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The world-leading biomedical science of Thailand

MONTHLY

ORIGINAL ARTICLE

Clinical Outcomes of Preoperative Music Medicine and Relaxation Techniques in Elderly Surgical Patients: A Randomized Controlled Trial

Methods

Elderly patients undergoing elective surgery at university hospital between 2020-2024
N = 104

Randomized

Music	Relaxation	Combine	Control
N = 26	N = 26	N = 28	N= 24

Seven days prior to surgery

Measurement

Anxiety level: HADS-A score
- Baseline,
- Preoperative day 1
- Postoperative day 3, and month 1 and 3

Quality of Recovery: QoR-35
- Postoperative day 3, and month 1 and 3

Results

Anxiety level

The Relaxation group showed a significantly greater reduction in anxiety one day before surgery compared to the control group (mean difference: −1.25, p = 0.04)

Quality of Recovery

The Relaxation group showed significantly higher QoR-35 scores than controls on postoperative day 3 (mean difference: 2.34, p = 0.04)

Conclusion

Preoperative **relaxation techniques** effectively reduced anxiety and improved early postoperative recovery.

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Association between Internet Gaming Disorder and Associated Parental and Peer Attachment: A Cross-sectional Study among Thai Adolescents

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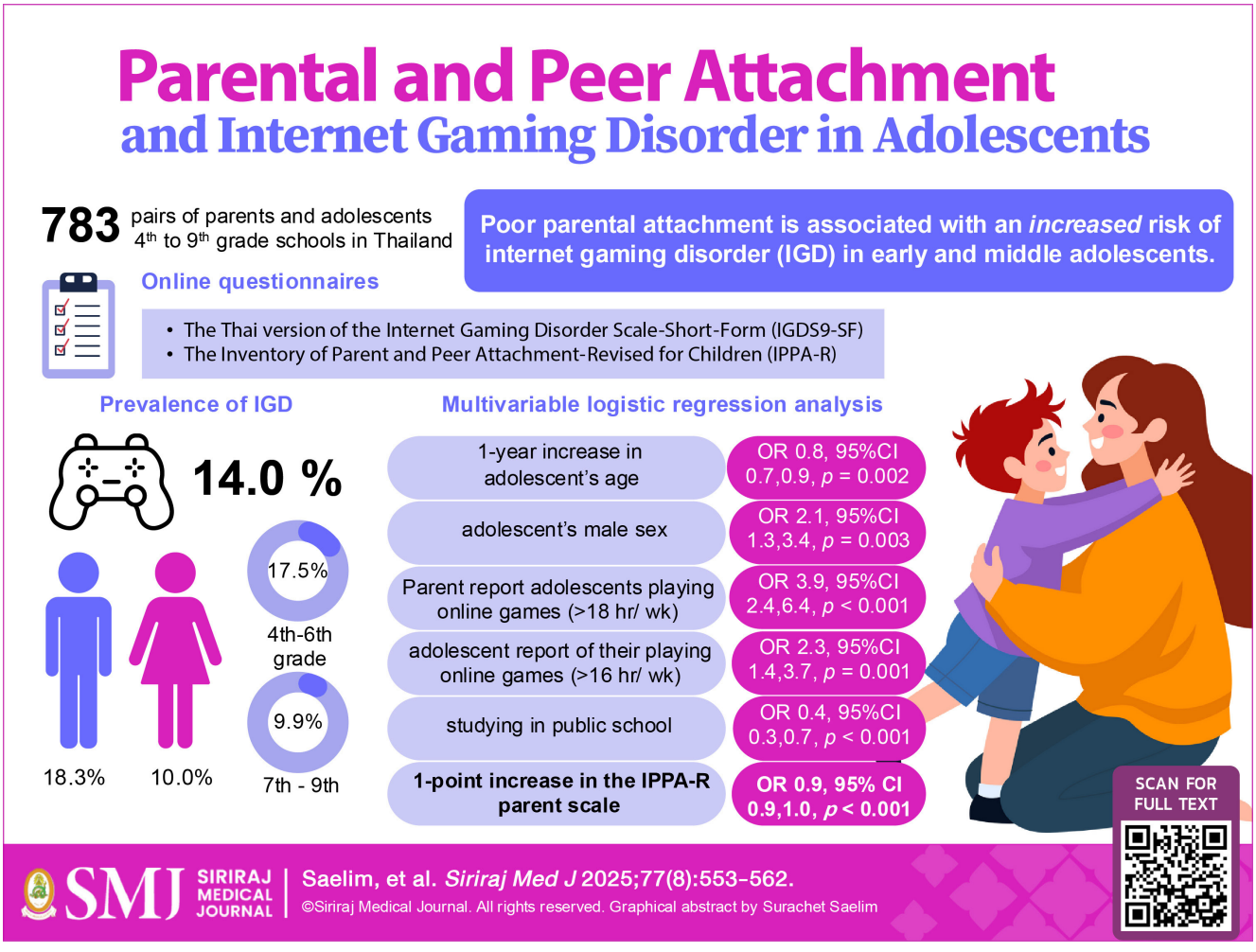

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ABSTRACT

Objective: This study examined the prevalence of Internet Gaming Disorder (IGD) and its association with parental and peer attachment among Thai adolescents, accounting for gender and developmental stages.

Materials and Methods: A cross-sectional design involved 783 parent-adolescent pairs (4th-9th grade, Thailand). Online questionnaires, including the Thai version of the Internet Gaming Disorder Scale-Short-Form (IGDS9-SF) and the Inventory of Parent and Peer Attachment-Revised for Children (IPPA-R), were used. Multivariable logistic regression analyzed the data.

Results: The overall IGD prevalence was 14.0%, higher in males (18.3%) and 4th-6th graders (17.5%). Multivariable logistic regression analysis showed that a 1-year increase in adolescent age (OR 0.8, p=0.002), male sex (OR 2.1, p=0.003), parental report of adolescents playing online games (>18 hours/week) (OR 3.9, p<0.001), adolescent report of their playing online games (>16 hours/week) (OR 2.3, p=0.001), and studying in public school (OR 0.4, p<0.001), and a 1-point increase in the IPPA-R parent scale (OR 0.9, p<0.001) were significantly associated with IGD. No significant interaction terms for gender and developmental stages were identified.

Conclusion: Early male adolescents are at higher IGD risk. Poor parental attachment is associated with increased IGD likelihood. Preventive strategies focusing on strengthening parental attachment may help mitigate IGD in this population.

Keywords: Internet gaming disorder; prevalence; parental attachment; peer attachment; adolescents (Siriraj Med J 2025; 77: 553-562)

INTRODUCTION

Internet gaming has grown in popularity, with the number of players exceeding 3.2 billion in 2022. By 2025, this figure is expected to reach 3.6 billion. Over half of the players are from the Asia-Pacific region.[1] Excessive gaming can negatively affect physical and mental health, as well as education, career, and relationships of the gamer.[2] The American Psychiatric Association (APA) has recognized Internet Gaming Disorder (IGD) as a behavioral condition characterized by excessive gaming that leads to considerable impairment.[3]

A meta-analysis reported a pooled IGD prevalence of 4.6% among adolescents, a rate higher than that in other age groups, with the highest prevalence observed in Asian populations.[4,5] This increased prevalence in Asia may be attributed to more permissive attitudes toward gaming and greater accessibility to gaming environments.[5] During the COVID-19 pandemic, IGD prevalence increased;[6] however, post-pandemic rates remain underexplored.[7,8] In Thailand, the prevalence of IGD among school-aged individuals before the COVID-19 pandemic ranged from 5.4% to 15.0%.[9-11] Male adolescents consistently exhibit higher rates of gaming addiction than females.[4] Despite these findings, research examined post-pandemic prevalence across different adolescent age groups remains limited.

IGD is associated with both internal and external factors.[2, 12-14] Internal factors include being male, younger age, poor self-regulation, low social competence, mood dysregulation, feelings of loneliness, and comorbidities such as attention-deficit/hyperactivity disorder, depression, and social anxiety. External factors include the type of game (genre), role-playing games with multiple players online (MMORPGs) and first-person shooter (FPS) games being particularly influential, as they engage reward systems at the neurobiological level. The aforementioned factors may interact.

In the first year of life, infants seek and maintain proximity to their parents through "attachment behavior".[15] Additionally, infants use their mother as a "secure base" for exploration of the world around them.[16] This parental attachment continues into adolescence and adulthood and can shift toward other persons.[15] Those with secure parental attachments often maintain strong peer relationships[17], generally experience higher psychological well-being, self-esteem, and life satisfaction.[18,19] In contrast, studies showed a negative association between IGD and both parental and peer attachment in middle and late adolescent.[20,21] Internet gaming can act as an escape from real-life challenges for those from families with disorganized attachments, while also enabling the formation of new relationships online.[13,20] However, current literature has not sufficiently explored the association between IGD and parental or peer attachment among early adolescent subgroups. Furthermore, this relationship has not been examined in the context of gender and age group differences, which are essential for designing effective preventive strategies tailored to specific populations.

Aims of this study were to analyze the prevalence of IGD in Thailand among adolescents and to analyze the relationship between IGD and parental and peer attachment of adolescents corrected for the effect of gender and developmental stage.

MATERIALS AND METHODS

The study was approved by the Siriraj Institutional Review Board, Faculty of Medicine Siriraj Hospital (257/2565(IRB3)). All participants provided written informed consent, and participation was voluntary.

Study design and participants

This cross-sectional study was conducted between January to March 2023, and involved students from the 4th to 9th grade across four public and four private schools, randomly selected from a total of 595 public and 356 private primary and secondary schools in Bangkok, Thailand. Participants were stratified into two age groups for sampling: early adolescence (4th to 6th grade, ages 10-12 years) and middle adolescence (7th to 9th grade, ages 13-15 years)[22] as well as by school type (public and private). Inclusion criteria were proficient in Thai and having internet access to complete online questionnaires via Google Forms. After a detailed explanation of the study was provided, questionnaires were distributed to students at school by teachers and parent versions were sent home to be completed by parents. Teachers assisted students in completing the questionnaire if needed. They did not fill in answers to prevent information bias. Unreliable responses or failure to give consent were excluded from the study. An unreliable response was defined as one resulting from incorrect coding, selecting a single answer across all Likert scale items, or providing exaggerated numerical responses. Since the questionnaire had to be fully completed before submission, there were no missing data in this study.

Measurements

Participant characteristics data

The questionnaire for the adolescents asked for gender (with 'other' referring to sexual minorities), year of birth, education level, and weekly hours spent on online study and gaming. The questionnaire for the parents asked for gender, year of birth, highest education level, relationship to the adolescent, and monthly family income. It also asked for school record of the adolescent over the past year and weekly online hours spent studying and gaming. Additionally, it asked how long parent and adolescent had lived together.

Internet Gaming Disorder Scale 9–Short-Form (IGDS9-SF) Thai Version

The Thai version of the self-version IGDS9-SF questionnaire,[23,24] was used to assess IGD. It is designed to screen individuals aged 6 to 25 for IGD, according to DSM-5 criteria.[3] It consists of nine questions, answered on a 5-point Likert scale. The total score ranges from 9 to 45. A score above 29 indicates IGD. The parent-version questionnaire, developed from the self-version,[24] consists of the same nine questions and has an identical scoring system. Both versions demonstrated excellent internal consistency Cronbach's α; 0.913 for the self-version and 0.922 for the parent-version.[24]

The Inventory of Parent and Peer Attachment – Revised (IPPA-R) Thai Version

The Thai version of the IPPA-R is a self-report questionnaire designed to measure attachment to parents and peers among children and adolescents aged 9 to 15.[19,25] The questionnaire consists of 28 statements on the parent scale and 25 statements on the peer scale answered on a 3-point Likert scale with no cut-off points. Higher scores suggest stronger attachment. The Thai version of IPPA-R demonstrated strong internal consistency, Cronbach's α 0.88 for the parent scale and 0.85 for the peer scale.[25]

Statistical analysis

Data analysis was conducted using IBM SPSS Statistics for Windows, Version 29.0. We reported descriptive statistics as mean ± standard deviation (SD), median (interquartile range), numbers, and percentages. For comparisons between the IGD and non-IGD groups, we utilized the independent t-test for normally distributed data, the Mann-Whitney U-test for non-normal data, and the Chi-square or Fisher's exact test for categorical variables. Associated factors for IGD were presented as odds ratio with 95% confidence intervals, calculated using univariate logistic regression. Multivariable models were then applied to adjust for confounding factors in a forward stepwise selection manner with probability of score statistic for variable entry of 0.05 and probability of score statistic to remove a variable of 0.1. Interaction terms were explored. A p-value of <0.05 was considered statistically significant.

RESULTS

Out of 1,458 adolescents, 23 refused to give consent and 19 provided unreliable responses, leaving 1,416 available for data analysis. Among the 969 parents,

62 refused to give consent and 28 provided unreliable responses, resulting in 879 available for analysis. A total of 783 matched parent-adolescent pairs were included in the final analysis. Among these adolescents, 52.2% were female, with an average of 13.0 years (SD = 1.7). A majority attended public schools (52.2%) and co-educational institutions (71.9%), primarily from grades 4 to 6 (54.8%). Additionally, 99.1% maintained a grade point average of 2.0 (60%) or above over the past year. Of the parents 70.4% were mothers, mean age of 44.8 years (SD = 8.7), 55.9% had attained a bachelor's degree or higher, and 90.5% reported living with their adolescents since birth.

Adolescents in the IGD group had a mean age of 12.5 years (SD = 1.6), with 60% being male, and 68.2% were grades in 4 to 6. They predominantly attended all-boys (18.2%) and private schools (62.7%). The median weekly online study and internet gaming times were 9 hours and 28 to 30 hours, respectively. Adolescents with IGD scored lower on the IPPA-R parent scale and peer scales than those without IGD. Parents of the IGD group reported a family income of 100,001 baht or above (25.9%) (Table 1).

The overall prevalence of IGD among adolescents was 14.0%. When classified by gender, the prevalence was 18.3% in males, 10.0% in females, and 23.1% in sexual minorities (SM). When classified by age, the prevalence was 17.5% in early adolescents (4th to 6th grade) and 9.9% in middle adolescents (7th to 9th grade). The differences in prevalence between gender and age groups were statistically significant (Table 1).

Participants reported an average score of 64.8 (SD = 9.3) on the IPPA-R parent scale and 57.0 (SD = 8.2) on the peer scale. Males had a significantly higher average score on the parent scale (65.9, SD = 8.8), while females scored higher on the peer scale (58.6, SD = 8.5). When considering developmental stages, early adolescents scored higher on the parent scale (65.6, SD = 9.2), whereas middle adolescents had higher scores on the peer scale (58.0, SD = 8.1) (Table 2).

Multivariable logistic regression showed that higher adolescent's age, and higher IPPA-R parent scale score decreased the likelihood of IGD. While factors that increased the likelihood of IGD were playing online games for more than 16 hours per week as reported by the adolescent, playing for over 18 hours as reported by parents, attending a private school, being male, and identifying as SM. These results were adjusted for the adolescent's age, gender, duration of online gaming, type of school attended, and scores on the IPPA-R parent scale. No significant interaction terms were identified.

DISCUSSION

The primary objectives of this study were examine the prevalence of IGD in Thai adolescents and to explore the relationship between IGD and parental and peer attachment.

Prevalence of internet gaming disorder

In this study, 14.0% of participants were classified in the IGD group, consistent with a previous study in Thailand reporting a 15.0% prevalence.[9] Contrary to our hypothesis that suggested a higher prevalence due to the COVID-19 pandemic, the prevalence remained stable, potentially due to the resumption of in-person schooling. During the global pandemic, a study employing measurements based on the DSM-5 proposed criteria for IGD in the same age group reported a similar prevalence.[26] However, other studies have reported widely varying prevalence rates of gaming addiction among children and adolescents, ranging from 2.3% to 29.4%.[6] Variations in research methodologies complicate direct comparisons across studies. The increased prevalence has been particularly observed in studies with predominantly male participants and has been associated with increased time spent gaming during lockdown periods.[27-29]

Regarding gender differences, the highest prevalence of IGD was observed among SM adolescents at 23.1%, followed by males at 18.3%. This study highlights IGD prevalence in SM adolescents and is consistent with findings that problematic gaming is more prevalent among SM individuals over 15 years old and SM women (women who did not identify as heterosexual).[30] SM individuals may use online games to cope with psychological distress, social stigmatization, and isolation.[30] However, further research is needed to conclusively determine the prevalence of IGD within the SM subgroup. The differences in IGD prevalence between males and females aligns with previous studies in similar age groups[4,9,11], which have linked these disparities to variations in gameplay duration, frequency, and preferred genres. Male adolescents are also more likely to favor role-playing, fighting, and strategy games, which are associated with a higher risk of addiction.[4,12]

IGD prevalence in early adolescents (17.5%) was nearly twice that of middle adolescents (9.9%), with the mean age of IGD onset being 12.5 years. These results could be linked to neurobiological factors, as early adolescence is characterized by an imbalance between the maturing prefrontal cortex and limbic regions, which may increase vulnerability to addictive disorders.[31] Additionally, prevalence rates for both subgroups were higher than those observed in other age groups.[5,10,11,32] Adolescents often perceive their parental relationships as less trusting,

TABLE 1. Characteristics of participants and associated factors of IGD.

Characteristics	Total n	IGD		p-value
		Yes n(%)	No n(%)	
1.1 Adolescents	783	110(14.0%)	673(86.0%)	
Sex[a]				
Male	361	66(18.3%)	295(81.7%)	0.003
Female	409	41(10.0%)	368(90.0%)	
Other#	13	3(23.1%)	10(76.9%)	
Education level (age group)[a]				
4th - 6th (early adolescent)	429	75(17.5%)	354(82.5%)	0.002
7th - 9th (middle adolescent)	354	35(9.9%)	319(90.1%)	
Age (years)[b]				
Mean ± SD	13.0±1.7	12.5±1.6	13.1±1.7	0.001
Online studying (hours/week)[c]				
Adolescent report median [Q1, Q3]	5[0, 30]	9[0, 31.3]	4[0, 30]	0.034
Parent report median [Q1, Q3]	0[0, 4]	0[0, 6]	0[0, 4]	0.827
Playing online games (hours/week)[c]				
Adolescent report median [Q1, Q3]	14[4, 30]	30[14, 56]	12[3, 28]	< 0.001
Parent report median [Q1, Q3]	14[4, 28]	28[14, 35.3]	12[3, 21]	< 0.001
School type[a]				
Private	374	69(22.6%)	305(77.4%)	0.001
Public	409	41(11.1%)	368(88.9%)	
Co-educational school[a]				
Co-educational school	563	71(14.4%)	492(85.6%)	0.008
All-boys school	78	20(34.5%)	58(65.5%)	
All-girls school	142	19(15.4%)	123(84.6%)	
School record[a]				
<60%	7	0(0.0%)	7(100.0%)	0.272
61-69%	107	20(23.0%)	87(77.0%)	
70-79%	464	65(16.3%)	399(83.7%)	
80-100%	191	23(13.7%)	168(86.3%)	
Not available	14	2(16.7%)	12(83.3%)	
IPPA-R parent scale[b]				
Mean ± SD	64.8 ± 9.3	60.1 ± 9.2	65.5 ± 9.1	<0.001
IPPA-R peer scale[b]				
Mean ± SD	57.0 ± 8.2	54.8 ± 8.7	57.4 ± 8.0	0.002

TABLE 1. Characteristics of participants and associated factors of IGD. (Continue)

Characteristics	Total n	IGD		p-value
		Yes n(%)	No n(%)	
1.2 Parents				
Sex[a]				
Male	164	21(14.7%)	143(85.3%)	0.606
Female	619	89(16.8%)	530(83.2%)	
Age (years)[b]				
Mean ± SD	44.8±8.7	43.7±6.7	44.9±9.0	0.166
Highest education level[a]				
Below Bachelor's degree	344	39(12.8%)	305(87.2%)	0.174
Bachelor's degree	309	53(20.7%)	256(79.3%)	
Above Bachelor's degree	127	18(16.5%)	109(83.5%)	
Not available	3	0(0.0%)	3(100.0%)	
Parental role[a]				
Father	149	21(16.4%)	128(83.6%)	0.035
Mother	551	86(18.5%)	465(81.5%)	
Relatives	77	3(4.1%)	74(95.9%)	
Other[#]	6	0(0.0%)	6(100.0%)	
Family income (THB/month)[a]				
0-30,000	329	34(11.5%)	295(88.5%)	0.003
30,001-50,000	144	19(15.2%)	125(84.8%)	
50,001-100,000	152	27(21.6%)	125(78.4%)	
100,001 and above	143	28(24.3%)	115(75.7%)	
Not available	15	2(15.4%)	13(84.6%)	
Living with adolescent since[a]				
Birth	698	99(16.5%)	599(83.5%)	0.411
6 months old	17	4(30.8%)	13(69.2%)	
2 years old	56	6(12.0%)	50(88.0%)	
Not available	12	1(9.1%)	11(90.9%)	

[#] Other = Sexual minorities

[a] Chi-square test [b] Independent t-test [c] Mann-Whitney U-test

Abbreviations: IGD, Internet gaming disorder; IPPA-R, The Inventory of Parent and Peer Attachment – Revised; THB, Thai Baht

TABLE 2. IPPA-R parent and peer scale scores classified by gender and age group.[b]

Characteristics	Total n	IPPA-R parent scale Mean ± SD	IPPA-R peer scale Mean ± SD
Sex			
Male	361	65.88 ± 8.8	55.41 ± 7.5
Female	409	63.94 ± 9.5	58.63 ± 8.5
Other[#]	13	59.31 ± 10.8	50.85 ± 7.6
p-value		0.002	<0.001
Education level (age group)			
4th - 6th (early adolescent)	429	65.60 ± 9.2	56.19 ± 8.2
7th - 9th (middle adolescent)	354	63.74 ± 9.3	58.02 ± 8.1
p-value		0.005	0.002
Total	**783**	**64.76 ± 9.3**	**57.02 ± 8.2**

[#] Other = Sexual minorities

[b] Independent t-test

Abbreviations: IPPA-R, The Inventory of Parent and Peer Attachment – Revised

TABLE 3. Multivariable logistic regression analysis of factors associated with IGD in adolescents.

Factors	Beta	S.E.	Adjusted OR (95% CI)	p-value
Adolescent's age (1-year increase)	-0.230	0.075	0.8 (0.7, 0.9)	0.002
IPPA-R parent scale (1-point increase)	-0.080	0.013	0.9 (0.9, 1.0)	<0.001
Playing online games (hours/week)				
>16 hour/week (adolescent report)	0.816	0.249	2.3 (1.4, 3.7)	0.001
>18 hour/week (parent report)	1.362	0.253	3.9 (2.4, 6.4)	<0.001
School type				
Private school	reference		reference	
Public school	-0.896	0.247	0.4 (0.3, 0.7)	<0.001
Child's sex				
Female (ref)	reference		reference	
Male	0.745	0.248	2.1 (1.3, 3.4)	0.003
Other[#]	0.629	0.802	1.9 (0.4, 9.0)	0.432
Intercept (constant)	4.956	1.305	-	<0.001

[#] Other = Sexual minorities

Abbreviations: IPPA-R, The Inventory of Parent and Peer Attachment – Revised

Note: Adjusted for child's age, gender, playing online games more than 18 hours/week, studying in private school, and IPPA-R parent scale

characterized by lower levels of communication and support,[33] and may turn to gaming as a form of escapism or to seek online relationships.[34] These findings highlight the need for targeted interventions among specific age groups.

Parental attachment and internet gaming disorder

In our study, higher parental attachment scores were negatively associated with IGD after adjusting for covariates. This finding is consistent with previous studies[21,35,36], indicating that parent-child closeness predicts a decrease in problematic gaming behavior.[35] Specifically, the quality of attachment with mothers measured by trust, communication, and alienation and with fathers, particularly in terms of alienation, has been linked to less internet gaming addiction in adolescents.[21] Secure parental attachment is associated with higher life satisfaction as it enables individuals to maintain relationships and share emotions with others, thereby lowering the risk of gaming addiction.[36]

However, some studies suggest that parental attachment does not significantly predict IGD.[37-39] These discrepancies may be due to differences in age groups studied. Our study, focusing on younger adolescents, found that early adolescents reported higher parental attachment scores than middle adolescents. A poorer quality of parent-child relationship has been associated with problematic internet gaming,[34] in which parental attachment is also a key component of this relational dynamic.[15] Among the age range studied, no significant interaction was found between age group and parental attachment in relation to IGD. Although parental attachment may shift during adolescence as new attachment figures emerge,[15] such changes did not substantially weaken parental attachment to a degree that influenced IGD within the studied age range. The higher prevalence of IGD in males may be attributed also to other factors, as previously discussed. Further research involving a broader age range is needed to explore the interaction between age group and parental attachment in relation to IGD.

When considering the interaction term between gender and parental attachment, no significant interaction was found to be associated with IGD. Although female adolescents may seek alternative attachment —such as peers—rather than their parents for trust, communication, and emotional intimacy,[40] this may not considerably influence the relationship between parental attachment and IGD.

Peer attachment and internet gaming disorder

Interestingly, after adjusting for other factors, peer attachment was not significantly associated with IGD in our study sample. This finding is consistent with results of another study,[41] which also found no direct association between peer attachment on gaming addiction among out-of-school adolescents. However, several studies have identified a negative association between peer attachment and IGD.[36,42-44] One possible explanation for our results may relate to the inclusion of parental attachment in the analysis, which could influence the relationship between peer attachment and IGD, particularly in early adolescents who may rely more on their parents for security than on peers. Another explanation is the 'counterbalance effect,' in which peer attachment may shape adolescents' gaming behavior through modeling, as adolescents tend to emulate peers in the pursuit of social validation and identity development.[45,46] Additionally, peer attachment may support adolescents in problem-solving through social support and may be associated with higher self-esteem, which facilitates their ability to regulate behavior and avoid gaming addiction.[18,36]

Limitations

This study has some limitations. First, it utilizes a cross-sectional design, which inhibits our ability to establish causal relationships. Second, data collection was based on self-report questionnaires, which may result in an underestimation of the reported hours of gaming. To mitigate this problem, we gathered information from both adolescents and their parents to improve accuracy of the data. Third, the sample was exclusively composed of school-based participants from 4th to 9th grade, which limits the generalizability of the findings to other groups. Future research should consider utilizing a longitudinal design using a community-based samples with a broader age range to enhance generalizability and better illustrate the associations.

CONCLUSION

This study provides updated prevalence data on IGD and its association with parent and peer attachment among early to middle adolescents in Thailand. To establish causal relationships, further research is recommended. Based on these insights, preventive strategies and interventions to promote and maintain secure parental attachment should focus on individuals at risk of IGD.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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DECLARATIONS

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Conflicts of Interest

The authors declare no potential conflicts of interest.

Registration Number of Clinical Trial

None.

Author Contributions

Conceptualization and methodology, S.S., T.H., and S.H.; Data curation, S.S.; Funding acquisition, T.H.; Investigation, S.S.; Supervision, T.H., and S.H.; Visualization, S.S.; Writing - original draft preparation, S.S.; Writing - review and editing, S.H. All authors have read and agreed to the final version of the manuscript.

Use of Artificial Intelligence

The authors used ChatGPT (OpenAI) and Perplexity ai to assist with grammar correction, sentence refinement, and reference formatting. All AI-assisted content was thoroughly validated and approved by the authors to ensure accuracy and compliance with academic and ethical standards.

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Clinical Outcomes of Preoperative Music Medicine and Relaxation Techniques in Elderly Surgical Patients: A Randomized Controlled Trial

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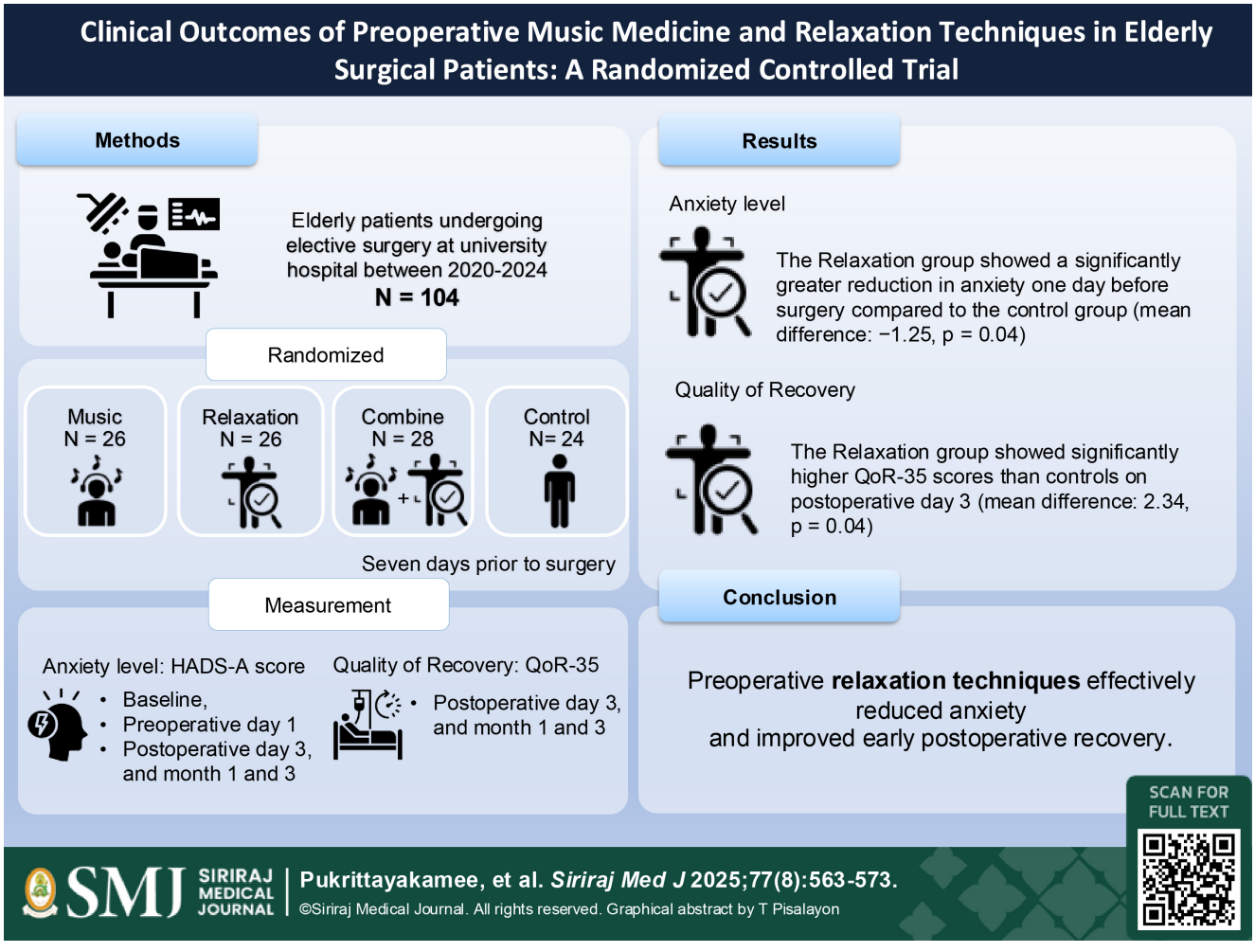

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ABSTRACT

Objective: This study examined the short- and long-term effects of one week of preoperative music medicine and relaxation techniques on perioperative anxiety and postoperative recovery.

Materials and Methods: Patients aged ≥60 years undergoing elective surgery at a university hospital were randomized into four groups: music medicine, relaxation techniques, combined intervention, and control. Interventions were administered for seven days prior to surgery. Anxiety was assessed using the Hospital Anxiety and Depression Scale–Anxiety subscale (HADS-A) at baseline, one day before surgery, and on postoperative day 3, and months 1 and 3. Postoperative recovery was evaluated using the Quality of Recovery-35 (QoR-35) questionnaire. Data were analysed using a linear mixed model.

Results: Of the 140 enrolled participants, 104 completed the study. Baseline characteristics were comparable across all groups. Compared to the control group, the relaxation group showed a significantly greater reduction in anxiety one day before surgery (mean difference: −1.25, p = 0.04), though no significant differences were found at subsequent time points. The music and combined groups exhibited nonsignificant reductions in anxiety. On postoperative day 3, the relaxation group had significantly higher QoR-35 scores than controls (mean difference: 2.34, p = 0.04), whereas the other intervention groups showed nonsignificant higher QoR-35 scores. By months 1 and 3, QoR-35 scores had slightly increased in all intervention groups, but without statistical significance compared with the control group.

Conclusion: Preoperative relaxation techniques effectively reduced anxiety and improved early postoperative recovery. However, their long-term benefits, along with those of music interventions, were not evident.

Keywords: Anxiety; music therapy; relaxation therapy; perioperative care; geriatric patients (Siriraj Med J 2025; 77: 563-573)

INTRODUCTION

Preoperative anxiety is defined as an unpleasant emotional response to uncertainty regarding surgical outcomes.[1] Its prevalence ranges from 60% to 80%, depending on the type of surgery.[2,3] Causes of preoperative anxiety include fear of unsuccessful surgery, anesthesia awareness, medical errors, pain, financial burden, and concern about family members.[4,5] Preoperative anxiety can lead to increased cortisol levels, which are associated with impaired immune responses, infections, poor wound healing, and electrolyte imbalances. It can also result in poor compliance with treatment and inadequate self-care, contributing to negative postoperative outcomes such as increased pain, prolonged hospital stays, and reduced quality of life.[1] The risks of these adverse outcomes are heightened in elderly patients, as physiological decline increases their vulnerability to physical stress. Therefore, presurgical elderly patients should receive comprehensive care addressing both physical and psychological needs to minimize postoperative complications.[6,7]

Psychological and behavioral interventions with evidence supporting their effectiveness in reducing preoperative anxiety include cognitive behavior therapy, music medicine, massage therapy, and relaxation techniques.[1,8] Among these, music medicine and relaxation techniques may be more feasible for presurgical elderly patients, as these techniques are easy to practice and can be self-administered at home. Music medicine, a subset of music therapy, involves listening to music to enhance health and well-being.[9-11] Focused music listening can alleviate anxiety through psychological and physiological mechanisms, such as synchronizing body rhythms, reducing adrenergic activity, influencing the limbic system, and stimulating endorphin release. These processes promote physical relaxation, as evidenced by decreases in pulse rate and blood pressure.[12] A systematic review study revealed that music medicine was effective in reducing preoperative anxiety.[13]

Practicing relaxation techniques, such as breathing exercises and body scans, is a feasible approach to reducing preoperative anxiety in elderly patients. Deep diaphragmatic breathing—slow inhalation followed by gradual exhalation—enhances parasympathetic activity, promoting relaxation.[14] A body scan, a mindfulness-based stress-reduction technique, involves nonjudgmental awareness of bodily sensations from the toes to the head. This practice helps patients stay present and reduces distraction from negative thoughts and emotions, leading to a calmer state of mind.[15] A systematic review and meta-analysis of 11 clinical trials revealed that relaxation techniques combined with psychological interventions effectively improved negative emotions following surgery.[8]

Although evidence supports the effectiveness of music medicine and relaxation techniques in reducing perioperative anxiety, limitations remain in the literature. First, most studies focus on short-term effects, with limited research on their long-term impact. Second, few studies have examined the effects of these interventions on postoperative outcomes, such as recovery quality. Since anxiety is a known risk factor for negative postoperative outcomes[1], it can be hypothesized that reducing anxiety may also enhance recovery. Finally, most research has focused on short-duration interventions—hours or a single day before surgery—while studies on longer interventions and their potential lasting benefits are scarce. This study aimed to assess the short- and long-term effects of a one-week preoperative intervention involving music medicine, relaxation techniques, or a combination of both on preoperative anxiety, postoperative anxiety, and recovery quality.

MATERIALS AND METHODS

Ethical considerations

Ethics approval was granted by the Siriraj Institutional Review Board. The certificate of approval was Si 471/2020. Documented informed consent was obtained from all participants before they participated in the research. The study has been officially registered with the Thai Clinical Trial Registry under the identifier TCTR20200910002.

Participants

Participants were recruited during their visit to the preanesthetic clinic prior to admission for elective surgery at Siriraj Hospital between August 10th, 2020 and September 26th,2024. Patients aged ≥60 years with American Society of Anesthesiologists (ASA) physical status classification I–III who were scheduled for elective surgery under general or regional anesthesia were eligible for inclusion. Exclusion criteria included a history of dementia, delirium, intellectual disability, or psychiatric disorders; current use of psychiatric medications; or scheduled surgery involving vital organs such as the brain or heart.

Study design

A randomized controlled trial was conducted to examine the effectiveness of music medicine, relaxation techniques, and music medicine plus relaxation techniques on preoperative and postoperative anxiety and quality of recovery after surgery. A total of 140 participants were randomized into 4 groups, including music medicine, relaxation techniques, music medicine plus relaxation techniques, and controls using block-of-4 randomization.

Interventions and control

Music medicine

The participants were provided with a list of classic songs that had been selected by a music therapist. These songs were assessed by a music therapist in terms of relaxation effects and appropriateness for elderly individuals. The characteristics of these songs that can produce relaxation effects are smooth melody and slow tempo without accented beats or percussion.[13] The participants were requested to choose at least 10 songs they liked from the list. They could listen to these songs from their own copyright video compact disc or cassette tape or from online streaming services offering copyright music. They were also given earphones to help them focus on listening to music and to eliminate auditory disturbances. The participants initially practiced listening to music under supervision by a music therapist before they started self-practicing at home. Then, they were assigned to listen to the songs they chose through the earphones at home for 30 minutes daily for 7 consecutive days before surgery.

Relaxation techniques

The participants were trained by a psychologist to practice relaxation techniques, including breathing exercises and body scans, and were provided with a guided video containing instructions and demonstrations of these techniques. The breathing exercises were performed by using a diaphragmatic breathing technique to breathe in and breathe out slowly and deeply.[14] A body scan was performed by nonjudgmentally paying attention to any sensation in each part of the body without any response, sweeping from the toes to the head.[15] The relaxation technique began with a 10-minute breathing exercise followed by a 20-minute body scan. The participants were assigned to practice relaxation techniques at home with a guided video for 30 minutes daily for 7 consecutive days before surgery.

Music medicine plus relaxation techniques

The participants were provided with both music medicine and relaxation technique interventions. They were assigned to practice 30-minute music medicine and 30-minute relaxation techniques at home daily for 7 consecutive days before surgery.

Control

The participants received standard care without any intervention related to music or relaxation techniques.

Instruments

The HADS-A consists of 7 items measured using

a 4-point Likert scale: 0 indicates absence or rarely, 1 indicates mild or occasionally, 2 indicates moderate or often, and 3 indicates extreme or very often/most of the time. Total scores range from 0 to 21, with higher scores indicating greater anxiety. An evaluation of the psychometric properties of both the original and Thai versions of the HADS demonstrated good validity and reliability, with a sensitivity of 100%, specificity of 86%, and internal consistency (Cronbach's alpha) of 0.86.[16,17]

Postoperative recovery quality was assessed using the Thai version of the Quality of Recovery–35 (QoR-35) questionnaire, which covers five domains: physical comfort, emotional state, physical independence, support received, and pain. The QoR-35 includes 35 items rated on a 5-point Likert scale, where 1 = very poor, 2 = poor, 3 = fair, 4 = good, and 5 = excellent. Total scores range from 35 to 175, with higher scores indicating better quality of recovery. Psychometric evaluations of both the original and Thai versions demonstrated strong validity and reliability, with high internal consistency at three time points (Cronbach's alpha = 0.88, 0.89, and 0.91, respectively; $p < 0.01$) and a split-half reliability coefficient of 0.65 ($p < 0.001$).[18]

Data collection

The data collected included demographic characteristics, anxiety level, quality of recovery after surgery, number of participants with adverse effects, and number of drop-out participants. Anxiety level was assessed via the Thai version of the Hospital Anxiety and Depression Scale–Anxiety subscale (HADS-A). The HADS consists of anxiety and depression subscales that measure the severity of anxiety and depression, respectively, in general hospital settings. On the day of recruitment (before starting the interventions), demographic characteristics were collected, and baseline HADS-A scores were assessed (baseline assessment). On the day of admission, which was 1 day before surgery (after the interventions were completed), HADS-A scores were assessed a second time. After surgery, the HADS-A scores and the QoR-35 scores were assessed at postoperative day 3, month 1, and month 3.

Statistical analysis

Sample sizes were calculated via a two-sided *t* test equation on the basis of previous studies.[19-21] The calculated sample size was 30 people per group. To account for potentially incomplete data or participant withdrawal from the research project, data will be collected from an increased number of volunteers, with 35 participants per group, totaling 140 participants.

The data were analyzed by using Stata Statistical Software, release 14 (StataCorp LLC, College Station, TX, USA). The demographic characteristics of the 4 groups were compared via independent *t* tests and chi-square tests. The number of participants with adverse effects and the number of drop-out participants in the 4 groups were compared via the chi-square test. The linear mixed model was used to determine changes in HADS-A scores over time, differences in changes in HADS-A scores between each intervention group and the control group, differences in QoR-35 scores between each intervention group and the control group, and differences in changes in QoR-35 scores between each intervention group and the control group. As the QoR-35 scores were not normally distributed, these data were transformed into logarithmic values for analysis.

RESULTS

Number of participants

A total of 140 participants were recruited for the study. The participants were randomly allocated to the music group, relaxation group, music plus relaxation group, or control group, with 35 participants in each group. Nine participants in the music group, 9 participants in the relaxation group, 7 participants in the music plus relaxation group, and 11 participants in the control group were excluded from the study. Participants in the three intervention groups were excluded because their surgeries were postponed after they had already completed a 7-day intervention. Participants in the control group were excluded because their surgeries were cancelled or postponed for an indefinite period. The remaining number of participants was 104 (26 in the music group, 26 in the relaxation group, 28 in the music plus relaxation group, and 24 in the control group). Fig 1 represents the CONSORT diagram.

Demographic characteristics

The demographic characteristics of the participants are shown in Table 1. The mean age of the participants was 70.81 years. The proportions of males (51%) and females (49%) were nearly equal. Most participants had a history of previous surgery (76.9%). The mean length of stay of all participants was 5.86 days. The mean baseline HADS-A score of all participants was 1.99. The demographic characteristics of the 4 study groups (3 intervention groups and 1 control group) were not significantly different.

Changes in HADS-A scores over time in each study group

The mean changes in HADS-A scores from baseline

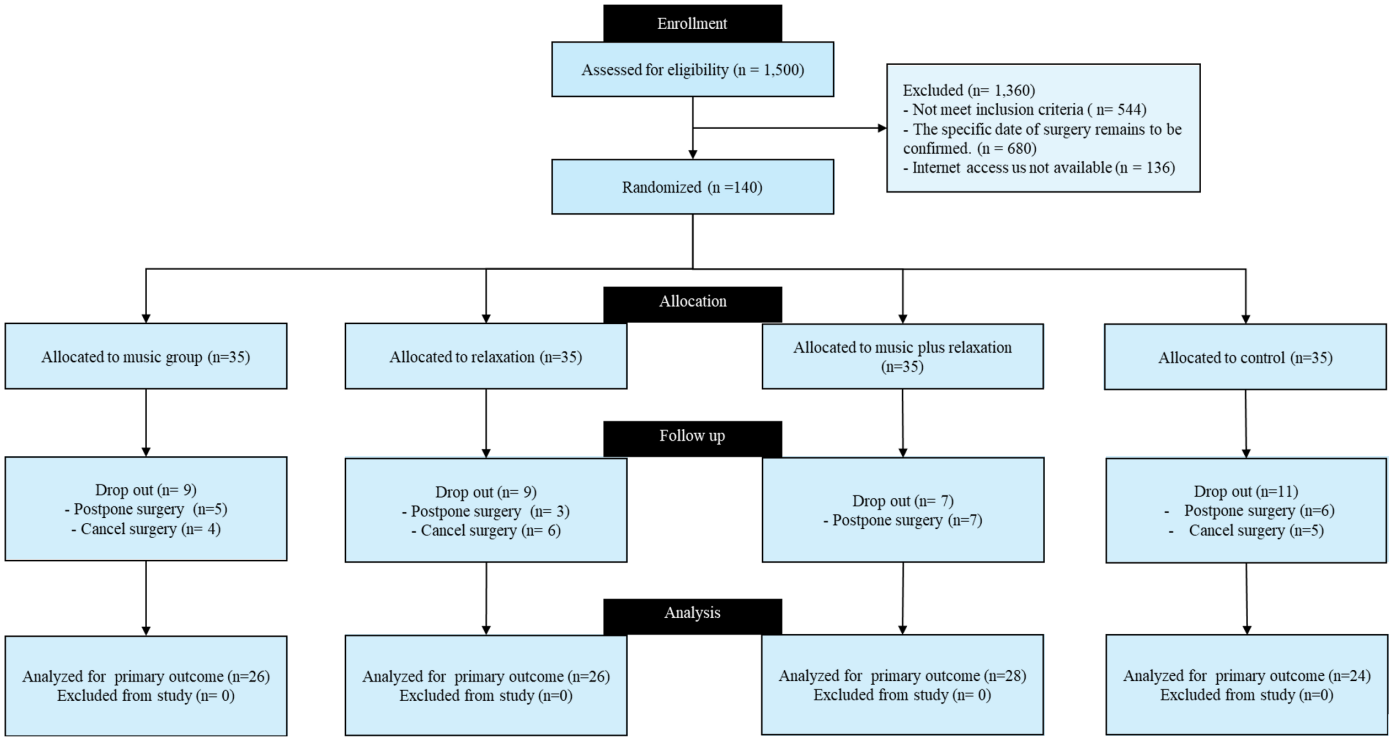

Fig 1. CONSORT diagram
Data collection took place during the COVID-19 pandemic (2020–2024), which impacted participant recruitment and surgical scheduling.

TABLE 1. Baseline demographic and clinical characteristics by study group (n = 104).

Variable	All participants (n = 104)	Music group (n = 26)	Relaxation group (n = 26)	Music plus relaxation group (n = 28)	Control group (n = 24)
Age, mean (SD)	70.81 (6.57)	72.54 (8.44)	70.70 (5.78)	70.04 (5.85)	69.91 (5.85)
Sex, n (%)					
Male, n (%)	53 (51)	14 (26.4)	12 (22.6)	14 (26.4)	13 (24.5)
Female, n (%)	51(49)	12 (23.5)	14(27.5)	14(27.5)	11 (21.6)
ASA					
ASA I, n (%)	15 (14.4)	5 (33.3)	4 (26.7)	3 (20)	3(20)
ASA II, n (%)	49 (47.1)	12 (24.5)	14 (28.6)	13 (26.5)	10 (20.4)
ASA III, n (%)	40 (38.5)	9 (22.5)	8 (20)	12 (30)	11 (27.5)
Experienced surgical procedure, n (%)	84 (80.8)	23 (27.4)	22 (26.2)	22(26.2)	17(20.2)
Length of stay (days), mean (SD)	5.86 (4.01)	5.71 (5.78)	6.52 (4.18)	5.78 (2.67)	5.33 (2.76)
Baseline HADS-A, mean (SD)	1.99 (2.22)	1.96 (2.31)	2.04 (2.26)	2.36 (2.26)	1.52 (2.06)

Abbreviations: ASA, American Society of Anesthesiologists physical status classification; HADS-A, Hospital Anxiety and Depression Scale–Anxiety subscale.

(preintervention) to each time point (postintervention) in each study group are shown in Table 2. The music group, relaxation group, and music plus relaxation group presented significant reductions in the mean HADS-A scores at every postintervention time point (the reduction in the mean scores ranged from −1.15 to −2.18, with *p* values ranging from less than 0.001 to 0.006). The control group showed a nonsignificant reduction in the mean HADS-A score at admission (a reduction in the mean score of −0.29, *p* 0.506) but a significant reduction at postoperative day 3, month 1, and month 3 (a reduction in the mean score ranging from −0.88 to −1.46, *p* values ranging from 0.001 to 0.046).

Comparison of the changes in HADS-A scores between each intervention group and the control group

Differences in the mean changes from baseline HADS-A scores between each intervention group and the control group are shown in Table 3. Relative to the control group, the relaxation group presented a significantly greater reduction in the mean HADS-A score at admission (difference in mean change −1.25, 95% CI −2.44 to −0.05, *p* 0.04) but showed a nonsignificantly greater reduction at postoperative day 3, month 1, and month 3. Compared with the control group, the music group and music plus relaxation group presented nonsignificantly greater reductions in the mean HADS score at every postintervention time point.

Comparison of the QoR-35 scores between each intervention group and the control group at postoperative day 3

Differences in the mean QoR-35 scores between each intervention group and the control group at postoperative day 3 are shown in Table 4. Compared with the control group, the relaxation group had significantly higher mean QoR-35 scores (mean difference 2.34, *p* 0.04). The music group and music plus relaxation group also presented nonsignificantly higher mean QoR-35 scores (mean difference of 1.04, *p* 0.32 in the music group and mean difference of 0.21, *p* 0.68 in the music plus relaxation group).

TABLE 2. Within-group change in HADS-A scores from baseline through 3 months.

Study group	Mean changes in the HADS-A scores from baseline [a]			
	Admission	Postoperative day 3	Postoperative month 1	Postoperative month 3
Music	−1.15 95% CI (−1.98, −0.33) *p* = 0.006	−1.38 95% CI (−2.21, −0.56) *p* = 0.001	−1.77 95% CI (−2.60, −0.94) *p* < 0.001	−1.81 95% CI (−2.63, −0.98) *p* < 0.001
Relaxation	−1.54 95% CI (−2.36, −0.71) *p* < 0.001	−1.69 95% CI (−2.52, −0.87) *p* < 0.001	−1.92 95% CI (−2.75, −1.10) *p* < 0.001	−1.96 95% CI (−2.79, −1.14) *p* < 0.001
Music plus relaxation	−1.43 95% CI (−2.22, −0.63) *p* < 0.001	−1.43 95% CI (−2.22, −0.63) *p* < 0.001	−2.04 95% CI (−2.83, −1.24) *p* < 0.001	−2.18 95% CI (−2.97, −1.38) *p* < 0.001
Control	−0.29 95% CI (−1.15, 0.57) *p* = 0.506	−0.88 95% CI (−1.73, −0.02) *p* = 0.046	−1.38 95% CI (−2.23, −0.52) *p* = 0.002	−1.46 95% CI (−2.32, −0.60) *p* = 0.001

Abbreviations: HADS-A, Hospital Anxiety and Depression Scale–Anxiety subscale.

[a] Change = mean HADS-A score at each postintervention time point minus mean baseline HADS-A score. Negative values indicate anxiety reduction.

TABLE 3. Between-group differences in HADS-A score change: intervention versus control.

Intervention group	Differences in the mean changes in the HADS-A scores between intervention and control [a, b]			
	Admission	Postoperative day 3	Postoperative month 1	Postoperative month 3
Music	–0.86 95% CI (–2.05, 0.33) *p* = 0.16	–0.51 95% CI (–1.70, 0.68) *p* = 0.40	–0.39 95% CI (–1.59, 0.80) *p* = 0.52	–0.35 95% CI (–1.54, 0.84) *p* = 0.57
Relaxation	–1.25 95% CI (–2.44, –0.05) *p* = 0.04	–0.82 95% CI (–2.01, 0.37) *p* = 0.18	–0.55 95% CI (–1.74, 0.64) *p* = 0.37	–0.50 95% CI (–1.70, 0.69) *p* = 0.41
Music plus relaxation	–1.14 95% CI (–2.31, 0.03) *p* = 0.06	–0.55 95% CI (–1.73, 0.62) *p* = 0.35	–0.66 95% CI (–1.83, 0.51) *p* = 0.27	–0.72 95% CI (–1.89, 0.45) *p* = 0.23

Abbreviations: HADS-A, Hospital Anxiety and Depression Scale–Anxiety subscale.

[a] Difference = (change in HADS-A score in the intervention group) minus (change in HADS-A score in the control group).

[b] Change in HADS-A score = mean score at each postintervention time point minus mean baseline score. More-negative values denote a greater decrease in anxiety in the intervention group relative to control.

TABLE 4. Quality of recovery (QoR-35) on postoperative day 3: intervention versus control.

Study group	Mean QoR-35 score (SD)	Differences in the mean QoR-35 score between intervention and control at postoperative day 3 [a]		
		Differences in mean	Logarithmic values	*p* value
Music	170.58 (5.57)	1.04 95% CI (–1.37, 3.45)	0.008 95% CI (–0.008, 0.023)	0.32
Relaxation	171.88 (3.97)	2.34 95% CI (–0.07, 4.75)	0.016 95% CI (0.0004, 0.031)	0.04
Music plus relaxation	169.75 (4.63)	0.21 95% CI (–2.16, 2.58)	0.003 95% CI (–0.012, 0.018)	0.68
Control	169.54 (10.60)	–	–	–

Abbreviations: QoR-35, Quality of Recovery-35 questionnaire

[a] Difference = mean QoR-35 score in the intervention group minus that in the control group. Positive values represent better perceived recovery in the intervention group.

Comparison of the changes in the QoR-35 scores between each intervention group and the control group

All study groups had increased their mean QoR-35 scores from postoperative day 3 to both postoperative months 1 and 3. Differences in the mean changes from postoperative day 3 in the QoR-35 scores between each intervention group and the control group are shown in Table 5. Compared with the control group, the music group, relaxation group, and music plus relaxation group presented nonsignificant increases in the QoR-35 score at both postoperative months 1 and 3.

Feasibility and adverse effects of the interventions

No participants dropped out during the intervention period or after the postoperative period. No participants experienced adverse effects.

DISCUSSION

This study revealed that practicing relaxation techniques, such as breathing exercises and body scans, for 7 days preoperatively reduced anxiety and improved recovery in elderly patients undergoing elective surgery. Compared with the control group, the relaxation group presented a significantly greater reduction in preoperative anxiety scores after completing the intervention. Additionally, the quality-of-recovery score was significantly greater in the relaxation group than in the control group on postoperative day 3. Similar findings have been reported in systematic reviews and meta-analyses, which demonstrated the effectiveness of relaxation techniques in reducing postoperative anxiety, depression, pain, and recovery duration across various surgeries—including head and neck, cardiac, gastrointestinal, gynecological, and orthopedic procedures. The duration of relaxation interventions in these studies ranged from 1 to 7 days.[8,22] The beneficial effects of relaxation techniques on both psychological and physical recovery may stem from psychological and neuroimmunological mechanisms. Psychologically, reducing anxiety lowers pain perception and encourages health-promoting behaviors, such as early ambulation and exercise.[8,23] Neuroimmunologically, decreased stress supports wound healing through sympathomedullary and hypothalamic–pituitary–adrenal pathways, which regulate inflammatory cytokines.[24]

This study revealed that multiple sessions of music medicine, relaxation techniques, and a combination of both were feasible for elderly patients, with no adverse effects. Feasibility was assessed on the basis of participant retention, and all participants completed daily 30- to 60-minute sessions over 7 days without dropouts. Feasibility is crucial in elderly populations, as long-duration interventions may be challenging to tolerate.

TABLE 5. Between-group differences in QoR-35 improvement from postoperative day 3 to months 1 and 3.

Intervention group	Differences in the mean changes in the QoR-35 scores between intervention and control [a,b]					
	Postoperative month 1			Postoperative month 3		
	Differences in mean changes	Logarithmic values	*p* value	Differences in mean changes	Logarithmic values	*p* value
Music	–0.87 95% CI (–3.49, 1.76)	–0.007 95% CI (–0.02, 0.01)	0.44	–0.98 95% CI (–3.61, 1.64)	–0.008 95% CI (–0.03, 0.01)	0.40
Relaxation	–1.63 95% CI (–4.26, 0.99)	–0.012 95% CI (–0.03, 0.01)	0.19	–1.91 95% CI (–4.53, 0.71)	–0.013 95% CI (–0.03, 0.004)	0.14
Music plus relaxation	–1.39 95% CI (–3.97, 1.18)	–0.010 95% CI (–0.03, 0.01)	0.24	–1.11 95% CI (–3.69, 1.46)	–0.008 95% CI (–0.03, 0.01)	0.33

Abbreviations: QoR-35, Quality of Recovery-35 questionnaire

[a] Difference = (change in QoR-35 score in the intervention group) minus (change in QoR-35 score in the control group).

[b] Change = mean QoR-35 score at postoperative month 1 or postoperative month 3 minus the mean score on postoperative day 3. More-negative values indicate a smaller gain in recovery score in the intervention group compared with control.

A previous study on relaxation techniques in elderly individuals reported a high attrition rate (35%), despite the effectiveness of relaxation techniques in reducing anxiety and depression. Common barriers included unclear instructions, low motivation, insufficient time, lack of privacy, and physical discomfort. Conversely, factors promoting compliance included normalizing anxiety experiences and immediate relaxation benefits.[25,26] In this study, several factors likely contributed to high compliance. Patients received clear instructions and ample opportunities for questions before starting the interventions. They initially practiced under expert supervision, allowing them to experience immediate relaxation and learn to manage discomfort. Additionally, potential barriers, such as time constraints and a lack of private space, were addressed collaboratively among patients, caregivers, and researchers.

This study did not demonstrate the effects of music medicine or music medicine plus relaxation techniques in reducing preoperative anxiety. This outcome may be attributed to low baseline anxiety levels among participants, which could limit the ability to detect treatment effects due to floor effects.[27] Additionally, participants in the control group with low anxiety may have managed their symptoms independently without requiring intervention. As a result, anxiety improvement did not significantly differ between the music/music plus relaxation groups and the control group.

This study did not demonstrate the long-term postoperative effects of any intervention on anxiety or recovery quality, possibly due to the participants' uncomplicated surgical conditions. Since they underwent elective procedures, their surgeries were classified as uncomplicated, leading to favorable clinical outcomes and recovery. These positive outcomes may have reduced postoperative anxiety and enhanced recovery, even without intervention. This explanation aligns with a previous study, which reported that successful surgery alleviated depression in 48% of patients with preoperative depression.[28] Thus, the beneficial effects of favorable surgical outcomes in the control group may have diminished the ability to detect long-term treatment effects in the intervention groups.

Owing to limitations in participant characteristics—including low baseline anxiety and uncomplicated surgical conditions—detecting the effects of interventions was challenging. Future research should address these limitations. First, studies should recruit participants with higher anxiety levels, such as those with HADS scores above 7, indicating possible anxiety disorders.[17] Since severe anxiety is less likely to be self-managed, music medicine may be effective in reducing symptoms. Second, future studies should include participants with more complicated surgical conditions. Because unfavorable postoperative outcomes are more common in complex cases, the confounding effects of positive recovery can be minimized. Reducing these confounding effects may increase the sensitivity needed to detect long-term treatment benefits of music medicine and relaxation techniques if they are effective. Lastly, data collection took place during the COVID-19 pandemic (2020–2024), which impacted participant recruitment and surgical scheduling. Due to a relatively high dropout rate, we consulted a statistician to guide data analysis. Consequently, a linear mixed model was employed to address the presence of missing data. Despite the slightly smaller sample size than originally planned, the results indicated that the study retained sufficient statistical power.[29] Furthermore, a previous study highlighted the impact of the COVID-19 pandemic on the mood states of individuals with anxiety.[30] However, anxiety is often shaped by a variety of contextual stressors. Future research should therefore aim to assess anxiety in relation to a broader spectrum of challenges, including economic instability, social disruption, emerging infectious diseases, and natural disasters. Such an approach would provide a more nuanced and comprehensive understanding of the complex factors influencing mental health, particularly among vulnerable populations.

CONCLUSIONS

The study demonstrated that a 1-week preoperative relaxation technique intervention was feasible and had immediate effects on reducing preoperative anxiety and improving the quality of recovery after surgery in elderly patients without adverse effects. However, further research should be conducted by recruiting patients with higher levels of anxiety and with more complicated surgical conditions to clearly determine the short-term effects of music medicine as well as the long-term effects of music medicine and relaxation techniques in reducing perioperative anxiety and improving the quality of recovery after surgery.

Data Availability Statement

The authors confirm that the data supporting the findings of this study are available within the article.

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DECLARATIONS

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Conflicts of Interest

None.

Registration Numbers of the Clinical Trial

The study has been officially registered with the Thai Clinical Trial Registry under the identifier TCTR20200910002.

Author Contributions

Conceptualization and methodology: PP, SP, PY, AS; Investigation: PP, PY, GC,AS; Data analysis: PP , TP, AS; Visualization and writing–original draft: PP; Writing–review and editing: AS, TP; Supervision: AS.; Essentially Intellectual Contributor: AS. All the authors read and agreed with the final version of the manuscript.

Use of Artificial Intelligence

None.

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Frailty and Upper Gastrointestinal Surgery: Initial Findings from Thailand's First Surgical Frailty Study

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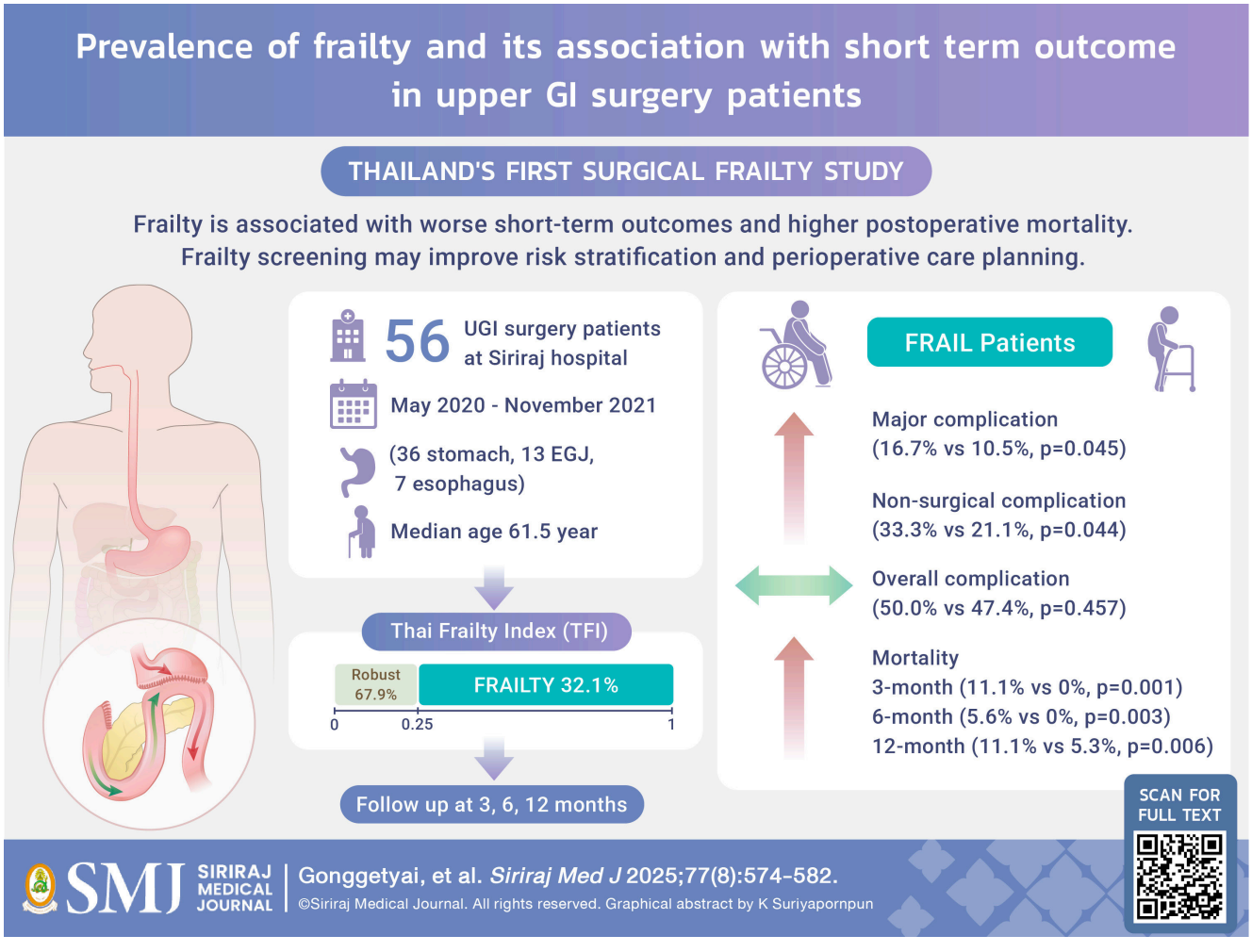

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ABSTRACT

Objective: Thailand's aging population has led to an increase in elderly patients undergoing major surgery. Frailty is a key predictor of adverse surgical outcomes, but its impact in Thai patients remains underreported. This study aimed to determine the prevalence of frailty and its association with short-term postoperative outcomes among patients undergoing upper gastrointestinal (UGI) surgery.

Materials and Methods: This prospective cohort study included all adult patients undergoing elective UGI surgery at Siriraj Hospital between May 2020 and November 2021. Preoperative frailty was assessed using the Thai Frailty Index (TFI), with scores >0.25 indicating frailty. Demographic data, surgical details, and postoperative outcomes — including complications and survival at 3, 6, and 12 months — were compared between frail and robust groups.

Results: Among 56 patients (median age 61.5 years), 18 (32.1%) were classified as frail. Frail patients were significantly older and had poorer functional status and nutritional risk. Frail patients also underwent fewer resection procedures (61.1% vs 84.2%, p=0.001). While the overall complication rate did not differ significantly between groups (50.0% vs 47.4%; p=0.457), frail patients experienced higher rates of major complications (16.7% vs 10.5%; p=0.045) and non-surgical complications (33.3% vs 21.1%; p=0.044). Mortality was significantly higher in the frail group at 3, 6, and 12 months postoperatively (p=0.001, 0.003, 0.006 respectively).

Conclusion: Frailty is common among Thai patients undergoing UGI surgery and is associated with worse short-term outcomes and higher postoperative mortality. Routine frailty screening using the TFI may improve preoperative risk stratification and perioperative care planning.

Keywords: Frailty; Thai frailty index; Upper gastrointestinal surgery; Postoperative complication; Mortality (Siriraj Med J 2025; 77: 574-582)

INTRODUCTION

At present, Thailand is experiencing a demographic shift towards an aging society, attributed to advancements in medical care. According to data from the National Statistical Office in 2017, approximately 11 million people in Thailand are aged 60 years or older, representing approximately 16% of the total population. However, previous studies have shown that chronological age does not always accurately reflect actual physical fitness or functional performance in elderly individuals.[1] This discrepancy between chronological age and physiological age can significantly influence postoperative recovery and the risk of complications. Frailty, a clinical condition characterized by increased vulnerability due to age-related decline across multiple physiological systems, has gained considerable attention in geriatric medicine.[2,3] The reduced physiological reserve seen in frail individuals renders them especially susceptible to the adverse effects of surgical stress, leading to unfavorable postoperative outcomes in approximately 25%-50% of patients.[4] Previous studies have highlighted the impact of frailty on post-surgery outcomes, revealing that elderly patients classified as frail are more likely to experience higher rates of complications, lower quality of life after surgery, and lower survival rates compared to robust patients.[5-13] However, no studies to date have examined the relationship between frailty and surgical outcomes in Thailand.

Frailty can be identified and assessed using various tools, such as the Modified Frailty Index[14], Preoperative Modified Frailty Index[15], Clinical Frailty Scale[16], assessments of Sarcopenia[17], the Groningen Frailty Indicator[18], and the Study of Osteoporotic Fractures (SOF).[6] However, there is currently no universally accepted gold standard for frailty assessment. In Thailand, the Thai Frailty Index (TFI) was developed to predict long-term mortality in the elderly population[3]. Despite this, surgical patients in Thailand have not yet been evaluated using this tool.

Diseases affecting the upper gastrointestinal (UGI) tract, particularly cancer, continue to pose significant public health challenges. Surgery remains the mainstay treatment modality for most UGI diseases, but it is associated with a high overall complication rate, including procedure-related adverse events and prolonged hospital stays. Adequate preoperative preparation, including nutritional assessment and frailty assessment, is crucial for reducing morbidity.[19-21] In recent years, the Enhanced Recovery After Surgery (ERAS) program has become increasingly popular,[22] including in UGI surgery. The ERAS protocol aims to facilitate faster recovery and minimize surgical stress through a comprehensive approach involving pre-operative optimization, minimally invasive surgical techniques, and postoperative care.[23-26] Compared to the era of traditional peri-operative care, ERAS has demonstrated its advantages in promoting faster recovery and reducing

hospital stay.[27] The objective of this study is to determine the prevalence of frailty among surgical patients and to evaluate its impact on short-term postoperative outcomes.

MATERIALS AND METHODS

Patient selection

This single-center prospective cohort study was conducted at Siriraj Hospital. We recruited patients aged 18 years and older who underwent elective upper gastrointestinal surgery for either benign or malignant diseases between May 2020 and November 2021. Emergency cases, individuals with limited understanding or inability to answer the questionnaire, and those who were bedridden or unable to perform physical tests were excluded. Frailty was assessed preoperatively using the Thai Frailty Index (TFI), which includes 30 dichotomous variables covering medical comorbidities, functional status, and physical and emotional health. The frailty index was calculated by dividing the number of deficits identified by the total number of items. Patients with a TFI > 0.25 were classified as frail, while those with TFI ≤ 0.25 were considered robust. In this study, the TFI was used to categorize patients as either frail or robust prior to surgery. Subsequent treatment decisions were made through standard counseling between the doctor and patient in the outpatient department, without considering frailty status. Starting in 2020, all surgical patients were managed according to the ERAS protocol, in accordance with our faculty's policy. The details of our protocol were previously published in a separate study.[26]

Data collection

Clinicopathological characteristics were recorded, including age, gender, body mass index (BMI), the American Society of Anesthesiologists (ASA) classification, Eastern Cooperative Oncology Group (ECOG) scale, Charlson comorbidity index, comorbidities, nutritional status screening and assessment, preoperative diagnosis, disease location, operative approach, and surgical procedure. Cancers of the esophagus, esophagogastric junction (EGJ), and stomach were staged based on the 8th edition of the American Joint Committee on Cancer (AJCC) staging system.[28] Nutritional status was assessed using the Nutritional risk screening[29] and the Modified Nutrition Alert Form.[30]

After surgery, we analyzed short-term postoperative outcomes, including length of hospital stay and postoperative complications, graded according to the Clavien-Dindo classification.[31] Severe complications were defined as grade III or higher. Patients were followed up at 3, 6 and 12 months after hospital discharge. Data were collected during scheduled outpatient clinic visits. In cases where a patient was unable to attend or did not have an appointment, follow-up data were obtained via telephone. During these follow-up assessments, we collected information on the patient's survival status.

The primary objective of this study was to determine the prevalence of frailty among patients undergoing UGI surgery and to assess its impact on short-term postoperative outcomes, including complication rates and survival. The study protocol was approved by the Institutional Review Board (IRB) of the Faculty of Medicine Siriraj Hospital, Mahidol University (certificate of approval no. Si 249/2020).

Statistical analysis

Continuous variables were presented as means with standard deviations or as medians with interquartile ranges. Group comparisons were conducted using the Student's t-test or the Mann-Whitney U test. Categorical variables were expressed as numbers and percentages, and comparisons were made using the chi-square test or Fisher's exact test. Univariable and multivariable logistic regression analyses were performed to identify factors associated with postoperative complications. Hazard ratios (HRs) and 95% confidence intervals were estimated using multivariate analysis. Variables with a P-value less than 0.05 in the univariate analysis were included in the multivariable model. A two-tailed P-value less than 0.05 was considered statistically significant. All statistical analyses were conducted using SPSS® version 30.0 (IBM, Armonk, New York, USA).

RESULTS

Demographic and baseline characteristics data

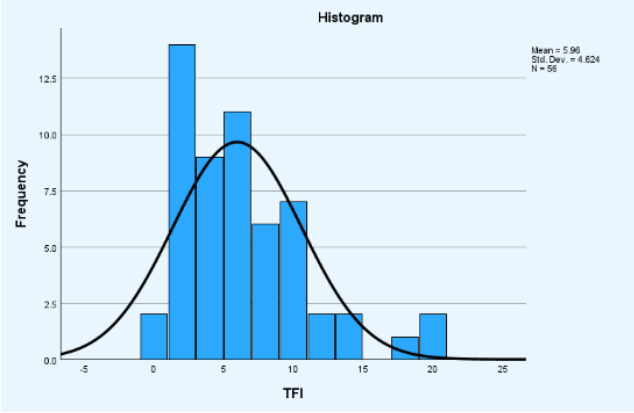
A total of 56 patients were enrolled in this study, comprising 29 male and 27 female patients. The median age was 61.5 years (IQR 56.25-74.75 years). The stomach was the most common primary disease site in this cohort, observed in 36 patients (64.3%), followed by the esophagogastric junction in 13 patients (23.2%), and the esophagus in seven patients (12.5%). Among the study population, 49 patients (87.5%) were diagnosed with malignant conditions, including 32 cases (57.1%) of adenocarcinoma, 13 cases (23.2%) of subepithelial tumor, and four cases (7.1%) cases of squamous cell carcinoma of the esophagus. The remaining seven patients (12.5%) were diagnosed with benign diseases. The median duration of symptoms prior to presentation was 2 months (IQR 1-6 months). In terms of surgical approach, 27 patients (48.2%) underwent open surgery, 15 patients (26.8%) underwent laparoscopic surgery, and 14 patients (25.0%) underwent a robot-assisted procedure.

Based on the Thai Frailty Index evaluation, the mean TFI score in this cohort was 6.0 ± 4.6. The prevalence of frailty among upper gastrointestinal surgical patients was 18 cases (32.1%) (Fig 1). Patients in the frailty group had significantly higher median age (71.0 years vs 60.0 years, p=0,042), and a higher proportion of female patients (66.7 vs 39.5%, p<0.001). Frail patients also showed a trend toward lower BMI than robust patients. There were no significant differences between the two groups in terms of ASA classification or age-adjusted Charlson Comorbidity Index. However, the ECOG score was significantly higher in the frailty group (p=0.003), indicating worse functional status. Regarding preoperative nutritional status, frail patients were at significantly higher risk of malnutrition (p<0.001). Moreover, the Nutrition Alert Form assessment showed a trend toward more severe malnutrition among frail patients (Table 1).

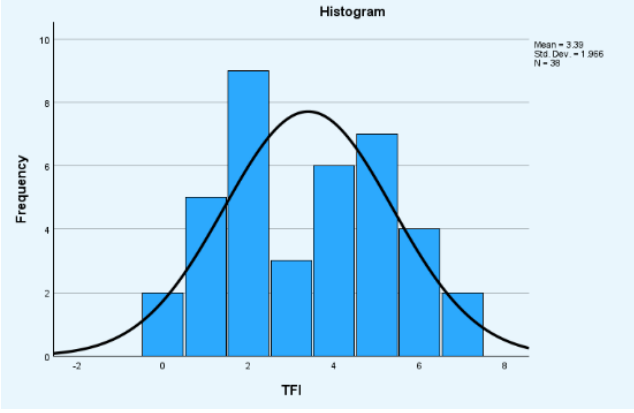
Surgical data and postoperative outcomes

All patients underwent surgical treatment according to standard clinical protocols. The operative approaches, either open or minimally invasive surgery, did not differ significantly between groups. However, a lower proportion of patients in the frailty group underwent resection surgery compared to the robust group (61.1% vs 84.2%, p=0.001). There was no significant difference in the overall postoperative complication rate between the frailty and robust groups (50.0% vs 47.4%, p=0.457). However, the incidence of major postoperative complications was significantly higher in the frailty group (16.7% vs 10.5%, p=0.045), as was the rate of non-surgical complications (33.3% vs 21.1%, p=0.044). There were no significant differences between the two groups in total hospital stay or postoperative length of stay.

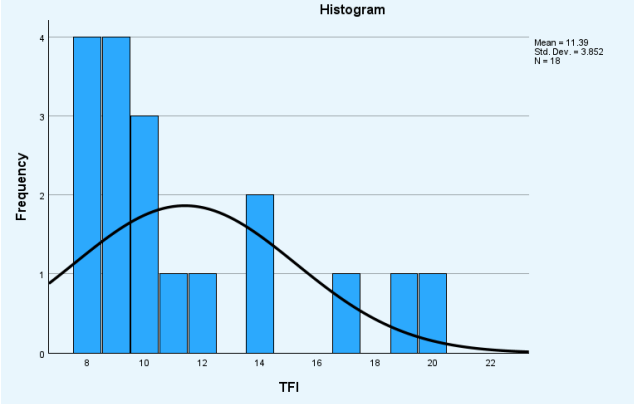
Among the study participants, only one case of in-hospital mortality was observed, occurring in a robust patient with esophageal squamous cell carcinoma who underwent transthoracic esophagectomy with three-field lymphadenectomy. Prior to the operation, this patient exhibited borderline pulmonary function and subsequently experienced postoperative respiratory failure and required intubation. The patient developed hospital-acquired pneumonia and, despite treatment, passed away on postoperative day 30. As a result, the in-hospital mortality rate was slightly higher in the robust group (2.6% vs 0%, p=0.001). However, at 3-month, 6-month, and 12-month follow-up, the frailty group showed significantly higher rates of postoperative mortality (p=0.001, 0.003, 0.006, respectively) (Table 2).



A. All patients



B. Robust group



C. Frailty group

Fig 1. Thai Frailty Index (TFI) scores among upper gastrointestinal surgical patients

DISCUSSION

Frailty is an emerging topic in the field of geriatric medicine but it remains poorly understood in the surgical context in Thailand. To the best of our knowledge, this study is the first of its kind within the country. In our study, the prevalence of frailty was 32.1%. This finding is comparable to other studies, such as one by *Tegels et al*

TABLE 1. Demographic data.

Characteristics	Robust (N=38)	Frailty (N=18)	P-value
Age (years), median (IQR)	60.0 (54.5-72.5)	71.0 (59.5-77.0)	**0.042**
Female gender, n (%)	15 (39.5)	12 (66.7)	**<0.001**
Mean BMI (kg/m^2) (min-max)	23.6 (17.1-35.5)	21.2 (15.6-30.9)	0.067
ASA classification, n (%)			0.474
1-2	30 (78.9)	14 (77.8)	
3-4	8 (21.1)	4 (22.2)	
ECOG scale, n (%)			**0.003**
0-1	38 (100)	15 (83.3)	
≥2	0	3 (16.7)	
Age-adjusted Charlson comorbidity index, n (%)			0.203
1-2 (mild comorbidity)	5 (13.2%)	1 (5.5)	
3-4 (moderate comorbidity)	13 (34.2)	4 (22.2)	
≥5 (severe comorbidity)	19 (50.0)	13 (72.2)	
Disease localization, n (%)			**0.003**
Esophagus	6 (15.8)	1 (5.5)	
Esophagogastric junction	10 (26.3)	3 (16.7)	
Stomach	22 (57.9)	14 (77.8)	
Disease pathology			**<0.001**
Neoplastic diseases, n (%)	34 (89.5)	15 (83.3)	
Esophageal cancer	3 (7.9)	1 (5.5)	
Gastric cancer	21 (55.3)	11 (61.1)	
Subepithelial tumor	10 (26.3)	3 (16.7)	
Non-neoplastic diseases	4 (10.5)	3 (16.7)	
Duration of symptoms (months), median (IQR)	3 (0-12)	1 (0-6)	0.542
Nutrition screening score (SPENT), n (%)			**<0.001**
0-1	27 (71.1)	5 (27.8)	
2-3	11 (28.9)	13 (72.2)	
Nutrition assessment score (NAF), n (%)			0.177
Normal to mild malnutrition (0-5)	18 (47.4)	4 (22.2)	
Moderate malnutrition (6-10)	13 (34.2)	6 (33.3)	
Severe malnutrition (≥11)	7 (18.4)	8 (44.4)	

Abbreviations: ASA, American Society of Anesthesiologists; BMI, Body mass index; ECOG, Eastern Cooperative Oncology Group; IQR, Interquartile range; NAF, Nutrition alert form; SPENT, Society of Parenteral and Enteral Nutrition of Thailand

TABLE 2. Surgery-related data.

Characteristics	Robust (N=38)	Frailty (N=18)	P-value
Operative approach, n (%)			0.104
Open	17 (44.7)	10 (55.6)	
Laparoscopic or robotic	21 (55.5)	8 (44.4)	
Surgery type, n (%)			**0.001**
Resection surgery	32 (84.2)	11 (61.1)	
Non-resection surgery	6 (15.8)	7 (38.9)	
Complication, n (%)			
Minor (CD grade I-II)	14 (36.9)	6 (33.3)	0.214
Major (CD grade III-V)	4 (10.5)	3 (16.7)	**0.045**
Complication category, n (%)			
Surgical related	13 (34.2)	5 (27.8)	0.082
Non-surgical related	8 (21.1)	6 (33.3)	**0.044**
Length of stay, median (days) (IQR)			
Total	7 (5.5-12)	9 (5-16)	0.565
Post-operative	6 (4-11)	5 (4-12.5)	0.662
Mortality, n (%)			
In-hospital	1 (2.6)	0	**0.001**
3-month	0	2 (11.1)	**0.001**
6-month	0	1 (5.6)	**0.003**
12-month	2 (5.3)	2 (11.1)	**0.006**

Abbreviation: CD, Clavien-Dindo classification

(2012), which reported a frailty rate of 24% among patients with gastric adenocarcinoma, using the Groningen Frailty Indicator (GFI) and the Short Nutritional Assessment Questionnaire (SNAQ)[18] for evaluation. Similarly, *Mazzola et al's* study (2017) reported a frailty prevalence of 54%[14] in patients with malignant UGI tumors, based on a modified frailty index. Furthermore, a systematic review encompassing 70 studies revealed a wide range in the prevalence of frailty among older patients undergoing general surgery, ranging from 8% to 77.8%.[12] Notably, a previous report focusing on community-dwelling older adults in Thailand using the Thai Frailty Index found a frailty prevalence of 22.1%.[3]

Consistent with several previous publications,[13,16,17] our study found no significant difference in overall postoperative morbidity between frail and robust patients. However, the incidence of major complications and non-surgical complications was significantly higher in the frailty group. Our results align with a recent study by *Chaoyang Gu et al.* (2022) in China, which included 246 patients undergoing gastrointestinal surgery. In that study, 47 patients (19.1%) were classified as frail based on the Frailty Index score. Although overall morbidity did not differ significantly between groups, the frail group had higher rates of ICU admission, mortality, and 30-day postoperative complications (57.1% vs 16.1%) compared to the robust group. A subgroup analysis focusing on minor surgical procedures found no significant association between frailty and intraoperative or postoperative parameters.[32] Postoperative morbidity is influenced by several factors, such as age, co-morbidities, and the type of surgery. While many previous studies have primarily focused on screening frailty in elderly patients, our study diverges by assessing the frailty score in all surgical patients regardless of age or surgical type. Furthermore, the variation in diagnostic tools used to assess frailty contributes to the

wide range of reported prevalence rates across studies. It is important to acknowledge that our findings may be limited by the relatively small sample size. Hence, future investigations involving larger cohorts or subgroup analyses may provide more definitive insights.

However, frailty appears to play a significant role in quality-of-life (QoL) outcomes. QoL is a concept that lacks a universally accepted definition and remains a subject of ongoing debate. The World Health Organization (WHO) defines QoL as an individual's perception of their position in life within the context of their culture, societal expectations, personal goals, expectations, standards, and worries.[33] When frailty is present, a decline in various domains of functioning, including psychological, social capabilities, and physical ability, is commonly observed. It is estimated that approximately 20% to 30% of individuals aged 75 years and older are vulnerable to frailty.[34] This evaluation will be further demonstrated in our future prospective cohort study.

A key question that arises is whether the implementation of ERAS improves postoperative morbidity and quality of life in both frail and robust patients undergoing UGI surgery. Enhanced recovery is an integrated interdisciplinary perioperative pathway that offers a standardized approach to perioperative care. Its primary goal is to reduce the catabolic stress response to surgery and promote functional recovery through a series of interventions.[35] Its implementation has been proven to be suitable despite the advanced age of the patients.[36] A study by *Wang et al* in 2010 reported improved QoL scores and Visual Analog Scale (VAS) ratings in the ERAS group.[37] In our study, we compared outcomes in frail and robust patients who received perioperative care under an ERAS protocol with those who underwent conventional care. Interestingly, we found no significant difference in immediate postoperative morbidity between the ERAS and conventional care groups in either the frail or robust patients. This lack of significance may be attributed to the limited sample size. Future publications and research may provide additional insights into the potential benefits of implementing ERAS in this patient population.

Clinical implication and future research direction

This study highlights the importance of recognizing and addressing frailty, which was detected in approximately one-third of our patient cohort based on the Thai frailty Index score. Early identification of frailty allows for timely interventions aimed at optimizing overall patient health. Several interventions have been proposed to address the impact of frailty:[38,39]

1) Adherence to ERAS protocols[40,41]: Following ERAS protocols can facilitate early recovery and reduce surgical stress, potentially benefiting frail patients.

2) Implementation of a prehabilitation program[42]: Prehabilitation aims to enhance patients' physical and functional status prior to surgery. Previous studies have shown that prehabilitation can reduce the incidence of postoperative pneumonia and length of hospital stay.

3) Conducting early geriatric interdisciplinary assessments[43]: Involving a multidisciplinary team of healthcare professionals with expertise in geriatric care can facilitate a comprehensive evaluation of the patient's health status and tailor interventions to their specific needs.

By implementing these interventions, healthcare providers can effectively address frailty and potentially improve outcomes for frail patients undergoing upper gastrointestinal surgery.

Limitations and strengths

Several limitations of this study should be acknowledged. First, the relatively small sample size limits the generalizability of the findings reported in this study. This limitation was primarily due to the short recruitment period, which spanned only one and a half years. Further analysis of the prospective cohort is expected to include a larger patient population, which may yield a more accurate estimate of frailty prevalence and its true impact on short-term surgical outcomes, long-term recovery, and quality of life among patients with upper gastrointestinal diseases. Second, the heterogeneity of included diseases presents a challenge. This study encompassed a broad range of both benign and malignant conditions affecting the esophagus, esophagogastric junction, and gastric diseases. Each disease entity has its own unique prognosis. In future studies with a larger sample size, our aim is to conduct subgroup analyses based on the specific organ involved and the nature of the disease. This approach will allow for a more comprehensive understanding of outcomes associated with each disease and procedure.

CONCLUSION

This study is the first prospective investigation in Thailand to evaluate the impact of frailty on surgical outcomes in patients undergoing upper gastrointestinal surgery. We found that frailty was prevalent in nearly one-third of the study population and was significantly associated with advanced age, poorer performance status, and increased nutritional risk. Although overall complication rates were similar between frail and robust patients, frailty was linked to a higher incidence of major and non-surgical

complications. Furthermore, frail patients demonstrated significantly lower survival rates at 3, 6, and 12 months postoperatively. These findings underscore the importance of preoperative frailty assessment as a valuable tool for identifying high-risk patients and tailoring perioperative care accordingly. Future studies with larger cohorts and multi-center designs are needed to validate these findings and further explore the integration of frailty screening into standard surgical pathways in Thailand.

Data Availability Statement

Data are available upon reasonable request.

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DECLARATION

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Conflict of Interest

The authors declare no conflicts of interest.

Registration Number of Clinical Trial

This research project has been approved by Thai Clinical Trial Registry (ID number TCTR20250731006).

Author Contributions

G.G. was the first author and was responsible for study design, data collection, data analysis and manuscript writing. N.T. analyzed the data and edited the original manuscript. C.N., J.S., A.M. designed the study, collected and analyzed the data, edited and reviewed the manuscript. A.S., O.C., V.S. designed the study, collected the data and reviewed the manuscript. T.P. was the corresponding author and was responsible for conceptualization, study design, study methodology, data collection and analyses, and final manuscript editing. All authors approved the final manuscript.

Use of Artificial Intelligence

None.

Statement of Ethics

This study was reviewed and approved by the Institutional Review Board (IRB) of the Faculty of Medicine Siriraj Hospital, Mahidol University (certificate of approval no. Si 249/2020). All participating patients provided written informed consent prior to enrollment.

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The Use of Therapeutic Drug Monitoring to Personalize Once-daily Intravenous Busulfan in Thai Pediatric Patients Underwent Hematopoietic Stem Cell Transplantation

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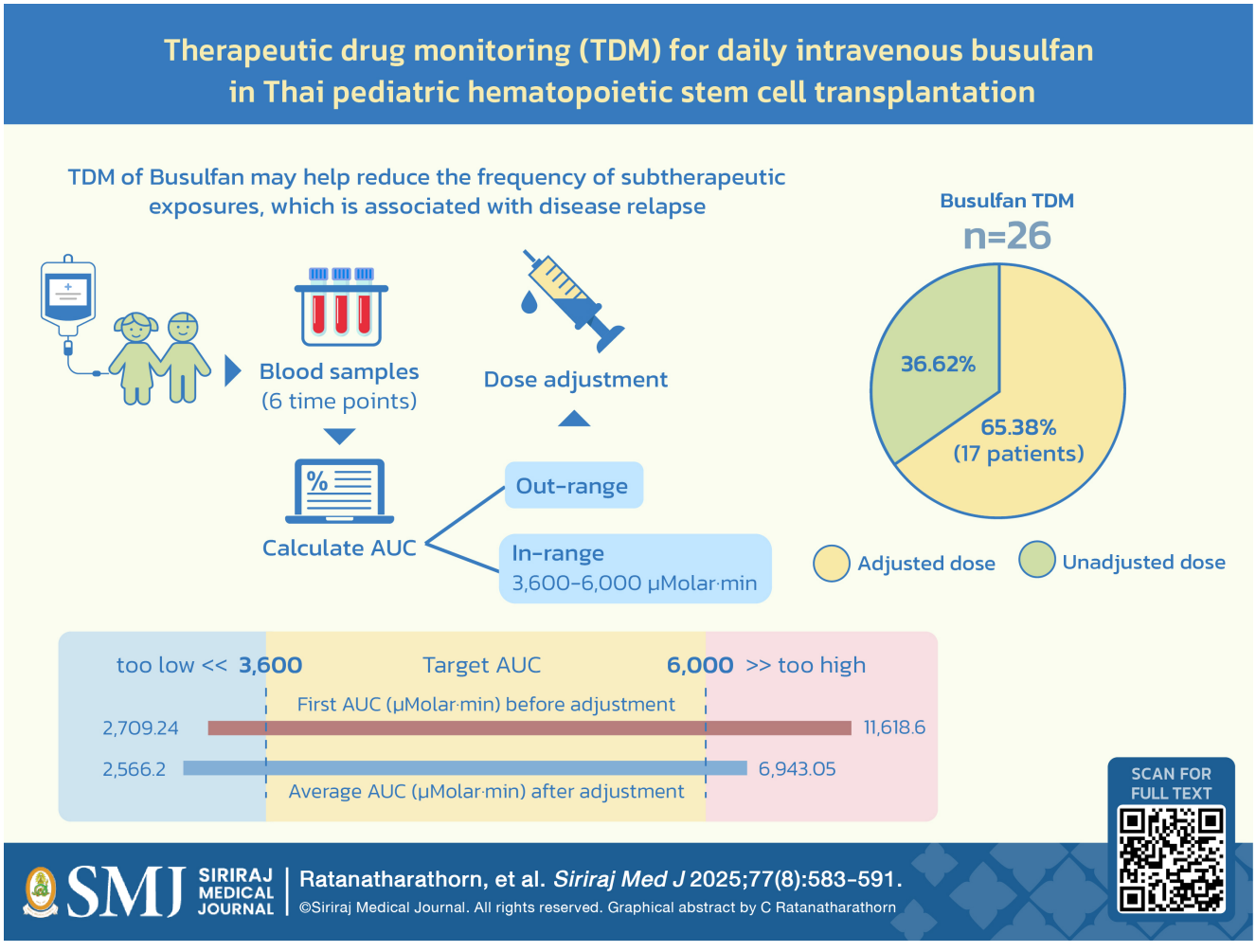

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ABSTRACT

Objective: Therapeutic drug monitoring (TDM) for personalizing busulfan dosing in pediatric hematopoietic stem cell transplantation (HSCT) is recommended. The proportion of patients requiring dose adjustments and the frequency of achieving the target area under the time curve (AUC) was observed.

Materials and Methods: This study included children who underwent once-daily intravenous busulfan-conditioning HSCT during October 2020 to April 2024. The initial busulfan dosage followed the European Medicines Agency nomogram, set between 3.2 and 4.8 mg/kg/day. Blood samples were collected to analyze pharmacokinetics and calculate AUC. Dose adjustments were made if AUC fell outside the target of 3,600 to 6,000 μMolar·min.

Results: The study comprised 26 children. Dose adjustments for busulfan were performed in 17 patients (65.4%). Individual average AUCs ranged from 2,566.2 to 6,943.05 μMolar·min. Patients under 10 years had a higher likelihood of an out-of-range target AUC following dose adjustment compared to those aged ≥ 10 years (43.8% and 0%, respectively; P=0.023). A lower-than-target average AUC was significantly related to an earlier disease relapse compared to non-lower range AUCs (P<0.005). Conversely, higher AUCs did not correlate with busulfan-related side effects or treatment-related mortality.

Conclusion: Our findings support TDM as a strategy to enhance the efficacy of once-daily intravenous busulfan in HSCT among Thai pediatric patients. TDM may help reduce the frequency of subtherapeutic exposures, which is associated with disease relapse. Patients under 10 years face more difficulties in achieving the target AUC, indicating the need for careful monitoring and dose adjustments in this age group.

Keywords: Therapeutic drug monitoring; Busulfan; Hematopoietic Stem Cell Transplantation (Siriraj Med J 2025; 77: 583-591)

Abbreviations

Abbreviation	Meaning
AUC	Area under the time curve
AUC1	First day of area under the time curve
EMA	European Medicines Agency
GST	Glutathione S-transferase
HSCT	Hematopoietic stem cell transplantation
TDM	Therapeutic drug monitoring

INTRODUCTION

Busulfan, an alkylating agent with a narrow therapeutic index, is widely used in conditioning regimens for pediatric hematopoietic stem cell transplantation (HSCT) conditioning regimens in both malignant and nonmalignant diseases.[1] Intravenous administration of busulfan is preferred over oral forms due to reduced intrapatient pharmacokinetic variability from gastrointestinal absorption.[2] A lower area under the time curve (AUC), specifically under 950 μMolar·min for every-6-hour intravenous busulfan, increases the risk of disease relapse post-transplantation. Conversely, an AUC exceeding 1,500 μMolar·min is associated with heightened mucositis and veno-occlusive disease/sinusoidal obstructive syndrome, which may escalate to life-threatening conditions.[3]

The American Society for Blood and Marrow Transplantation guidelines recommend therapeutic drug monitoring (TDM) and personalized dose adjustments of busulfan within myeloablative conditioning regimens. Achieving target AUC enhances treatment efficacy, reduces side effects, and lowers treatment-related mortality.[1] Studies in Europe, Japan, and Thailand administered busulfan intravenously every 6 hours using five fixed weight-based dosages initially, as recommended by the European Medicines Agency (EMA)[4], without subsequent dose modification. The percentage of patients achieving target AUC was 75%, 76%, and 42.86%, respectively, across these geographical regions.[5-7]

The escalating number of transplantation centers in Thailand presents a growing challenge regarding the implementation of TDM for busulfan. Despite global recommendations advocating its use, many transplant centers lack the capacity to perform TDM, highlighting a critical need to optimize busulfan dosing strategies within the Thai population. Research by Jansing et al in Thailand indicated that Thai pediatric patients exhibit a

lower rate of achieving target AUC compared to other studies, suggesting a need for personalized busulfan dosing in this population.[7] The traditional schedule of intravenous busulfan administration every 6 hours has been modified to a once-daily regimen. This change enhances convenience without altering pharmacological characteristics, therapeutic efficacy, or side effects.[8,9] The optimal target AUC_{0-24} for once-daily intravenous busulfan is 3,600-6,000 μMolar·min. This range aims to avoid under or over-exposure to prevent disease relapse, improve overall survival, minimize toxicity, and reduce treatment-related mortality risks.[1,10]

The primary objective of this study was to determine the proportion of patients requiring dose adjustments and the frequency of those adjustments needed to achieve the target AUC, with the secondary objective of observed time to relapse, toxicity, mortality and the relationship between AUC and clinical outcomes.

MATERIALS AND METHODS

Study design and population

This retrospective study included patients under 18 years old who underwent HSCT with a once-daily intravenous busulfan conditioning regimen at the Pediatric Department, Faculty of Medicine Siriraj Hospital, Bangkok, Thailand, from October 2020 to April 2024. Ethical approval was granted by the Mahidol University Multi-Faculty Cooperative IRB Review (MU-MOU 305/2567 [IRB2]). Informed consent was waived for this retrospective analysis.

Conditioning regimen and supportive care

Busulfan-containing myeloablative conditioning regimens varied based on HSCT type and disease, as detailed in Supplementary data (Table S1). Initial busulfan dosing followed the EMA nomogram's five fixed-dose model[4] : 4 mg/kg/day for patients under 9 kg, 4.8 mg/kg/day for those 9-16 kg, 4.4 mg/kg/day for 16-23 kg, 3.8 mg/kg/day for 23-34 kg, and 3.2 mg/kg/day for those over 34 kg. Busulfan was administered for 3-4 days, depending on the specific regimen. Busulfan was further diluted with normal saline to a final concentration of approximately 0.5 mg/ml and infused intravenously over a 3-hour period once daily.

Levetiracetam was provided for seizure prophylaxis at 10 mg/kg/dose every 12 hours, starting 12 hours before busulfan infusion and continuing until 48 hours post-infusion. Graft-versus-host disease prophylaxis varied by HSCT type and conditioning regimen (Table S1). Filgrastim, at 5-10 mg/kg/day, was administered intravenously from day+1 until the absolute neutrophil count exceeded 1,000/cumm. Veno-occlusive disease/sinusoidal obstructive syndrome prophylaxis used ursodeoxycholic acid at 20 mg/kg/day, divided into two doses, starting with the conditioning regimen and continuing for 14-30 days.

Antifungal prophylaxis used itraconazole at 5 mg/kg/day twice daily from day+1 to day+100. Patients with a prior fungal infection before HSCT received management based on the specific infection. Acyclovir, dosed at 250 mg/m^2/dose intravenously every 8-12 hours, was used in herpes simplex virus seropositive patients from day+1 until engraftment. For Pneumocystis jirovecii pneumonia prophylaxis, sulfamethoxazole/trimethoprim was administered at 5 mg/kg/day of trimethoprim three times per week after engraftment.

Busulfan TDM

Blood samples were collected for at least 2 days, using sodium heparin tubes, during once-daily intravenous busulfan administration to analyze pharmacokinetics and calculate the AUC. The plasma concentration of busulfan was mainly determined using gas chromatography-mass spectrometry[11], but liquid chromatography-mass spectrometry was also utilized. Both methods underwent internal validation by the Siriraj Poison Control Center, focusing on selectivity, accuracy, precision, stability, and linearity across a calibration range of 50-12,000 ng/ml ($r^2 > 0.995$).

On the first day, blood samples were collected at six time points[1]: immediately after finishing the busulfan administration, and then at 15 minutes, 1 hour, 2 hours, 3 hours, and 5 hours post-administration. The AUC of busulfan was calculated using the trapezoidal method. If the AUC_{0-24} did not fall within the recommended range (3,600-6,000 μMolar·min), or as determined by the physician, dose adjustments were made using equation (a) shown below. On the subsequent day, samples were collected before starting the infusion, immediately after completing the administration, and at 15 minutes, 1 hour, 3 hours, and 5 hours afterward. Daily blood sample collection continued until the target AUC was achieved.

$$\text{Personalized dose} = \frac{(\text{Administered dose} \times \text{target AUC})}{AUC_{0-24}} \quad \text{(a)}$$

Toxicity, mortality and disease relapse

Busulfan-related side effects and treatment-related mortality were monitored for 100 days post-transplantation. Hepatic veno-occlusive disease/sinusoidal obstructive syndrome was diagnosed according to the Baltimore criteria, which include hyperbilirubinemia ≥2 mg/dL

combined with at least two of the following findings: hepatomegaly, ascites, or ≥5% weight gain. All toxicities were graded using the Common Terminology Criteria for Adverse Events version 5.0. Disease relapse was defined as the re-emergence of the primary disease for which the transplantation was indicated. The specific criteria for relapse were determined by the characteristics of the individual disease.

Statistical analyses

Statistical analyses were performed using Python version 3.11 with the lifelines library for survival analysis and Stata version 17 SE for other statistical computations. Descriptive statistics summarize patient demographics, clinical characteristics, busulfan pharmacokinetics, and treatment outcomes. The normality of continuous variables was assessed using the Shapiro-Wilk test, with results expressed as means with standard deviations or medians with ranges. Categorical variables are presented as frequencies and percentages.

Patients were grouped based on their average busulfan AUC into three categories: below target range (< 3,600 μMolar·min), within target range (3,600-6,000 μMolar·min), and above target range (> 6,000 μMolar·min). Survival analysis was conducted to evaluate the time to disease relapse among these AUC groups. Kaplan-Meier survival curves were created, and differences between survival distributions were assessed using the log-rank test.

The study analyzed the relationships between HSCT type, EMA dosing groups, and age (< 10 vs ≥ 10 years) with busulfan in-range versus out-of-range of a first day AUC (AUC1) and mean AUC after adjusted levels using Fisher's exact test. The association between type of disease (cancer/ non-cancer) and AUC1 range was analyzed using the Chi-square test, while the association between type of disease and mean AUC was analyzed using Fisher's exact test. All statistical tests were two-sided, with a *P* value of less than 0.05 indicating statistical significance.

RESULTS

Twenty-six children, aged between 2 and 15 years (median age 8.5 years), were included in the study. Detailed patient characteristics are presented in Table 1.

AUC of busulfan and dosage adjustments

The average AUC of busulfan per patient varied from 2,566.2 to 6,943.05 μMolar·min, compared to a AUC1 range of 2,709.24 to 11,618.6 μMolar·min (Fig 1). The pharmacokinetics of busulfan were observed in

TABLE 1. Patient demographics and clinical characteristics.

Characteristics	N (%)
Sex	
Female	7 (26.9)
Male	19 (73.1)
Indication	
Malignant	15 (57.7)
ALL	7
APL	1
MDS	1
AML	4
CML	1
JMMoL	1
Nonmalignant	11 (42.3)
Thalassemia	9
Age < 10 years	6
Age ≥ 10 years	3
Severe congenital neutropenia	1
Wiskott–Aldrich syndrome	1
Stem cell source	
Bone marrow	8 (30.8)
PBSC	18 (69.2)
Donor source	
Autologous	1 (3.8)
Allogeneic	
MRD	11 (42.3)
MUD	6 (23.1)
Haploidentical	8 (30.8)
Duration of busulfan	
3 days	9 (34.6)
4 days	17 (65.4)

Abbreviations: ALL, acute lymphoid leukemia; AML, acute myeloid leukemia; APL, acute promyelocytic leukemia; CML, chronic myeloid leukemia; JMMoL, Juvenile myelomonocytic leukemia; MDS, Myelodysplastic syndrome; MRD, match related donor; MUD, match unrelated donor; PBSC, peripheral blood stem cells

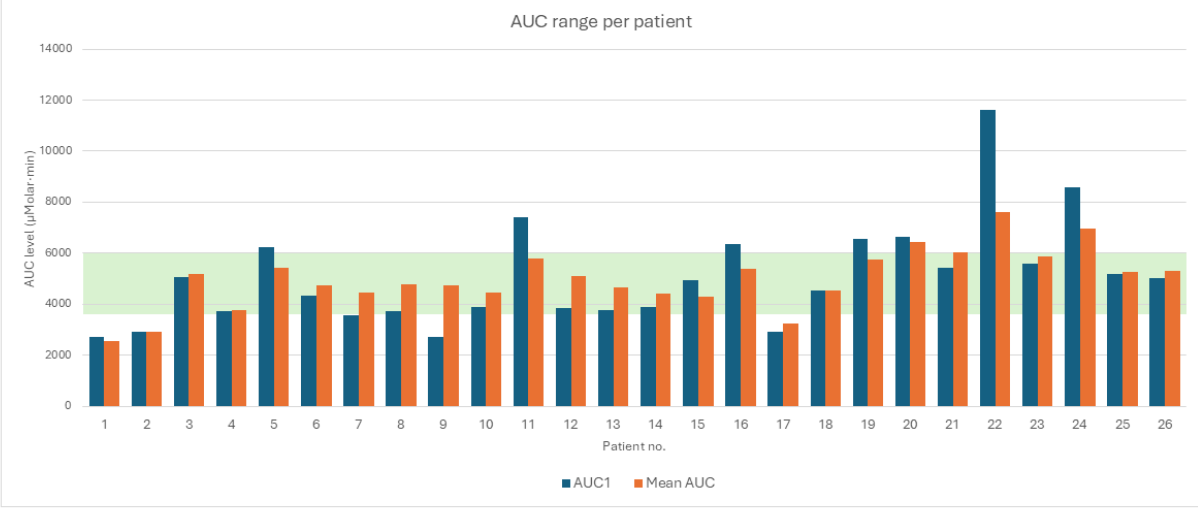

Fig 1. Distribution of area under the time curve ranges for first AUC (AUC1) and total mean AUC per patient (n = 26). The recommended target AUC (3,600–6,000 μMolar·min) is highlighted in green.

dose 1 (N=26), dose 2 (N=24) and dose 3 (N=9). The median of clearance was 0.2 (0.08-0.43), 0.19 (0.07-0.31) and 0.2 (0.1-0.4) L/hr/kg. The median half-life of busulfan was 2.28 (1.42-4.51), 2.19 (0.42-5.97) and 2.69 (1.9-3.59) hours respectively. AUC1 was within the recommended range for 14 patients (53.84%). However, in the case of two patients who had AUC1 values in the lower normal range, the physician decided to adjust the busulfan dose the next day. Busulfan TDM was initially conducted over a 2-day period, with blood samples collected on day 1 and day 3 for two patients, and on day 1 and day 2 for the remainder. Dosage adjustments were made in 17 patients (65.38%). Among these, eight patients required a single dose adjustment; five required two adjustments; and another four needed three adjustments. For three patients, the target AUC was not achieved even after three dose adjustments. Of the 14 patients receiving dose adjustments after AUC1, half required an increase in dosage (12%-44% change), while the other half required a decrease (17.81%-55.56%). Three patients with AUC1 within the target range had their doses decreased one time after the second AUC to reach the target AUC (11.11%-16.67% change).

Clinical outcomes and toxicity

Three patients experienced confirmed disease relapse. Two of these had mean AUC values below the target range (2,566.2 and 3,226 μMolar·min), while one had an in-range mean AUC (3,746.99 μMolar·min). One patient with a below-target mean AUC (2,897.38 μMolar·min) maintained complete remission 3.4 years post-HSCT. A lower average AUC than the target range was significantly correlated with earlier time to disease relapse compared to those non-lower target range of average AUCs, although the statistical analysis was underpowered ($P < 0.005$; Fig 2).

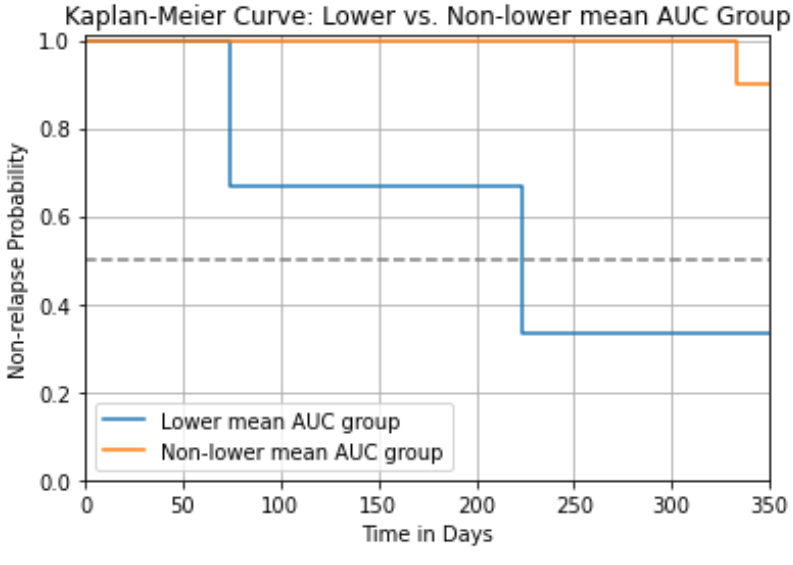

Fig 2. Kaplan–Meier curve of time to relapse in patients with lower-range and non-lower range mean area under the time curve.

In contrast, a higher average AUC did not correlate with an increase in busulfan-related side effects ($P = 0.598$) or treatment-related mortality ($P = 1$) when compared to non-high average AUC. No patient in higher average AUC group died, while four patients with an in-range average AUC died from infection post-transplantation. Busulfan toxicity was mainly associated with veno-occlusive disease/sinusoidal obstructive syndrome and mucositis. Three patients (11.5%) developed veno-occlusive disease/sinusoidal obstructive syndrome of grades 1 to 3, with onset typically observed between Day +13 and Day +21 post-transplant. Their mean AUCs were consistently in the lower or in-target range, and no patient with a mean AUC in the higher or above-target range experienced this adverse effect. Mucositis occurred in 13 patients (50%), with onset typically observed between Day +3 and Day +10 post-transplant. Of these, 12 patients had lower or in-target mean AUCs, while one patient with a higher mean AUC experienced grade 3 mucositis.

Relationship between AUC and treatment variables

There were no significant differences in AUC1 or mean AUC when stratifying by disease type (malignant vs nonmalignant), HSCT type (autologous, human leukocyte antigen-matched related and unrelated donor, and haploidentical), or EMA dosing group (Table 2). No statistical difference was seen in AUC1 between patients younger than 10 years and those aged 10 years or older ($P = 0.701$). However, an out-of-range target average AUC after dose adjustment was significantly more common in patients under 10 years of age (43.75%) compared to older patients, all of whom were within the target AUC range ($P = 0.023$; Fig 3).

TABLE 2. Relationship between AUC and treatment variables.

	AUC1			Mean AUC		
	In-range (n)	Out-range (n)	*P* value	In-range (n)	Out-range (n)	*P* value
Type of disease			0.126			1
Malignant	10	5		11	4	
Nonmalignant	4	7		8	3	
Type of HSCT			0.310			0.895
Autologous	1	0		1	0	
Allogeneic						
MRD	4	7		8	3	
MUD	3	3		5	1	
Haploidentical	6	2		5	3	
Busulfan OD dose			0.185			0.365
4 mg/kg	0	0		0	0	
4.8 mg/kg	2	2		3	1	
4.4 mg/kg	6	1		6	1	
3.8 mg/kg	1	4		2	3	
3.2 mg/kg	5	5		8	2	
Age			0.701			0.023*
<10 years	8	8		9	7	
≥10 years	6	4		10	0	

*; *P* value was statistical significant

Abbreviations: AUC, area under the time curve; AUC1, first day of area under the time curve; HSCT, Hematopoietic stem cell transplantation; MRD, match related donor; MUD, match unrelated donor; OD, once daily

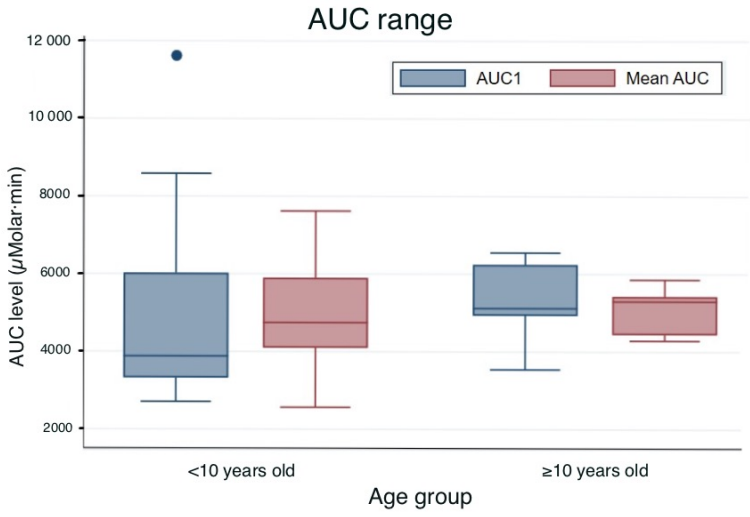

Fig 3. Comparison of area under the time curve (AUC) ranges across patient age groups.

DISCUSSION

Our protocol for busulfan initial dosing and TDM in this study followed the American Society for Blood and Marrow Transplantation guidelines.[1] However, alternative dosing recommendations exist, particularly those from the EMA and the US Food and Drug Administration. The recommended initial dosing of busulfan for every 6-hour administration of EMA guidelines dosing is determined by actual body weight: patients weighing ≤ 9 kg are recommended 1 mg/kg; those between 9 and < 16 kg receive 1.2 mg/kg; individuals from 16 to < 23 kg are prescribed 1.1 mg/kg; patients from 23 to 34 kg are given 0.95 mg/kg; and those weighing ≥ 34 kg are administered 0.8 mg/kg. The acceptable AUC range for EMA guidelines is 900–1,500 μMolar·min. Conversely, the US Food and Drug Administration guidelines base dosing on the lower value between actual and ideal body weight: patients weighing less than 12 kg are recommended 1.1 mg/kg, while those 12 kg or more receive 0.8 mg/kg with acceptable AUC range between 900–1,350 ± 5% μMolar·min. These guidelines use population pharmacokinetics modeling to target an AUC of 1125 μMolar·min for busulfan administered every 6 hours. The EMA method is particularly favored by the American Society for Blood and Marrow Transplantation and achieved target AUCs of approximately 70% in several studies.[1,5] In Thailand, previous research using the EMA dosing model for every-6-hour busulfan administration reported that only 42.86% of patients reached the target AUC.[7] In comparison, our study achieved a target AUC of 53.84% in the initial AUC (AUC1) before any dose adjustments. While some localized research exists, there is a recognized absence of nationally validated guidelines or broad, generalizable evidence in Thailand regarding busulfan dosing strategies specifically tailored for pediatric patients. Consequently, current practices are often limited to institutional protocols rather than comprehensive, evidence-based recommendations applicable across all transplant centers.

The EMA dosing method typically uses actual body weight for dosage calculations. However, in one case within our study, the physician decided to use adjusted body weight[12,13] due to the patient's high body mass index of 30.9 kg/m^2 and a total body weight/ideal body weight ratio of 1.45. For this particular patient, the initial AUC1 was within the target AUC range (5,197.14 μMolar·min), eliminating the need for dose adjustments. Existing literature on busulfan dosing for overweight patients, particularly children, is limited. As this study's only patient with a body mass index categorized as overweight, no direct comparisons could be made with other patients. This single case underscores the importance of further research into dosing strategies for pediatric patients with elevated body mass index to optimize treatment outcomes and ensure safe pharmacokinetic profiles.

There are no definitive recommendations for the number or specific time points for collecting busulfan blood samples. While the European Society for Blood and Marrow Transplantation recently suggested a sampling protocol of four time points[14], various studies incorporate 5-7 samples per AUC calculation, although at different time points.[15-18] Our institution follows the American Society for Blood and Marrow Transplantation guideline[1], collecting six plasma concentrations at specified intervals. Initially, we scheduled blood sampling for days 1 and 3 of busulfan infusion due to time constraints in reporting levels. The busulfan levels from day 1 and the AUC1 were calculated after the day-2 infusion, allowing for dose adjustments on day 3 if necessary. For two patients, the day-3 AUC remained below target, and further dose adjustments were not feasible by day 4. One of these patients experienced disease relapse and died 1 year

after transplantation. This prompted us to reschedule busulfan infusions to the afternoon, facilitating timely dose adjustments before the next infusion day. Consequently, blood collection primarily occurred on days 1 and 2, with the option to extend if required.

The study's limitations include a small sample size and a lack of all daily plasma busulfan concentration monitoring throughout the infusion course. Many studies advocate maintaining the total AUC for the entire 4-day busulfan infusion as the target.[1,14] We collected and analyzed busulfan AUC for at least 2 days, assuming pharmacokinetic consistency when the AUC was within the target range.

While busulfan-related toxicities are a critical focus, including severe veno-occlusive disease or sinusoidal obstructive syndrome and mucositis, other complications from methotrexate, used for GVHD prophylaxis, notably include severe methotrexate-induced mucositis —a consistent finding in our patient cohort often leading to drug discontinuation by day +11—and lymphoproliferative disorders[19] frequently necessitate intensive care interventions for pediatric patients, a population characterized by chronic conditions and elevated mortality risks.[20]

Busulfan metabolism involves hepatic glutathione conjugation mediated by glutathione S-transferase (GST) enzymes. The GSTA1 subfamily, a key area of research, explores the impact of polymorphisms on metabolism[1,4,21], including a study in Thailand.[22] Certain GSTA1 alleles correspond to fast or slow metabolizers, affecting busulfan clearance and requiring careful consideration.[21] Nonetheless, genetic polymorphism testing is not currently recommended for routine clinical integration in busulfan dose personalization.[1]

The European Society for Blood and Marrow Transplantation guidelines advise caution with dose adjustments exceeding 25%, recommending repeated TDM on the adjustment day.[14] Our study observed dose changes of 12%-55%, tailored to achieve a narrower target AUC of 4,500-5,000 µMolar·min to avoid over- or underexposure. However, some studies suggest the optimal AUC in a myeloablative setting should range between 1,225-1,575 µMolar·min (equivalent to 4,900-6,300 µMolar·min for once-daily dosing), correlating with superior outcomes compared to previous recommendations for children.[23]

CONCLUSION

Our study supports TDM as an effective strategy to enhance the efficacy of once-daily intravenous busulfan in HSCT among Thai pediatric patients. Dose adjustments for out-of-range AUCs may help reduce the frequency of subtherapeutic exposures, thereby mitigating early relapse risks.

Data Availability Statement

The data supporting the findings of this study are not publicly available due to ethical restrictions related to privacy and confidentiality.

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Conflict of Interest

The authors declare no conflicts of interest related to this article.

Registration Number of Clinical Trial

None.

Author Contributions

Conceptualization and methodology, CD.R., U.M., CT.R. and K.S.; Investigation, CD.R.; Formal analysis, CT.R.; Visualization and writing – original draft, CD.R.; Writing – review and editing, CD.R., U.M., K.S.; Supervision, K.S. All authors have read and agreed to the final version of the manuscript.

Use of Artificial Intelligence

None.

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Association of Perineural Invasion of Adenocarcinoma in Prostate Biopsy with Pathological and Clinical Outcomes

Perineural invasion of adenocarcinoma in prostate biopsy

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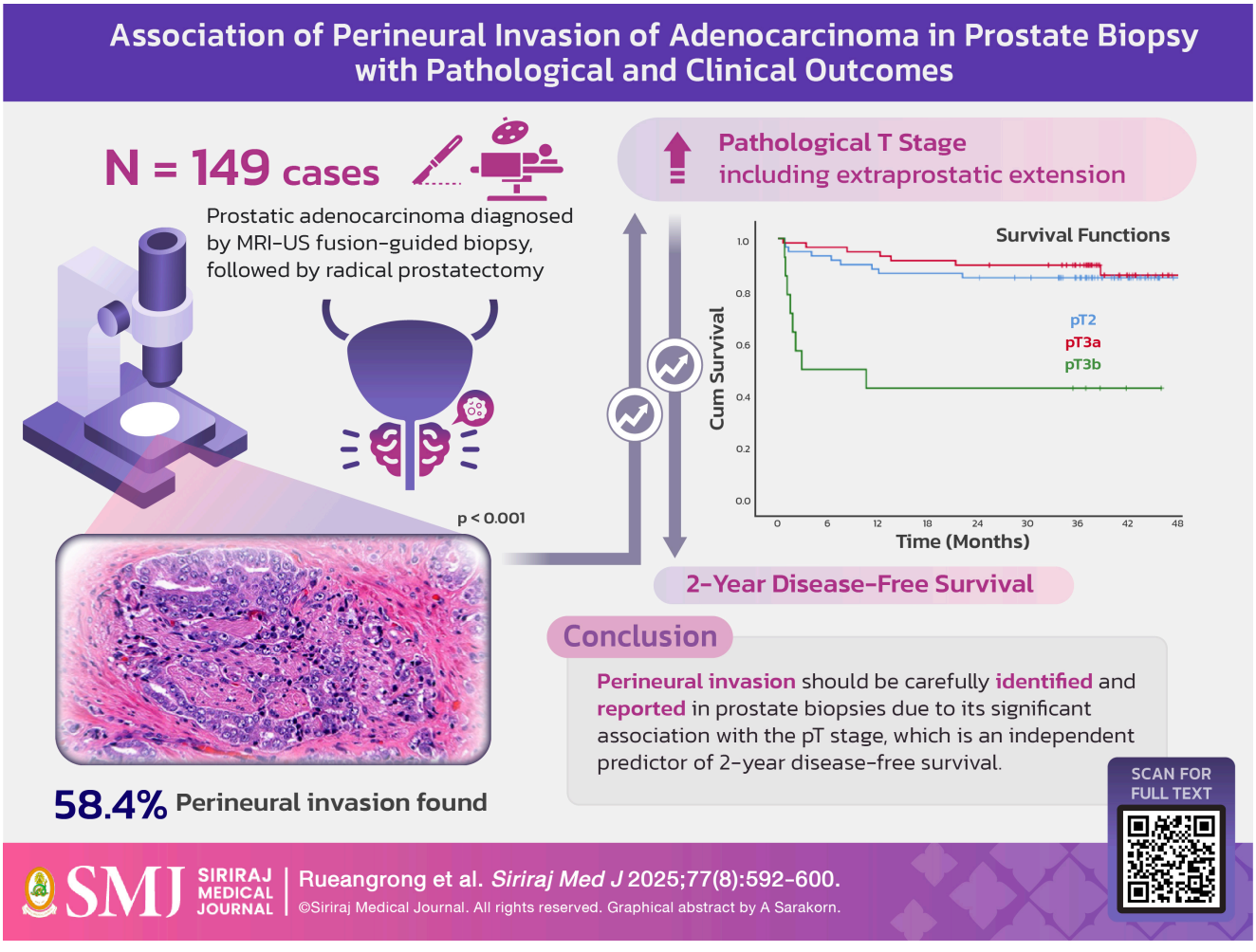

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ABSTRACT

Objective: This study aims to evaluate the association between perineural invasion and pathological stage, including extraprostatic extension, and its impact on prognosis.

Materials and Methods: A total of 149 men diagnosed with prostatic adenocarcinoma by magnetic resonance imaging/ultrasound (MRI-US) fusion-guided biopsy and radical prostatectomy between July 1, 2018 and December 31, 2019 at Siriraj Hospital were identified. Their pathological, clinical, and radiological findings were retrospectively analyzed. Patients with and without perineural invasion were compared using descriptive and inferential statistics.

Results: Perineural invasion was identified in 87 of 149 patients (58.4%) and showed no significant association with baseline features ($p > 0.05$). However, perineural invasion was significantly associated with higher pathological T stage (pT2, pT3a, pT3b) ($p < 0.001$), including extraprostatic extension (pT3 disease) in univariate analysis. Multivariate analysis demonstrated a notable correlation between the pathological T stage and 2-year disease-free survival ($p < 0.001$).

Conclusion: Perineural invasion should be carefully identified and reported in prostate biopsy specimens, due to its significant relationship with the pathological T stage, including extraprostatic extension.

Keywords: Prostate cancer; prostatic adenocarcinoma; image-guided biopsy; perineural invasion; pathological stage (Siriraj Med J 2025; 77: 592-600)

INTRODUCTION

In 2020, prostate cancer was the second most diagnosed cancer and the fifth leading cause of cancer-related deaths among men worldwide.[1] Prostatic adenocarcinoma accounts for over 95% of all prostate cancer cases.[2] Prostate needle biopsy is the gold standard for diagnosing prostatic adenocarcinoma.[3]

Perineural invasion (PNI), observed in up to 38% of prostate biopsies[4], is considered one of the pathognomonic features of prostate cancer.[2] It has been hypothesized that carcinoma cells spreads along nerve bundles in the dorsolateral aspect of the prostate gland, following a path of least resistance — an observation consistent with the known tropism of carcinoma cells for nerves.[5-10]

Several studies employing various research designs have demonstrated associations between perineural invasion (PNI) and adverse pathological features, disease progression, and recurrence in multivariate analyses.[9,11-16] Two cross-sectional studies similar to ours reported an association between PNI and extraprostatic extension.[13,14] A randomized controlled trial focusing on patients undergoing active surveillance also confirmed the association between PNI and clinical progression.[15] However, two other cross-sectional studies found no relationship between PNI and extraprostatic extension, pathological stage, or positive surgical margins.[4,17] Similarly, a case-control study evaluating long-term disease-free survival in patients who underwent radical prostatectomy found no significant association between PNI and biochemical disease-free survival.[8] Although these studies focus on the relationship between PNI in prostate biopsies and pathological or clinical outcomes, they differ in several aspects, such as research design, sample size, institutional setting, inclusion criteria, treatment modalities, study periods, and biopsy techniques, which may affect interpretation and contribute to variability in the results.

Harnden et al.[12] conducted the first systematic evaluation of PNI's prognostic value in biopsies, analyzing 10 surgical and 11 radiotherapy articles. Their findings support PNI as a prognostic factor for recurrence. However, the authors also highlighted inconsistencies in reporting and incomplete data, which affected the analysis of both positive and negative results. Factors such as biopsy technique, number of cores and sections influence the involvement of nerve detection but are rarely documented. Additionally, the lack of standardized reporting, limited reproducibility, and variability in treatment approaches and patient classification further complicate interpretation.

Two recent systematic reviews also identified perineural invasion (PNI) as an independent prognostic factor for biochemical recurrence, while acknowledging many of the same limitations. One review noted that variability in PNI detection methods may contribute to significant heterogeneity, potentially affecting the validity of study results.[18] Another reported a wide range in PNI frequency, from 6.7% to 33.0%, attributing this variability to differences in reproducibility among pathologists. The paper also highlighted that different biopsy techniques, such as conventional transrectal ultrasound (TRUS) guided and MRI-ultrasound fusion-guided methods, can influence PNI detection rates.[19]

These uncertainties have fueled decades of debate regarding the prognostic value of PNI in prostate biopsy. Thus, the objective of our study was to analyze the prognostic value of PNI, as a predictor of TNM classification and 2-year disease-free survival, using well-defined variables and comprehensive data. Ultimately, our goal is to increase awareness of PNI and aid physicians in disease evaluation and treatment planning.

MATERIALS AND METHODS

Patient selection

Following approval by the Siriraj Institutional Review Board (Certificate of Approval No. Si 228/2022), pathological and clinical data of patients diagnosed with prostatic adenocarcinoma were retrieved from the electronic database of the Siriraj Pathology Unit's electronic database (HCLAB). The inclusion criteria were: (1) patients diagnosed with prostatic adenocarcinoma by means of both core biopsy and radical prostatectomy performed at Siriraj Hospital between July 1, 2018, and December 31, 2019; (2) biopsies were conducted using magnetic resonance imaging/ultrasound (MRI-US) as fusion-guided techniques; (3) availability of pathology reports, glass slides, and complete medical records for review.

Data collection

All biopsy and radical prostatectomy specimens were submitted for evaluation after routine 10% formalin fixation, paraffin embedding, sectioning at a thickness of 3–5 micrometers, and hematoxylin and eosin staining. Specimens were blinded by masking patient identifiers and diagnostic details, and were reviewed by a genitourinary pathologist and an anatomic pathology resident utilizing light microscopy, following the College of American Pathologists' guidelines. PNI was defined as the presence of cancer cells abutting, indenting nerves, up to and including circumferential involvement[12], and was recorded as either present or absent.

Clinical data were collected and reviewed by a urologist and a research fellow, while radiologic data were collected and reviewed by a radiation oncologist. None of them were informed of the presence or absence of PNI in each patient. Biochemical recurrence was defined as a prostate-specific antigen (PSA) level greater than 0.2 ng/mL after radical prostatectomy.

Sample size calculations

nQuery Advisor was applied to determine the required sample size needed to detect differences with 80% power (2-sided type 1 error; $\alpha = 0.05$). Assuming a 1:1.5 enrollment ratio for patients undergoing MRI-US fusion-guided biopsy with and without PNI, and based on a previous study[14], reporting rates of extraprostatic extension of 66.7% in a group of patients with PNI and 39.7% in a group without PNI, the required sample size was calculated as 145 cases. Thus, with 149 subjects included, this study was adequately powered to detect significant differences.

Statistical analysis

All statistical analyses were performed using IBM SPSS Statistics, Version 26. Two-tailed tests were employed, and a p-value of <0.05 was considered statistically significant. Descriptive statistics were used to summarize characteristics of men with and without PNI in prostate biopsies.

For univariate analysis, continuous variables were compared using the Mann-Whitney U test and independent t-test. Categorical variables were evaluated using the chi-squared test. Kaplan-Meier survival curves were used to illustrate 2-year disease-free survival rates in patients stratified by pathological T stage, with comparisons made using the log-rank test.

In multivariable analysis, associations between 2-year disease-free survival and both pathological T stage and initial PSA levels were examined using Cox proportional hazards regression models. Results were summarized as hazard ratios with corresponding 95% confidence intervals.

RESULTS

Of the 149 patients who met the inclusion criteria, PNI was identified in 87 biopsy specimens (58.4%). Patients with and without PNI had similar mean ages at diagnosis. Initial PSA levels were similar between the groups. The number of core biopsies performed did not differ significantly between the two groups. PNI in the prostatectomy specimen was more frequent in the group with PNI in their biopsy (98%) compared to the group without PNI in their biopsy (74%) ($p < 0.001$) (Table 1).

PNI was significantly associated with higher pathological T stage (pT2, pT3a, pT3b), including extraprostatic extension (pT3 disease) ($p < 0.001$). (Table 2).

Furthermore, significant associations were observed between 2-year disease-free survival and pathological T stage in both univariate (Table 3) and multivariate analyses, with the strongest association seen in patients with pT3b (adjusted HR, 6.84; 95% CI, 2.43–19.27; $p < 0.001$) (Table 4).

Kaplan-Meier analysis further confirmed that more advanced pathological T stage was associated with poorer disease-free survival, especially in patients with pT3b tumors (log-rank $p < 0.001$) (Table 5, Fig 1).

TABLE 1. Characteristics of patients with and without PNI.

Variable	PNI in biopsy		p-value
	No (n=62)	Yes (n=87)	
Age (year)[a]	67.7 ± 6.5	67.7 ± 6.6	0.994
iPSA (ng/mL)[b]	8.3 (5.4, 11.4)	8.9 (6.8, 15.0)	0.176
Number of core biopsy[b]	25.0 (21.0, 29.3)	24.0 (20.0, 30.0)	0.633
PNI in prostatectomy[c]	46 (74.2%)	85 (97.7%)	**< 0.001**

[a] Normally distributed data are presented as mean ± standard deviation. Comparisons between groups were analyzed using the independent t-test.
[b] Non-normally distributed data are presented as median (interquartile range). Comparisons between groups were analyzed using the Mann-Whitney U test.
[c] Data are presented as n (%). Comparisons between groups were analyzed using chi-square tests.
Abbreviations: PNI, perineural invasion; SD, standard deviation; iPSA, initial prostate-specific antigen; ng/mL, nanograms per milliliter

TABLE 2. Association between PNI and pathological and clinical outcomes.

Variable	PNI in biopsy		OR (95% CI)	p-value
	No (n=62)	Yes (n=87)		
EPE	19 (23.2%)	63 (76.8%)	**5.94 (2.90; 12.20)**	**< 0.001**
Pathological T stage				**< 0.001**
pT2	43 (63.2%)	25 (36.8%)		
pT3a	18 (27.7%)	47 (72.3%)	**4.49 (2.16; 9.35)**	
pT3b	1 (6.3%)	15 (93.8%)	**25.80 (3.21; 207.22)**	
Pathological N stage				0.240
pN0	61 (43.0%)	81 (57.0%)		
pN1	1 (14.3%)	6 (85.7%)	4.52 (0.53; 38.52)	
Clinical M stage				1.000
cM0	62 (41.9%)	86 (58.1%)		
cM1	0 (0.0%)	1 (100.0%)	N/A	
2-year disease-free survival				0.697
No	46 (41.8%)	64 (58.2%)		
Yes	9 (37.5%)	15 (62.5%)	0.84 (0.34; 2.07)	

All data are presented as n (%). Comparisons between groups were analyzed using Chi-square tests.
Abbreviations: PNI, perineural invasion; OR, odds ratio; CI, confidence interval; EPE, extraprostatic extension; pT, pathological primary tumor; pN, pathological node; cM, clinical metastasis.

TABLE 3. Association between 2-year disease-free survival and patient characteristics and pathological outcomes.

Factors associated with DFS	2-year disease-free survival		p-value
	DSF (n=110)	Non-DSF (n=24)	
Pathological T stage[a]			**< 0.001**
pT2	51 (85.0%)	9 (15.0%)	
pT3a	53 (88.3%)	7 (11.7%)	
pT3b	6 (42.9%)	8 (57.1%)	
iPSA (ng/mL)[b]	8.3 (6.2, 11.4)	12.8 (7.3, 22.7)	**0.013**
Age (year)[c]	67.8 ± 6.7	68.4 ± 5.7	0.702

[a] Data are presented as n (%). Comparisons between groups were analyzed using chi-square tests.
[b] Non-normally distributed data are presented as median (interquartile range). Comparisons between groups were analyzed using the Mann-Whitney U test.
[c] Normally distributed data are presented as mean ± standard deviation. Comparisons between groups were analyzed using the independent t-test.
Abbreviations: DFS, disease-free survival; pT, pathological primary tumor; iPSA, initial prostate-specific antigen; ng/mL, nanograms per milliliter; SD, standard deviation

TABLE 4. Multivariate Cox regression analysis of the relationship between 2-year disease-free survival and patient characteristics and pathological outcomes.

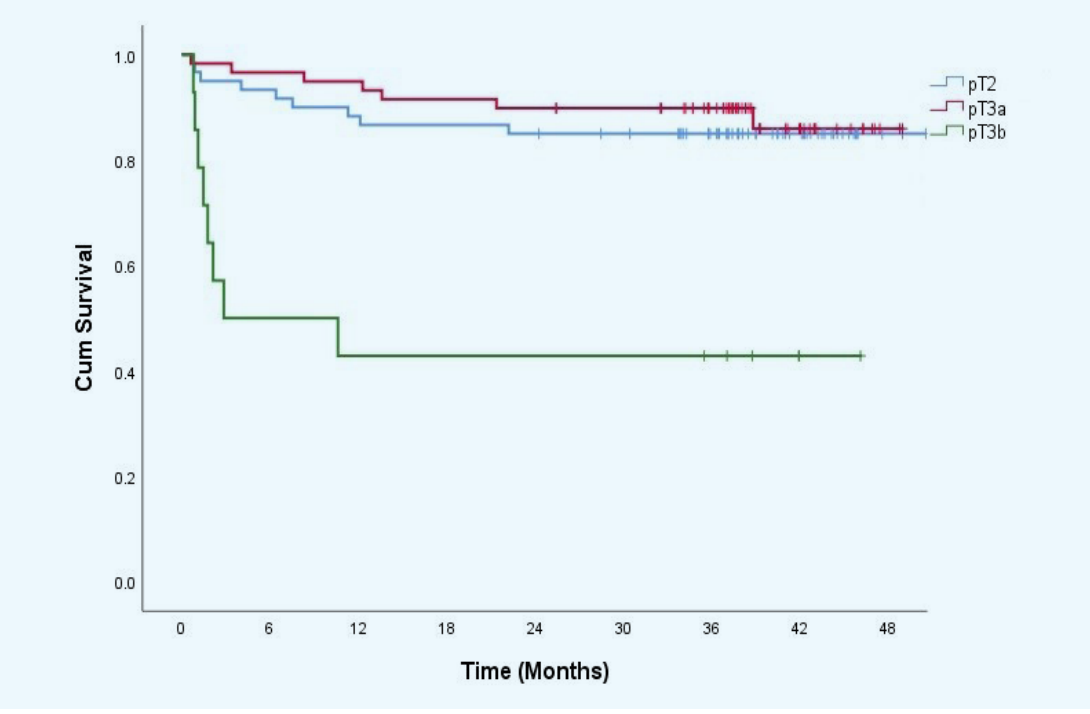
Factors associated with DFS	Multivariate	
	Adjusted HR (95%CI)	p-value
Pathological T stage		
pT2	1	
pT3a	0.78 (0.29-2.10)	0.627
pT3b	6.84 (2.43-19.27)	**< 0.001**
iPSA	0.99 (0.97-1.01)	0.525

Abbreviations: DFS, disease-free survival; HR, hazard ratio; CI, confidence interval; pT, pathological primary tumor; iPSA, initial prostate-specific antigen

TABLE 5. Association between pathological T stage and disease-free survival.

DFS (%)	Time			
	1 year	2 year	3 year	4 year
pT2	88.3	85.0	85.0	85.0
pT3a	94.9	89.8	89.8	85.9
pT3b	42.9	42.9	42.9	42.9

All data are presented as percentage (%).
Abbreviations: DFS, disease-free survival; pT, pathological primary tumor



	0 month	6 months	12 months	18 months	24 months	30 months	36 months	42 months	48 months
pT2	60	56	53	52	51	49	40	20	2
pT3a	59	57	56	54	53	51	41	16	2
pT3b	14	7	6	6	6	6	5	1	0

Fig 1. Kaplan-Meier analysis illustrating the relationship between pathological T stage (pT2, pT3a, pT3b) and disease-free survival. The study revealed a significant association, with more advanced pathological T stage linked to poorer disease-free survival outcomes ($p < 0.001$).
Abbreviation: pT, pathological primary tumor

DISCUSSION

PNI, a neoplastic process involving nerves[20], is a common yet clinically significant feature of prostatic adenocarcinoma.[7] Although substantial evidence supports PNI as a potential route for carcinoma spread[5–10], its prognostic value in prostate biopsies remains controversial due to conflicting pathological and clinical associations.[4,8-9,11-17,21]

Our study demonstrates a strong association between PNI in biopsy specimens and advanced pathological T stage, including extraprostatic extension. A systematic review indicates that patients at high risk of extraprostatic extension should avoid nerve-sparing surgery, which is associated with the preservation of erectile function and continence.[22] Given that the pathological T stage is a well-established independent predictor of survival in prostate cancer, as supported by previous research and our own findings[2,23-24], these findings underscore the clinical importance of recognizing PNI in patient management.

However, no significant association was observed between PNI and lymph node metastasis (N stage) or distant metastasis (M stage). Consistent with prior reports, including those by *O'Malley et al.*[8] and *Ahmad et al.*[25], our findings do not support PNI as a predictor of 2-year disease-free survival. A possible explanation is the relatively favorable prognosis of our cohort: all patients underwent radical prostatectomy, a treatment typically reserved for localized disease[26], and only a small proportion presented with lymph node metastases (N1 stage) or distant metastases (M1 stage).

A key strength of our study is the use of MRI-US fusion-guided biopsy, a technique that has been shown to enhance prostate cancer detection, improve tumor grading accuracy, and increase the detection of clinically significant prostate cancer and PNI.[14,27-31] In our study,

the detection rate of PNI was 58.4%, which is higher than previously reported rates, generally ranging from 7% to 43%[12], and 28.4% in a prior study that also employed MRI-US fusion-guided biopsy.[14] This elevated detection rate likely reflects the enhanced sampling precision of this technique. Although the number of biopsy cores can influence the sampled surface area and, consequently, the likelihood of detecting PNI, our statistical analysis found no significant difference in core numbers between PNI positive and negative cases, thereby reinforcing the validity of our results. These findings underscore the critical role of biopsy acquisition methods in evaluating PNI and highlight the need for standardized biopsy techniques in future studies to enhance data consistency.

Our study included only patients who underwent radical prostatectomy to obtain more comprehensive information on the relationship between PNI and pathological classification. By limiting the cohort to surgically treated patients, we were able to accurately determine the pathological stage, including the status of the primary tumor (pT) and lymph node metastasis (pN).[32]

Moreover, given that patients who remain free of biochemical relapse for two years after surgery have been reported to achieve a 90% recurrence-free survival rate,[33] our study incorporated a minimum two-year follow-up period to reduce the likelihood of false negative results. We also compared initial prostate-specific antigen levels, an established prognostic indicator in prostate cancer[34], between patients with and without PNI and found no significant difference between the groups. The sample size was determined through power calculation to ensure adequate statistical power.

Systematic reviews, such as that by *Harnden et al.*[12] have suggested that PNI in prostate biopsies is a significant prognostic indicator, supporting immediate treatment over watchful waiting. Similarly, *Cozzi et al.*[21], in line with our findings, support PNI as a predictor of extraprostatic extension. This has important clinical implications, which influence decisions regarding the preservation of the neurovascular bundle and seminal vesicles.[35] Therefore, these findings emphasize the importance of recognizing the prognostic value of PNI in patient management.

Although our findings confirm the association between PNI and adverse pathological outcomes, they also highlight the longstanding challenges in assessing its prognostic significance, which are issues that have persisted unresolved over three decades of research.[12] Given the heterogeneity in study designs, variations in biopsy techniques, and differences in patient selection, additional large-scale prospective studies are needed. These should incorporate diverse treatment strategies, detailed documentation of biopsy parameters, subgroup analyses, and extended follow-up periods to better define the role of PNI in guiding therapeutic decisions.

CONCLUSION

PNI in biopsy specimens is a predictor of advanced pathological T stage, including extraprostatic extension. As pathological T stage is an independent predictor of 2-year disease-free survival, the identification and documentation of PNI in prostate biopsy specimens are essential for accurate risk stratification and treatment planning.

Data Availability Statement

The data supporting the findings of this study are available from the corresponding author upon request due to confidentiality concerns.

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DECLARATIONS

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Conflict of Interest

The authors declare no conflicts of interest.

Registration Number of Clinical Trial

None.

Author Contributions

Conceptualization, N.T.; data curation, R.R.; Formal analysis, R.R; investigation, R.R., A.T., K.M. and N.T.; methodology, N.T.; project administration, N.T.; resources, C.S., A.T. and N.T.; supervision, N.T.; validation, C.S., A.T. and N.T.; visualization, R.R.; writing—original draft, R.R. and N.T.; writing—review & editing, R.R. and N.T. All authors have read and agreed to the final version of the manuscript.

Use of Artificial Intelligence

None.

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Factors Predicting Postoperative Quality of Life among Rectal Cancer Patients in Thailand: A Retrospective Cohort Study

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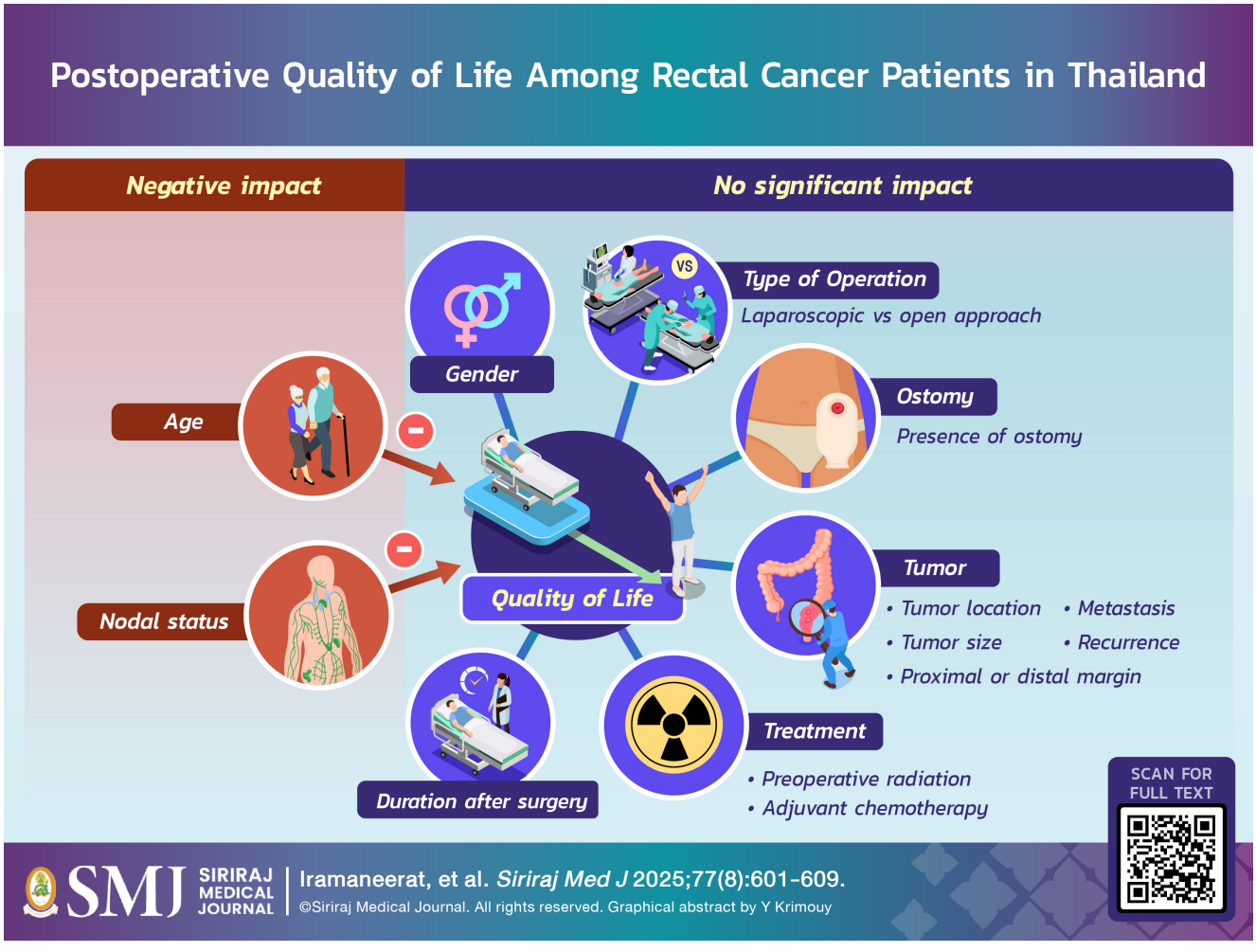

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ABSTRACT

Objective: The objectives of this study were to evaluate the postoperative quality of life (QoL) measures of Thai rectal cancer patients, and to determine which factors impact the QoL.

Materials and Methods: We reviewed the medical records of rectal cancer patients who underwent abdominoperineal resection or low anterior resection between 2009 and 2012. We sent out Functional Assessment of Cancer Therapy – Colorectal (FACT-C) questionnaires to patients who met the criteria. The T-test, Kendall's Tau-b, and Pearson correlation were used to select potentially significant predictors (p-value <0.1), which were then included in the multiple regression analysis to predict FACT-G (General QoL) and FACT-C (General QoL + concerns related to colorectal cancer) scores.

Results: We analyzed data from 144 patients (out of 480 patients who met the criteria). The average FACT-G and FACT-C scores were 87.34 and 106.79, respectively. The factor that had a significant negative impact on FACT-G was age (t = -2.67, p = 0.008). The factors that had a significant negative impact on FACT-C were nodal status (t = -1.98, p = 0.05) and age (t = -2.66, p = 0.009).

Conclusion: The postoperative QoL of Thai rectal cancer patients is similar to the QoL measures reported in a prior study. The QoL measures were found to be negatively impacted by age and lymph node status. Gender, the type of operation, presence of ostomy, location of the tumor, preoperative radiation, adjuvant chemotherapy, laparoscopic approach, duration after surgery, proximal and distal margins, tumor size, metastasis, and recurrence showed no impact on the QoL.

Keywords: Quality of life; rectal cancer; FACT-C, Multiple regression (Siriraj Med J 2025; 77: 601-609)

INTRODUCTION

Colorectal cancer is a significant public health problem in Thailand. Its incidence is high, being ranked the second and third most common cancer in males and females, respectively.[1] It is the only malignancy in Thailand showing an increased incidence in both genders in the past decade.[2] The treatment of rectal cancer is an important part of addressing this problem. One critical aspect of treating rectal cancer patients is considering their postoperative quality of life. Curing these patients often impacts their quality of life.[3] Rectal cancer patients can experience a wide range of sequelae after surgery such as fecal urgency, urinary incontinence, impotence, dyspareunia, anxiety, and depression. These sequelae can impact their quality of life (QoL).[3-5]

Many researchers have demonstrated that the quality of life of rectal cancer patients is influenced by many factors. Li et al. showed that the QoL could be impacted by age, gender, socioeconomic status, and the presence of stoma.[6] Some researchers have reported that low anterior resection patients have a better QoL than patients who underwent abdominoperineal resection (APR).[7] On the other hand, there are many studies that have shown that APR patients do not have a worse QoL than low anterior resection (LAR) patients.[8-10] Some researchers have suggested that the impact of the type of surgery on the QoL is inconclusive.[11] Many studies have shown that the QoL is influenced by the patient and tumor characteristics, the surgical technique, the use of preoperative radiation, and the method and level of anastomosis.[3,12] There are also some factors that have been shown to have no impact on QoL, such as gender, duration after surgery, the level of anastomosis[13], and the presence of permanent colostomy.[14] Clearly, determining the factors that impact the postoperative QoL in rectal cancer patients is quite difficult, and it is therefore not surprising that the data in the literature provide somewhat inconclusive findings. A patient's QoL could be changed significantly by several sociodemographic and clinical factors. However, there was a lack of evidence on which factors would impact QoL in Thai rectal cancer patients. A QoL study of Thai rectal cancer patients is needed to gain an insight into how to improve patients' QoL after surgery in the context of Thailand.

There are many quality of life measures that contain a module related to colorectal cancer patients. The most commonly used are: the European Organization for Research and Treatment of Cancer Quality of Life Questionnaires (EORTC) QLQ-C_{30} and QLQ-CR_{38}, and Functional Assessment of Cancer Therapy – Colorectal (FACT-C).[15] In this study, we employed FACT-C to assess quality of life because the instrument has already been validated and translated into the Thai language following the FACIT translation project procedure and guidelines.

The objectives of the present study were: (1) to evaluate the postoperative quality of life measures (FACT-C) of Thai rectal cancer patients, and (2) to determine which factors impact the quality of life.

MATERIALS AND METHODS

After obtaining ethical approval from The Institutional Review Board of our medical center (COA no. Si 230/2013), we retrospectively reviewed the medical records of patients aged 18–80 years old who were diagnosed with carcinoma of the rectum and who underwent APR (group 1) or LAR (group 2) between 2009 and 2012. The total number of eligible patients was 480. Power analysis prior to this study revealed that we needed 177 patients in order to reveal significant differences of FACT-C score of 10 points with power of 0.8 and Type I error rate of 0.05. We expected a 50% response rate from patients. We also considered the possibility of getting incomplete data from questionnaires. This led to our decision to send questionnaires to all 480 patients who met with the inclusion criteria. We excluded cases with non-adenocarcinoma. We assessed the patients' quality of life with a minimum postoperative time of 3 months to ensure the stability of the quality of life score. The retrieved data included age, gender, the type of operation, the presence of ostomy, location of the tumor from the anal verge (measured by colonoscopy), preoperative radiation, adjuvant chemotherapy, approach (laparoscopic or open surgery), duration after surgery, proximal and distal margins of the surgical specimen, pathological tumor size, TNM staging, and presence of recurrence.

We sent out Functional Assessment of Cancer Therapy – Colorectal (FACT-C) questionnaires to all cases that fit our inclusion criteria. If a patient had not returned the questionnaire within one month, they received a phone call to conduct the interview. If the questionnaire had missing data to the extent that QoL measures could not be calculated, the case would be excluded from the analysis. For missing data in other parameters, all data would be used for analysis without excluding any cases (pairwise missing value handling).

Quality of life measurements

The FACT-C questionnaire comprises five subscales: physical wellbeing (PWB, 7 items), social wellbeing (SWB, 7 items), emotional wellbeing (EWB, 6 items), functional wellbeing (FWB, 7 items), and colorectal cancer subscale (CCS, 9 items). The suggested quality of life indices are the Trial Outcome Index (TOI), FACT-general (FACT-G), and FACT-C. The Trial Outcome Index combines three subscales: PWB+FWB + CCS. FACT-G combines four subscales: PWB+SWB+EWB+FWB. FACT-C combines FACT-G with CCS.[16,17]

FACT-C has been demonstrated to give a valid and reliable measure of the quality of life of colorectal cancer patients. It has both concurrent and discriminant validity. FACT-C is sensitive to changes in the functional status. The subscale scores had Cronbach's Alpha scores in the range of 0.56–0.82. The Cronbach's Alpha scores of TOI, FACT-G, and FACT-C were 0.87, 0.84, and 0.87, respectively.[16,17]

Here, we report two measures for the quality of life: FACT-G (General quality of life: PWB+SWB+EWB+FWB) and FACT-C (Quality of life of colorectal cancer patients: PWB+SWB+EWB+FWB+CCS).

Statistical analysis

For dichotomous characteristics, we compared the quality of life measures between two groups of patients using the independent-samples t-test. For ordinal data, we conducted Kendall's tau-b correlation between the ordinal measures and quality of life measures. For interval measures, we conducted Pearson's correlation with the quality of life measures.

Based on the results of the univariate analysis, we selected independent variables that showed a statistically significant relationship ($p < 0.05$) and those that had a marginally significant relationship ($p < 0.10$) with the quality of life measures for inclusion in the multiple regression analysis. Basic assumptions for the regression analysis were checked, including the linearity, homoscedasticity, absence of multicollinearity, independent observations, and reliability of the measures. All the analyses were carried out with PASW Statistics 18.0.

RESULTS

Patient characteristics

Out of the 480 questionnaires sent out, we received back 70 completed forms (response rate 15%). We carried out phone interviews for 245 cases, with a response rate of 45% (109 patients). We excluded 34 patients from the analysis due to death and non-adenocarcinoma tumors. We excluded 1 patient from the analysis due to incomplete quality of life data in the returned questionnaire (Fig 1).

The patient characteristics are shown in Table 1. The mean age of the patients was 60.93 years old. There were 53% male participants. Most patients underwent low anterior resection (LAR, 71.5%). Abdominoperineal resection (APR) was performed in 28.5% of cases. Open surgery was the majority operative approach (83.3%). The average tumor location was 7.54 cm above the anal verge as determined by colonoscopy. The proximal

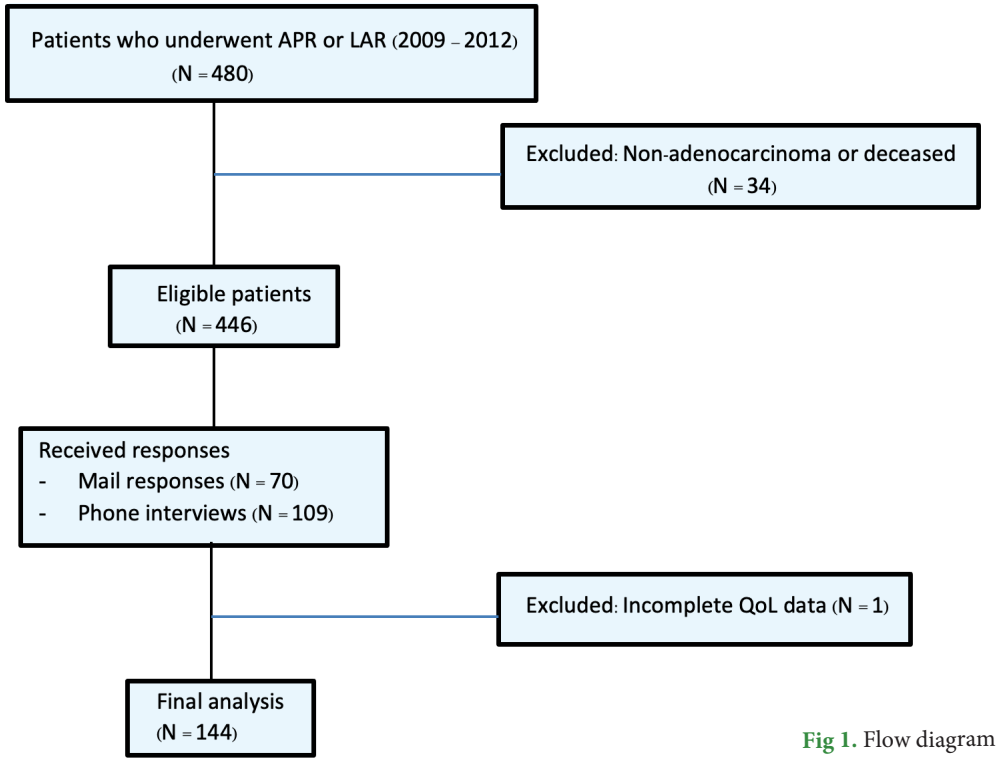

Fig 1. Flow diagram of the study.

TABLE 1. Characteristics of the study participants.

	N	Minimum	Maximum	Mean	SD
Age (years)	144	29	88	60.93	11.08
Distance from AV (cm)	133	2	15	7.54	3.41
Duration after surgery (months)	144	10	66	31.53	13.84
Proximal margin (cm)	144	0.50	61	10.39	6.82
Distal margin (cm)	144	0.10	10	2.25	1.71
Size of tumor (cm)	144	0.00	13.0	4.78	2.25

margin was 10.39 cm and the distal margin was 2.25 cm. The average size of tumor was 4.78 cm. The average duration after surgery was 31.5 months.

At the time of responding to the questionnaire, 51 patients (35.4%) had had ostomy. Most patients had no preoperative radiation (91%). Most patients (74.3%) were given adjuvant chemotherapy. There was local recurrence in 6.3% of cases and distant metastasis in 22.9%.

Quality of life measures

FACT-G and FACT-C scores are highly reliable measures. The FACT-G scores showed a Cronbach's Alpha of 0.93, based on 27 items. The FACT-C scores showed a Cronbach's Alpha of 0.94, based on 36 items.

The FACT-G scores ranged from 49 to 108, with an average of 87.34 and a standard deviation of 14.41. The FACT-C scores ranged from 59 to 136, with an average of 106.79 and a standard deviation of 17.78. Recently published data on Thai colorectal cancer surgical patients showed average postoperative FACT-C scores of 111.93.[18] Minimally important difference in FACT-C has been reported between 5 and 8.[19] This indicated that the QoL obtained from this study was slightly lower than the previous report, but not significant.

Univariate analyses

We carried out independent-samples t-tests to compare the quality of life between the two groups of patients, as shown in Table 2. The two parameters that revealed a significant difference between the groups were gender and surgical approach. Male patients have a better postoperative quality of life than female patients. Patients who underwent an open approach tended to have a better postoperative quality of life than those who underwent a laparoscopic approach.

Kendall's tau-b was used to examine the correlation between the T, N stages and quality of life (Table 3). The N stage showed a marginally significant negative correlation with both the FACT-G and FACT-C scores. A more advanced nodal status tended to be associated with a worse quality of life.

Table 4 shows the Pearson correlations between the interval measures and quality of life. Age was the only parameter that showed a significant correlation, whereby older people tended to have a worse postoperative quality of life (Fig 2).

TABLE 2. Comparisons of the quality of life between the patient groups.

		N	FACT-G	t	p	FACT-C	t	p
Gender	Male	76	89.40	1.83	0.07*	109.57	2.00	0.047**
	Female	68	85.03			103.69		
Operation	LAR	103	87.29	0.06	0.95	106.79	0.001	0.99
	APR	41	87.45			106.79		
Ostomy	Yes	51	86.73	0.37	0.71	106.01	0.39	0.70
	No	93	87.67			107.22		
Preop Radiation	Yes	13	86.62	0.19	0.85	105.46	0.28	0.78
	No	131	87.41			106.92		
Approach	Open	120	88.46	2.12	0.04**	108.31	2.32	0.02**
	Laparoscopy	24	81.71			99.21		
Postop chemo	Yes	107	86.67	0.95	0.35	105.73	1.22	0.22
	No	37	89.27			109.86		
M stage	0	137	87.11	0.82	0.41	106.47	0.95	0.35
	1	7	91.71			113.00		
Local recurrence	Yes	9	89.00	0.36	0.72	108.56	0.31	0.76
	No	135	87.22			106.67		
Distant metastasis	Yes	33	86.18	0.52	0.60	105.36	0.52	0.60
	No	111	87.68			107.22		

Note: * $p < 0.10$, ** $p < 0.05$.

TABLE 3. Correlation between the ordinal measures and quality of life.

Kendall Tau b	FACT-G	p	FACT-C	p
T stage	-0.10	0.14	-0.10	0.11
N stage	-0.11	0.09*	-0.12	0.06*

Note: * $p < 0.10$.

TABLE 4. Correlation between the interval measures and quality of life.

Pearson Correlation	FACT-G	p	FACT-C	p
Age (years)	-0.20	0.01**	-0.20	0.02**
Distance from anal verge (cm)+	-0.04	0.61	-0.03	0.70
Duration after surgery (months)	0.14	0.10	0.14	0.10
Proximal margin	0.10	0.22	0.12	0.15
Distal margin	-0.03	0.76	-0.01	0.87
Size of tumor (cm)	0.02	0.86	0.01	0.87

Note: ** $p < 0.05$.

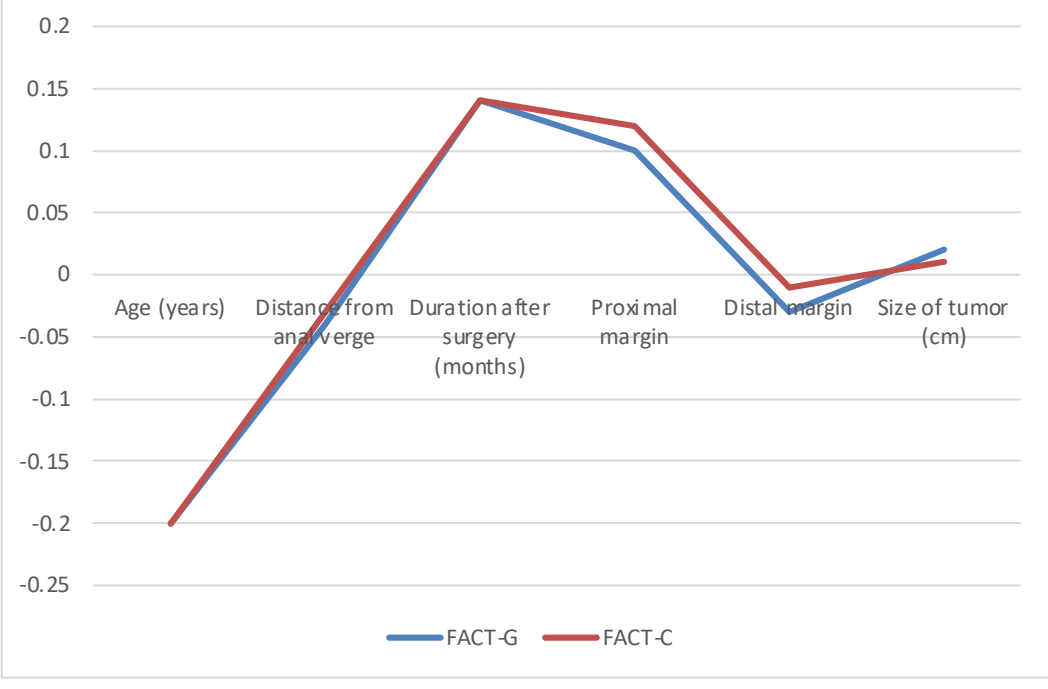

Fig 2. Correlation between predictors and QoL scores.

Multivariate analysis

Four parameters were selected as predictors in the multiple regression: gender, approach, age, and nodal status. We transformed the nodal status data from ordinal data into dichotomous data (0 = negative, and 1 = positive) prior to running the regression analysis.

A multiple regression analysis using gender, approach, age, and nodal status to predict FACT-G revealed a model that did not violate the regression assumptions. The model could predict FACT-G with a coefficient of determination (R^2) of 0.11, Adjusted R^2 of 0.08, F (4,139) = 4.18, p = 0.003. The only significant predictor was age (coefficient -0.28, t -2.67, p = 0.008, 95% confidence interval [-0.489, -0.073]).

Multiple regression analysis using gender, approach, age, and nodal status to predict FACT-C also revealed a model that did not violate the regression assumptions. The model could predict FACT-C with a coefficient of determination (R^2) of 0.12, Adjusted R^2 of 0.09, F (4,139) = 4.67, p = 0.001. The significant predictors were the nodal status (coefficient -5.76, t -1.98, p = 0.05, 95% confidence interval [-11.52, 0.00]), and age (coefficient -0.34, t -2.66, p = 0.009, 95% confidence interval [-0.60, -0.09]).

DISCUSSION

This cross-sectional observational study provided valuable insights regarding the postoperative QoL of rectal cancer patients. Our first objective was to evaluate the QoL of Thai rectal cancer patients. The FACT-G and FACT-C scores obtained from this study were very similar to the scores reported in the literature. The reported FACT-G and FACT-C scores from a previous validation study were 84.47–91.48 and 107.71–114.29, respectively.[16] These findings suggest that the postoperative QoL of Thai rectal cancer patients was comparable to that of people from other settings.

Our second objective was to determine the factors that impact the patient QoL. Our study revealed two important factors that can impact the postoperative quality of life in rectal cancer patients: age and lymph node status. Both factors had a negative impact on the quality of life. Every year's increase in age of a patient at the time of diagnosis led to a decrease of 0.28 and 0.34 points in FACT-G and FACT-C, respectively. Having a positive lymph node led to a decrease of 5.76 points in FACT-C. Yost et al. showed that a difference in FACT-C score of 5–8 points was clinically important.[19] Our findings suggested that only a few years' age difference might not have a significant impact on the QoL. A difference of age around 20 years would likely be needed to observe any clinically important impact on QoL. On the other hand, having a positive lymph node led to significant impact on the QoL. This is an important issue because the majority of rectal cancer patients in Thailand had positive lymph nodes. Our study revealed positive lymph nodes in 57.6 percent of cases. This concurred with prior study in Thailand which had a positive lymph node in 56.5% of cases.[20]

One notable finding in this study was QoL measures in patients who underwent open surgery were better than those of patients who underwent laparoscopic procedures. However, when exploring the data, we only observed this from univariate analysis. When conducting multiple regression analysis, after controlling age, nodal status, and gender, the surgical approach did not show significant impact on QoL measures. The observed impact of surgical approach in the univariate analysis seems to be a mediated effect. When investigating the relationship between surgical approach and nodal status, age, and gender, we found that patients who underwent laparoscopic approach were slightly older, had greater proportion of female, and more positive lymph node status.

What was also interesting in this study was the negative findings. For instance, many factors that were supposed to impact the postoperative quality of life turned out to have no significant impact. This seems to be conflicting with findings from prior studies which conducted in other settings.[3,6 – 10,12] This finding leads to a challenging issue related to QoL research, which is how to compare QoL impacts in different settings and populations. Consequently, how surgery impacts the QoL of rectal cancer patients in practice is a complicated issue. A study conducted on different groups of subjects with different healthcare systems, sociodemographic factors, and religious and spiritual belief systems could lead to different findings.

An important issue to consider is the extent to which the variability in QoL could be explained by the variables under study. Our regression model could explain only 12% of the variability in FACT-C. A large amount of unexplained variability in FACT-C is thus still unaccounted for and needs further investigation. This study only looked at patients' biological characteristics, tumor characteristics, and medical treatment factors. There was evidence suggesting that QoL could be influenced by sociodemographic factors.[18,21 - 23] Future study exploring the impact on the QoL by considering the sociocultural and psychological factors should be undertaken. Furthermore, future study employing prospective, multicenter design could be considered to validate the findings from this study.

There are several limitations to this study to note. First, this was a single center study conducted in Thailand. The QoL of the Thai patients in this study could be influenced by many factors that might be different between institutions or countries, such as pre- and postoperative care, surgical approaches, the support system, and healthcare structure. The second limitation is the small sample size. It is possible that failure to detect a significant impact on the QoL by some factors might be due to inadequate power in the sample set. The third limitation is the low response rate. Despite our best efforts to reach out to patients by mail and telephone, we obtained information from only 30% of those who fit our inclusion criteria. It is possible that the patients who we did not collect information from might have had different postoperative experiences. This could also lead to selection bias in the results. The fourth limitation is the wide range of postoperative durations included in this study. We obtained QoL data from patients from 10–66 months after surgery. There is some evidence in the literature that suggests that rectal cancer patients could experience an improvement in their QoL with a longer postoperative duration.[24] We explored this issue in our data by comparing the FACT-G and FACT-C scores between five groups of patients based on duration after surgery: less than one year, between

1–2 years, between 2–3 years, between 3–4 years, and more than 4 years. One-way ANOVA revealed that the QoL measures were not different between the different time points.

CONCLUSION

The postoperative QoL of Thai rectal cancer patients was similar to the QoL measures reported in a prior study.[16] Two factors showed a significant negative impact on the QoL: age and lymph node status. Gender, the type of operation, the presence of ostomy, location of the tumor, preoperative radiation, adjuvant chemotherapy, laparoscopic approach, duration after surgery, proximal and distal margins, tumor size, metastasis, and the presence of recurrence showed no significant impact on the QoL. When a surgeon provides preoperative counseling to rectal cancer patients, this information could be helpful in predicting the prognosis, especially among patients with advanced age and positive lymph node status. A surgeon should offer a tailored intervention to met with individual patients' situation, considering all potential factors that could impact their QoL.

Data Availability Statement

The datasets generated and analyzed in this study are not publicly available. However, they can be accessed upon reasonable request made to a corresponding author.

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Conflict of Interest

All authors confirm that they have no personal or professional conflicts of interest to declare relating to any aspect of this research study.

Registration Number of Clinical Trial

This study is not a registered clinical trial.

Author Contributions

Conceptualization and methodology, CI; Data collection NO; Data analysis, CI; Manuscript preparation, CI and NO; Critical review and editing, CI, NO, WR, VL, and SP. All authors reviewed the results and approved the final version of the manuscript.

Use of Artificial Intelligence

Artificial intelligence was not used in the preparation of the manuscript. All study concepts, analysis, interpretation, and writing were carried out by the authors. Artificial intelligence was used only in preparation of graphical abstract.

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