoglobulin E (IgE) on the surface of mast cells, leading to mast cell degranulation with the release of inflammatory mediators, such as histamine and other mediators.

anaphylactic reactions, emphasizing the need to consider exercise intensity and timing relative to food ingestion.[20] FDEIA can develop in both well-trained athletes and individuals engaging in sporadic activities like walking.[20] In addition to exercise, various augmenting factors can contribute to FDEIA, including aspirin, non-steroidal anti-inflammatory drugs (NSAIDs), higher temperature, alcohol consumption, atopic dermatitis, and the menstrual cycle.[5,21-25] These cofactors can significantly lower the food threshold needed to trigger a reaction,[26] enhance the severity of FDEIA episodes, and complicate diagnosis.

The interaction of allergens with IgE on sensitized mast cells[17,18] leads to mast cell activation and the release of inflammatory mediators such as histamine, leukotrienes, and prostaglandins.[10] These mediators initiate a cascade of immune responses, resulting in the clinical manifestations of anaphylaxis.

Clinical manifestations

The clinical symptoms of FDEIA typically develop when individuals engage in physical exertion within 30 to 120 minutes after ingesting the responsible food, with symptoms onset occurring between 10 to 50 minutes following exercise.[14] The clinical manifestations of FDEIA encompass a broad spectrum of symptoms related to IgE-mediated reaction, ranging from mild cutaneous reactions to severe systemic anaphylaxis.[20] Cutaneous involvement, such as urticaria, pruritus, flushing, and angioedema, is the most common manifestation, followed by respiratory and gastrointestinal symptoms. Cardiovascular symptoms like tachycardia, hypotension, and syncope may arise, with potential progression to shock and cardiac arrhythmias. Though less common, neurological symptoms include dizziness, confusion, and loss of consciousness. The reactions could evolve into anaphylaxis involving multi-organ systems that pose life-threatening risks.[27] The severity of symptoms may vary between episodes and among individuals, depending on the amount of ingested culprit food, exercise intensity, and immune system sensitivity.[28]

A recent meta-analysis found a significant association between FDEIA and coexisting atopic conditions.[11] Patients with FDEIA had a lower prevalence of atopy (56.9%) compared to those with food-dependent exercise-induced urticaria/angioedema without anaphylaxis (77.3%).[11] The most prevalent atopic conditions include allergic rhinitis, asthma, allergic conjunctivitis, and atopic dermatitis. Notably, a history of atopy, particularly allergic rhinitis, is a significant risk factor for recurrent FDEIA episodes.[29] Conversely, a history of urticaria was more common in FDEIA patients with wheals and/or angioedema (59.1%) compared to those without anaphylaxis (12.5%), with chronic spontaneous urticaria being the most prevalent subtype.[11] Both chronic urticaria and FDEIA involve mast cells in their pathophysiology, suggesting potential shared mechanisms that warrant further investigation. The concomitant treatment for chronic urticaria may obscure or delay the recognition of IgE-mediated reactions triggered by various allergens, thereby masking symptoms.[30] Clinicians should remain vigilant for unexpected changes in urticaria severity or the onset of systemic symptoms, which may indicate an underlying IgE-mediated reaction, such as FDEIA.

Diagnosis

The initial step in diagnosing FDEIA involves evaluating the patient's clinical history, focusing on the temporal association between food ingestion and subsequent exercise-induced symptoms. A wide array of foods, beyond wheat, can trigger FDEIA, underscoring the importance of considering various allergenic sources. Keeping a food diary containing details of cofactors and their timing about symptoms can offer valuable diagnostic insights. It is crucial to distinguish FDEIA from chronic or acute recurrent urticaria, exercise-induced anaphylaxis, idiopathic anaphylaxis, hereditary angioedema, and mastocytosis.[31] The World Allergy Organization criteria for wheat-dependent exercise-induced anaphylaxis can guide the diagnosis of FDEIA.[27] Table 1 provides an overview of commonly utilized diagnostic criteria for FDEIA, including clinical history, symptomatology, symptom timing, exclusion of alternative etiologies, and laboratory tests.

Laboratory tests, including in vivo and in vitro evaluations, can complement the diagnosis by identifying allergen sensitivities. Diagnostic tests include serum-specific IgE and skin prick tests targeting suspected trigger allergens.[3,14,32] Prick-to-prick skin testing with fresh food can increase diagnostic accuracy due to the relatively low sensitivity and specificity of commercial food extracts.[3] Identifying major allergenic components of food proteins, such as specific IgE for omega-5 gliadin in wheat, provides a valuable diagnostic marker.[33] However, the presence of food-specific IgE confirms only allergen sensitization and may not indicate clinical allergy, necessitating correlation with clinical history. For FDEIA patients experiencing recurrent anaphylaxis, measuring basal serum tryptase levels can help identify underlying mast cell disorders.[3] If the suspected allergens remain unclear, an exercise–food challenge test may be necessary to ensure an accurate diagnosis.[33-36] Provocative challenge protocols integrating multiple cofactors, such as aspirin and alcohol, have shown

TABLE 1. Diagnosis of FDEIA.[4]

Assessment	Clinical evaluation
Clinical history	History of anaphylactic reactions occurring after exercise, typically within 4 hours of food ingestion. Tolerance of the culprit food without exercise and safe exercise tolerance without ingesting the trigger food.
Symptom presentation	Manifestations of anaphylaxis, including skin, respiratory, gastrointestinal, or cardiovascular symptoms. Symptoms may range from mild cutaneous reactions to severe systemic manifestations.
Timing of symptoms	Symptoms typically occur within minutes to hours after the combination of food ingestion and exercise.
Exclusion of other causes	Rule out alternative diagnoses, such as exercise-induced bronchospasm or idiopathic anaphylaxis.
Specific diagnostic tests	Specific IgE, skin prick, and prick-to-prick tests. IgE for omega-5 gliadin for wheat-dependent exercise-induced anaphylaxis. Basal serum tryptase levels for mast cell disorders. Oral food challenge followed by physical exertion provocation.

promise in enhancing diagnostic yield.[21,37-39] However, incorporating additional augmenting factors alongside conventional exercise-food challenges requires careful patient selection and monitoring due to the potential for severe reactions. Tailoring diagnostic strategies to individual patient profiles and utilizing advanced testing modalities can enhance diagnostic accuracy and facilitate effective management.

Management

General management of FDEIA

Effective management of FDEIA involves both preventive and emergency strategies, as shown in Table 2. The cornerstone of prevention is identifying and avoiding trigger foods, along with minimizing physical exercise after ingesting such foods.[40] Patients must be educated about FDEIA triggers, symptoms, and emergency action plans, emphasizing the importance of carrying and utilizing self-injectable epinephrine. While completely avoiding physical activity may not be practical, individuals with FDEIA should avoid consuming culprit allergens at least four hours before and one hour after exercise to reduce the risk of reactions.[41] Proper management by healthcare providers is essential to prevent unnecessary dietary and exercise restrictions, helping patients maintain a balanced lifestyle.[42] Patients should always carry anaphylaxis identification cards and self-injectable epinephrine to be prepared for emergencies.[40]

Specific management of FDEIA

Managing acute anaphylactic reactions in FDEIA involves timely administration of epinephrine, with dosages tailored to the patient's weight and age.[40] In cases with cardiovascular involvement, early intravenous fluid administration is crucial to restore circulatory volume. Adjunctive therapy, like antihistamines and corticosteroids, may be used, although their efficacy is limited.[43,44] Inhaled β2-agonists are indicated for predominant bronchial obstruction,[40] while inhaled adrenaline via a nebulizer is recommended for suspected laryngeal/pharyngeal edema.[45]

Premedication with antihistamines, corticosteroids, and leukotriene receptor antagonists before culprit food ingestion or exercising is not recommended due to insufficient evidence of effectiveness.[40] Although immunotherapy and anti-IgE monoclonal antibodies may be considered for patients with IgE-mediated food allergies, their efficacy in FDEIA remains limited and requires further research.[46]

CONCLUSION

FDEIA presents a complex and potentially life-threatening challenge, characterized by IgE-mediated reactions triggered by specific food ingestion combined with physical exertion. Our systematic review synthesizes current literature to highlight key aspects of FDEIA epidemiology, pathogenesis and pathophysiology,

TABLE 2. Treatment modalities for FDEIA.[40-46]

Treatment modalities	Description
Epinephrine	Intramuscular epinephrine as first-line management of anaphylaxis. Dosage of 0.01 mg/kg for children (max 0.3 mg) and 0.3 mg for adults. Administered promptly upon recognition of symptoms related to anaphylaxis.
Antihistamines	Adjunctive therapy to reduce histamine-mediated symptoms such as itching and hives. May be administered in conjunction with epinephrine.
Corticosteroids	Administered after epinephrine and fluid replacement to prevent late-phase reactions; however, the benefit of corticosteroids remains inconclusive.
Allergen avoidance	Avoidance of trigger foods before exercise. Patients should be educated about potential sources of allergens and how to read food labels.
Emergency action plan	Development of personalized plans outlining steps to take in case of anaphylaxis. Includes instructions on how to use self-injectable epinephrine and when to seek medical attention.

diagnosis, and management. Despite its rarity, FDEIA poses significant risks if not promptly recognized and managed. Our data underscores the importance of integrating clinical history assessment, specific laboratory testing, and exercise–food challenge tests for precise diagnosis and optimal patient care. However, the literature reviewed exhibits limitations, including small sample sizes, variability in diagnostic criteria, and potential biases such as reliance on self-reported data. These limitations highlight the necessity for more rigorous and standardized research methodologies in future investigations. Key areas for advancement involve enhancing diagnostic tools, investigating biomarkers, and refining treatment strategies to improve diagnostic accuracy and optimize therapeutic results for individuals with FDEIA.

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