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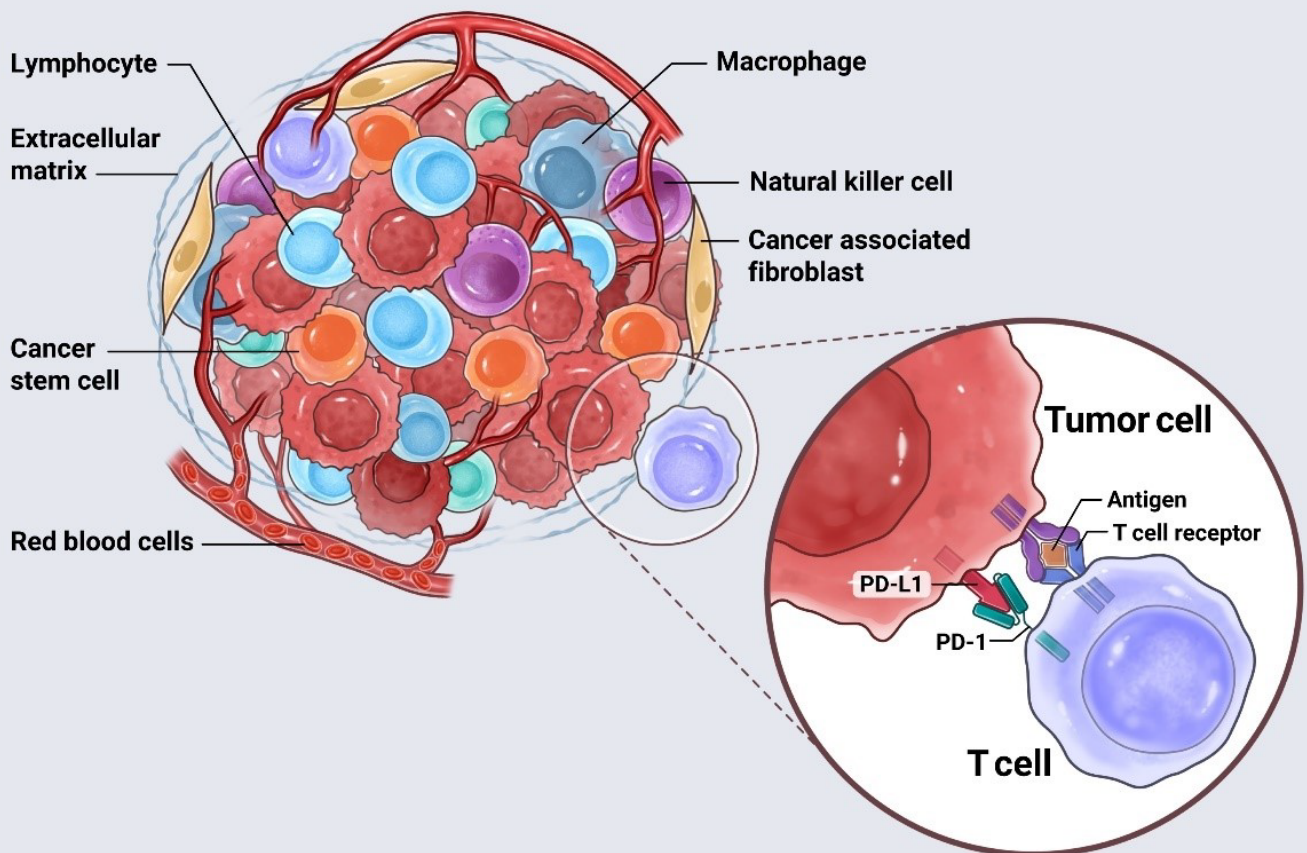
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MONTHLY

ORIGINAL ARTICLE

REVIEW ARTICLE

Tumor Microenvironment



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Factors Predicting Psychological Well-being among Survivors of Breast Cancer in A Tertiary Care Hospital, Thailand

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ABSTRACT

Objective: The primary aim of this study was to examine predicting the effect of stress, social support, self-efficacy, and resilience on psychological well-being in breast cancer survivors

Materials and Methods: This predictive analysis for the descriptive cross-sectional study was conducted by the theoretical underpinning of resilience and population consisted of eligible breast cancer survivors receiving care at an outpatient clinic within a tertiary hospital setting. The data collecting was proceeded through self-administered questionnaires in line with convenient sampling. The analytical approach encompassed descriptive statistics, Pearson's correlation coefficient, and multiple linear regression.

Results: Emanating from the study included the recruitment of 123 participants, with stress, social support, and resilience collectively elucidating 43% of the variance in psychological well-being among breast cancer survivors. Notably, resilience emerged as the most influential predictor ($\beta=.33$), followed by stress ($\beta=-.27$) and social support ($\beta=.26$), all of which significantly contributed to the prediction of psychological well-being.

Conclusion: Resilience, stress, and social support were three predictors of psychological well-being among survivors of breast cancer in this study. Recommendations extend to the integration of strategies that foster resilience and social support, while concurrently mitigating stress levels through activities and programs aimed at augmenting the psychological well-being of breast cancer survivors in the future.

Keywords: Breast cancer survivors; psychological well-being; resilience; self-efficacy; social support; stress (Siriraj Med J 2024; 76: 244-254)

INTRODUCTION

Breast cancer is one of the most common diseases among women.¹ According to a report by the World Health Organization (WHO) in 2022, new cases of breast cancer and the mortality rate were 2.26 and 0.68 million per year, respectively.² In Thailand, breast cancer is the most common cancer occurring among women, accounting for 22,158 new cases and 8,266 deaths annually.³

Moreover, new breast cancer cases have increasingly been diagnosed and reported globally, revealing breast cancer as a significant public health issue for Asian women worldwide. Even though cancer deaths are prevalent, early diagnosis through detecting cancer by screening provides asymptomatic patients a greater chance of recovery.³⁻⁴

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A cancer survivor is a term that refers to a patient diagnosed with cancer from their first diagnosis and subsequently lives life as a cancer patient. Most survivors face a variety of cancer-related effects, including physical, mental, and social consequences. After receiving treatments, patients experience physical symptoms such as chronic pain,⁴ dizziness, fatigue, insomnia, forgetfulness,⁵ and discomfort.⁶ Mental symptoms encompass stress, anxiety, and depression.⁷ Stress may contribute to anxiety and depression, leading to an increased risk of suicide. Social impacts entail discomfort with other family, friends, and colleagues, an inability to maintain family and social roles, and the risk of work problems due to frequent sick leave and compromised work performance.⁸ However, some of them have reported good psychological well-being without mental health problems, felt happy, had life satisfaction, and handled both disease conditions and lifestyle changes.

Psychological well-being (PWB) is a condition lacking any mental health problems and a vital indicator of personal mental health, mental strength, optimism, and the ability to live everyday life.⁹ The six dimensions of PWB consist of living with autonomy, purpose in life, self-acceptance, personal growth, positive relations with others, and environmental mastery.⁹⁻¹¹ Various studies have examined the factors influencing breast cancer survivors' PWB, including stress,^{12,13} self-efficacy,^{14,15} social support,^{16,17} and resilience.^{14,18}

Stress is a personal perception reacting to stimuli, which causes physical changes and physiological imbalances between biology and biochemistry in response to those stimuli.¹⁹⁻²³ Breast cancer is considered a life-threatening condition that leads to stress, which causes patients to evaluate their illness as a threat, affecting their perceptions and raising stress levels and psychological disruptions.²⁴

Social support is a key factor related to PWB,¹⁸ perceived interactions, support,²⁵ and illness management for breast cancer survivors. Social support helps promote appropriate adaptation, leading to beneficial mental health conditions. Optimal social support facilitates self-adaptation and promotes self-acceptance of the illness condition.^{26,27}

Self-efficacy refers to a personal belief in the capability to do something that supports how one lives. Self-efficacy includes personal feelings, thoughts, motivations, and behaviors.²⁸ Studies have demonstrated that self-efficacy is an essential characteristic of successful self-management for the effects of cancer and its treatments. On the contrary, cancer patients with low self-efficacy tend to be more likely to experience depression.²⁹ Generally, cancer patients aim to be successful in their self-management, which is one of the components of mental health.

Resilience is likewise associated with PWB, perceived growth, and quality of life among breast cancer survivors.³⁰ It is a personality trait that individuals employ to protect themselves from undesirable events and to overcome negative experiences happening in their lives,³¹ such as being diagnosed with cancer.³²

Although the above-mentioned factors were examined among patients with cancer and other chronic diseases in once a factor, limited research simultaneously tested all factors in the same study. Thus, it is inclusive of the magnitude of the effect for each factor. Moreover, most studies focused on promoting a patient's quality of life rather than PWB. It is unclear which factors predict PWB among breast cancer survivors.^{16,33,34}

Accordingly, this study aimed to examine the factors that predict PWB in breast cancer survivors in Thailand. It is hypothesized that stress, perceived social support, mindfulness, self-efficacy, and resilience would significantly predict PWB among breast cancer survivors in Thailand. The findings from this study would increase awareness among healthcare providers concerning PWB and should result in self-acceptance as well as the ability to live happily as a cancer survivor, maintaining good PWB.

Theoretical framework

This research was guided by Kumpfer's resilience framework,³⁵ comprising six core concepts including stressors and challenges, external environmental context, person-environment transactional processes, internal resilience factors, resilience processes, and positive outcomes. Considering Kumpfer's framework and the factors relating to PWB, one recognizes that breast cancer survivors need surveillance for a recurrence, requiring continuous monitoring of treatment results. Cancer-related stress may lead to poor mental health. However, environmental contexts (such as social support from family, friends, and significant people) can minimize the effects of stress. The internal resilience factor and resilience process can lead to good adaptation. Self-efficacy and well-resilience grounds the ability to deal with stress and threats as well as reduce the chances of problems in adapting to the stress of being a breast cancer survivor. These enabling factors result in a positive outcome of effective adaptation to mental health problems and facilitate PWB.

Breast cancer survivors are a group with life goals. They have self-acceptance and good relationships with others, can adapt to threats, have the potential for self-improvement, and can make choices themselves. Besides, they have purposeful lives, take good care of their health, work to reduce relapses, and achieve long-term survivorship.

This determination to survive is consistent with the Ryff and Keyes⁹ concept of PWB, which recognizes PWB as a personal commitment to a positive lifestyle. Its six dimensions consist of autonomy, self-acceptance, positive relationships with others, purpose in life, environmental mastery, and personal growth, as shown in Fig 1.

MATERIALS AND METHODS

Research design and participants

A predictive descriptive research design and convenience sampling were utilized. The target population included post-treatment breast cancer survivors from a breast surgery clinic at a large tertiary hospital in Bangkok, Thailand. In conclusion, female adults must meet the following inclusion criteria: (1) aged 18 years and older diagnosed with breast cancer stage 1-3 by attending doctors, (2) completed treatments, including surgery, radiation, chemotherapy, hormone therapy, or combined therapy for at least six months, and (3) were clinically stable as indicated by attending physicians. This study excluded people with a diagnosis of cancer recurrence, metastasis to various organs, and a history of mental disorders.

The sample size was determined by power analysis calculated with the G*Power version 3.1.9.4 program. A study examined the effect of resilience on PWB among breast cancer survivors³⁶ and generated a small effect size ($r = .30$, Cohen's $d = .10$). With this effect size, a significance level (α) of .05, power = 80%, four predicting variables, and at least 123 participants were required for this study.

Variables and measurements

There were two groups: tools for screening and data collection.

Screening tool

The Thai Mental State Examination (TMSE)³⁷ was developed by 14 international institutions of brain rehabilitation groups. Patients with total scores less than

or equal to 23 points would be a cut-off for cognitive impairment and excluded from this study.³⁸

Tools for data collection

PWB was evaluated by using the 18-item Thai-version psychological well-being scale (PWES),⁹ which was translated from the original PWES³⁹ and consisted of six components including autonomy, environmental mastery, purpose in life, personal growth, positive relations with others, and self-acceptance. The assessment form uses a six-point Likert scale. Scores for each item range from 1 to 6, with 1 (strongly disagree), 2 (very disagree), 3 (disagree sometimes), 4 (agree sometimes), 5 (very agree), and 6 (strongly agree), while summed scores range from 18 to 108 points, and high scores indicated a high degree of psychological wellbeing. Cronbach's alpha for the total scale was .80, and predictive validity was .75.³⁹

Stress was evaluated with the Thai version of the 10-item Perceived Scale (PSS).⁴⁰ The Thai version of the PSS was translated from the original PSS.⁴¹ It is a text style that measures perceived stress situations. It is a question about feelings and thoughts in the past month. The assessment form uses a five-point Likert scale. Scores for each item range from 0 (not at all), 1 (almost none), 2 (sometimes), 3 (quite often) to 4 (very often), while summed scores range from 0-40 points, and high scores indicate a high degree of perceived stress. Cronbach's alpha for the total scale was .85, and predictive validity was .80.⁴¹

Social support was evaluated with the Thai version of the 12-item Multidimensional scale of perceived social support (MSPSS).⁴² The Thai version of the MSPSS was translated from the original MSPSS.⁴³ It is a text style that measures perceived social support. The assessment form uses a seven-point Likert scale. Each item scored on a 7-point ordinal scale, ranging from 1 to 7 (1 = very strongly disagree, 2 = strongly disagree, 3 = mildly disagree, 4 = neutral, 5 = mildly agree, 6 = strongly agree, and 7 =

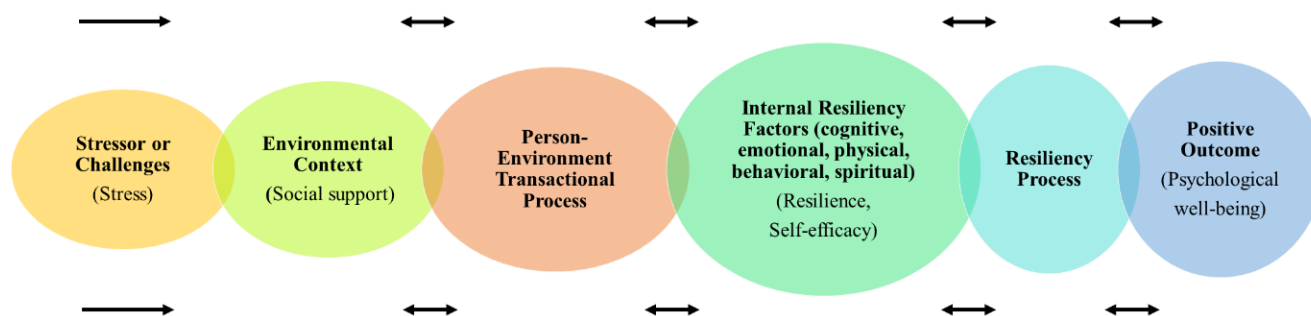


Fig 1. Psychological well-being factors of breast cancer survivors according to the conceptual framework of Kumpfer's resilience

very strongly agree). Summed scores ranged from 12-84 points, with a high score indicating a high degree of perceived social support. Cronbach's alpha for the total scale was .89, and predictive validity was .92.⁴³

Self-efficacy was evaluated with the Thai version of the 10-item General self-efficacy scale (GSES).⁴⁴ The Thai version of the GSES was translated from the original GSES.⁴⁵ It is a text style that measures self-efficacy. The assessment form uses a four-point Likert scale. Scores for each item range from 1 (not at all true), 2 (barely true), 3 (moderately true) to 4 (exactly true), while summed scores ranged between 10-40 points, and high scores indicated a high degree of self-efficacy. Cronbach's alpha for the total scale was .84, and predictive validity was .88.⁴⁵

Resilience was evaluated with the Thai version of the 10-item Connor-Davidson resilience scale (CD-RISC).⁴⁶ The Thai version of the CD-RISC was translated from the original CD-RISC.⁴⁷ It is a text style that measures resilience. The assessment form uses a five-point Likert scale. Scores for each item range from 0 (not at all true), 1 (rarely true), 2 (sometimes true), 3 (often true) to 4 (true nearly always). Summed scores would range from 0-40 points, so high scores indicated a high degree of resilience. Cronbach's alpha for the total scale was .86, and predictive validity was .89.⁴⁷

The collection of personal information consisted of age, marital status, education, occupation, religion, income, and perceived income sufficiency. Clinical data encompassed the right to medical treatment, body mass index (BMI), congenital or co-morbid diseases, history of drug allergy and food allergy, past illness history, and duration of illness.

Ethical considerations

Ethical approval was granted by the Institutional Review Board of the Faculty of Nursing for the study of universities (IRB-NS 2020/52.0212) and the study of hospitals (IRB No.072/2564). Participants completed informed consent forms, and all procedures complied with ethical guidelines and regulations. The study was conducted from November 2020 through July 2022, and participant recruitment took place from August 2021 to October 2021. The participants completed the questionnaires, comprising 73 items, which took approximately 30 to 45 min for each participant to complete.

Data collection procedure

After receiving ethical approval, the researchers required permission from the hospital Directors of Study and breast surgery clinic to commence data collection. After that, the

researchers met the director of the breast surgery clinic to clarify the objectives, methods of data collection, and research benefits. Afterward, the researchers coordinated with nurses working at the breast surgery clinic to identify and screen for eligible participants. Subsequently, the researchers approached eligible participants, explained the details concerning the research project, and invited them to participate in the study. Before completing the self-administered questionnaire, each participant received a participant information sheet and signed a consent form. Each completed questionnaire was checked to ensure that there were no missing data. For those who could not read the questionnaire clearly, the researchers assisted by reading for them and recording the data based on their responses. During the process, if participants experienced certain symptoms (such as headache), the researchers would allow them to discontinue answering the questionnaire and provide necessary care immediately. In addition, given that data collection took place during the COVID-19 outbreak, the researcher and participants complied strictly with measures for preventing the spread of infection, including screening for symptoms, checking body temperature, wearing masks, and maintaining social distances of at least two meters.

Data analysis

All data were analyzed by the Statistical Package for Social Science (SPSS), as follows:

1. Personal information (such as age, marital status, and education) and clinical data (such as medical treatments, and congenital or co-morbid disease) were analyzed by univariate statistics such as frequency, percentage, mean and standard deviation.
2. Study variables (stress, social support, self-efficacy, resilience, and PWB) were analyzed by descriptive statistics.
3. The factors predicting PWB among breast cancer survivors were stress, social support, self-efficacy, resilience, and PWB, which were analyzed by running Pearson's correlation coefficient and multiple regression using the enter method, with a statistical significance level of .05.

RESULTS

Demographics and clinical information of the participants

In total, the study comprised 123 breast cancer survivors with a mean age of 55.06 (SD =10.67), and most of them were in the age range of 50-59 (37.40%) (Table 1). The majority were married (52.80%; n=65) and Buddhist (94.30%; n=116), had graduated with a bachelor's degree or vocational certificate (52.00%; n=66), and qualified under the Civil Servant Medical Benefit Scheme (44.70%; n=55). Generally, they were

TABLE 1. Demographics and clinical information of the participants.

Demographics and clinical information	N	%	Demographics and clinical information	N	%
Age (years)			Religion		
30-39	6	4.90	Buddhism	116	94.30
40-49	30	24.40	Islam	4	3.30
50-59	46	37.40	Christianity	3	2.40
> 60	41	33.30			
(\bar{X} =55.06, S.D.=10.67, Max=85, Min=30)			Income (monthly)		
Marital Status			< 10,000	32	26.00
Single	34	27.60	10,000-29,999	30	24.40
Married	65	52.80	30,000-49,999	25	20.30
Divorced	12	9.80	> 50,000	36	29.30
Other	12	9.80	(\bar{X} =23,361.14, S.D.=28,001.99, Max=150,000, Min=0)		
Education			Medical Insurance plans		
Undergraduate	42	34.10	Cash	22	17.90
Graduated in bachelor's degree or vocational certificate	64	52.00	Civil servant plans	55	44.70
Master's degree	16	13.00	State Enterprise Officer	8	6.50
Doctor's degree	1	0.80	Health insurance	21	17.10
			Social insurance	16	13.00
			Other	1	0.80
Occupation			Body mass index (BMI: kg/m²)		
Unemployed	2	1.60	<18.5	5	4.10
Government officer	35	28.50	18.5-22.9	34	27.60
			23-24.9	28	22.80
Occupation			25-29.9	40	32.50
Employee	15	12.20	≥30	16	13.00
Self-Employed	33	30.90	(\bar{X} =25.16, S.D.=4.37, Max=42.24, Min=16.41)		
Other	38	26.80	Average duration of illness (monthly)		
Adequacy of income			< 12	71	57.70
Enough	106	86.20	12-24	24	19.50
Not enough	17	13.80	25-36	14	11.40
Congenital or co-morbid disease			>37	14	11.40
No co-morbid disease	48	39.00	(\bar{X} =21.31, S.D.=24.15, Max=132, Min=2)		
One disease	45	36.60			
Two diseases	18	14.60			
Three or more disease	12	9.80			
History of drug allergies, food allergies					
Yes	20	16.30			
No	103	83.70			
History of illness					
Yes	52	42.30			
No	71	57.70			

housewives, hired workers, or others (30.90%), with 50,000 baht or more being the average monthly income (29.30%). Participants had an average BMI of 25.16 (SD=4.37).

Psychological well-being, stress, social support, self-efficacy, and resilience

The results for psychological well-being, stress, social support, self-efficacy, and resilience are presented in Table 2. PWB (\bar{X} =83.19, SD=8.85), stress (\bar{X} =13.28, S.D.=6.16) social support (\bar{X} =70.33, S.D.=11.03), self-efficacy (\bar{X} =31.90, S.D.=4.61) and resilience (\bar{X} =31.39, S.D.=5.35).

Correlations between psychological well-being, stress, social support, self-efficacy, and resilience

According to the rule of Thumb for interpreting the size of a correlation coefficient, the correlation coefficient in the range of .90 to 1.00 (-.90 to 1.00), .70 to .90 (-.70 to -.90), .50 to .70 (-.50 to -.70), .30 to .50 (-.30 to -.50), .00 to .30 (.00 to -.30) are assigned to the positive (negative) correlation in the level of very high, high, moderate, low and negligible, respectively.⁵⁵ The correlations between psychological well-being, stress, social support, self-efficacy, and resilience are presented in Table 3. It is revealed that PWB was positively correlated with resilience ($r=.55$, $p<.01$), social support ($r=.44$, $p<.01$), and self-efficacy ($r=.34$, $p<.01$). On the other hand, stress showed

a negative correlation with psychological well-being ($r= -.49$, $p<.01$)

Predictors of mental health among participants

The model summary by an enter model of multiple linear regressions showed that stress, social support, self-efficacy, and resilience could explain the variance of PWB by 44% (adj $R^2=.43$, $F_{(4,118)}=23.58$, $p<.01$) are presented in Table 4. Resilience had the strongest and significant effect on PWB ($\beta=.33$, $p<.01$), followed by stress ($\beta=-.27$, $p<.01$) and social support ($\beta=.26$, $p<.01$). However, self-efficacy ($\beta=.05$, $p>.01$) did not affect PWB.

DISCUSSION

This study aimed to examine the factors that predicted PWB among breast cancer survivors in Thailand. The findings indicated that stress, social support, and resilience were significant predictors of PWB, except for self-efficacy. All variables explained 44% of the variance on PWB.

Breast cancer survivors with higher levels of stress were more likely to report lower PWB. Therefore, there is a need to help them manage stress, thus enhancing their mental health and PWB.^{24,48} The findings from the study indicate a significant negative relationship between stress and PWB in breast cancer survivors ($r= -.49$, $p<.01$). Moreover, stress emerged as a significant predictor of PWB at a confidence level of .01 ($\beta=-.27$,

TABLE 2. Descriptive statistics for the outcome measures (n=123).

Variables	Subscale		Item		
	Mean	S.D.	Score range	Scale range	Item range
Psychological wellbeing	83.19	8.85	60-103	18-108	1-6
Autonomy	11.61	1.94	6-15	3-18	1-6
Self-acceptance	11.60	1.88	6-18	3-18	1-6
Personal growth	12.52	1.96	7-17	3-18	1-6
Positive relationships with others	9.66	1.97	6-18	3-18	1-6
Environmental mastery	12.99	1.62	8-17	3-18	1-6
The purpose of life	11.45	2.04	6-17	3-18	1-6
Stress	13.28	6.16	0-31	0-40	1-4
Social support	70.33	11.03	23-84	12-84	1-7
Family	24.69	4.12	6-28	4-28	1-7
Friends	21.65	5.39	6-28	4-28	1-7
Intimate partners	23.98	3.61	11-28	4-28	1-7
Self-efficacy	31.90	4.61	13-40	10-40	1-4
Resilience	31.39	5.53	13-40	0-40	0-4

TABLE 3. The correlation coefficient between study variables (n=123).

Variables studied	1	2	3	4	5
Stress	1				
Social support	-.24**	1			
Self-efficacy	-.37**	.23*	1		
Resilience	-.45**	.32**	.39**	1	
Psychological well-being	-.49**	.44*	.34**	.55**	1

*Correlation is significant at the 0.05 level (two-tailed).

**Correlation is significant at the 0.01 level (two-tailed)

TABLE 4. Predictors of mental health among participants (n=123).

Variables studied	β	t	p-value
Constant		-7.76	.000
Stress	-.27	-3.35	.001
Social support	.26	3.60	.000
Self-efficacy	.05	.63	.532
Resilience	.33	4.01	.000

β =standardized regression coefficient

$p < .01$). These results are consistent with prior research, which similarly found a negative correlation between stress and PWB in breast cancer survivors ($r = -.44$, $p < .00$), with stress being a significant predictor of PWB ($\beta = -.59$, $p < .00$).^{24,46} A possible explanation for this relationship is that breast cancer survivors who experience stress may be better equipped to handle daily challenges, perceiving stress as a challenge and strengthening their ability to cope with stress effectively. Based on Kumpfer's resilience framework,³⁵ it has been suggested that stress can function as a personal characteristic that facilitates positive adaptation by encouraging individuals to perceive stressors as challenges. Breast cancer survivors are individuals who have undergone comprehensive treatment and are now in a monitoring phase where continuous follow-ups of treatment outcomes is necessary in case of recurrence. This ongoing process can significantly impact their lifestyle, potentially leading to heightened stress levels compared to their pre-diagnosis state. When individuals experience elevated stress levels and struggle to effectively manage it, they become increasingly aware of stress as a looming threat, difficult to handle. This can result in

mental health issues and hinder their ability to adapt to both their medical condition and its treatment, ultimately contributing to poor mental well-being. It is a process of stressors and challenges within the individual regarding the first component of Kumpfer's resilience framework. Therefore, it can be concluded that appropriate stress-coping strategies may support patients by helping them achieve good mental health and high levels of PWB.

The results of this study indicated a significant positive correlation between social support and psychological well-being (PWB) ($r = .44$, $p < .01$). These findings suggest that individuals with greater social support tend to report higher PWB levels. Additionally, social support emerged as a significant predictor of PWB at a confidence level of .01 ($\beta = .26$, $p < .01$). These results align with earlier research¹⁶, which similarly found a positive correlation between family support and improved mental health ($r = .42$, $p < .01$) in older cancer patients undergoing chemotherapy. Meanwhile, decreasing social support predicted stress and negatively affected PWB among breast cancer survivors.⁵⁰ In addition, this group of patients had to have prolonged follow-ups continuously,

allowing patients to meet with fellow patients who went for breast cancer treatment simultaneously. They also acted as consultants or shared their experiences with other patients and interacted about their illnesses and goals for treatment. In addition, this group of patients had to be followed regularly every three months in the first three years post-treatment.⁵⁴ The follow-ups could enable patients to meet fellow patients undergoing breast cancer treatment. Some served as consultants and interacted by sharing experiences about their illnesses and goals for treatment. In other words, social support is necessary for ill patients to balance their PWB and cope with stress appropriately. Afterward, it brings the individual's transition process within the inner resilience element.^{51,52} In line with Kumpfer's resilience framework,³⁵ social support is an external environmental cortex that balances and interacts with internal/external protective factors and environmental factors. Patients perceiving beneficial social support (especially from family members, friends, or intimate partners) would be able to balance their perceptions towards stress, thus contributing to better mental health and PWB. Additionally, people with high levels of PWB could build good relationships with others, value empathy in relationships, and establish mutual trust.⁴⁹

The findings of this study revealed a significant positive correlation between resilience and psychological PWB among breast cancer survivors ($r=.55, p<.01$). This suggests that those with higher levels of resilience are more inclined to report better PWB. Resilience emerged as a significant predictor of PWB with a confidence level of .01 ($\beta=.33, p<.01$). Moreover, a prior investigation similarly highlighted the association between resilience and PWB in breast cancer patients ($r = .80, p = .00$), with resilience significantly predicting PWB ($\beta =.58, p < .00$).¹⁸ Furthermore, resilience was correlated with growth perception ($r=.61, p<.00$), and it could predict growth perception ($\beta=.61, p < .00$).³⁰ A possible explanation is that breast cancer survivors with resilience could manage every obstacle in daily life. They perceived stress as a challenge, thus strengthening their ability to cope with stress effectively. Based on Kumpfer's resilience framework,³⁵ resilience is a personal characteristic that helps individuals perceive stress as a challenge and promotes positive adaptation. It is a process of change within the individual regarding flexibility, the fourth component of Kumpfer's resilience framework.

The results of this study imply that while self-efficacy demonstrates a significant correlation with PWB ($r=.34, p<.01$), it does not emerge as a significant predictor of PWB. Conversely, a prior study suggested that self-

efficacy correlated to quality of life via personal mental well-being ($r=.75, p<.00$). Patients with high self-efficacy tend to exhibit good PWB and considered as component of quality of life.⁵³ According to the present findings, self-efficacy could not be a significant predictor for PWB because it has a low correlation. It is implied that some other variables are incorporated into self-efficacy through the resilience process, as shown in Fig 1.

Limitations

The strength of this study was its utilization of acceptable and reliable validated instruments within the Thai population. Subjective data were collected via a questionnaire, allowing participants to express their feelings or needs. The study employed convenience sampling, a method known for its comprehensiveness and accuracy in selecting small sample groups. Furthermore, a cross-sectional design, enabling the simultaneous examination of multiple variables, was employed in this work. However, the findings could involve limitations because data were collected only at one hospital. Thus, the results herein should not be appropriately generalized to diagnose breast cancer patients and survivors of breast cancer in other hospitals at a similar level, primary and secondary hospitals.

CONCLUSION

The present research examined factors related to psychological well-being in survivors of breast cancer. Our results highlighted resilience, stress, and social support factors that could predict psychological well-being. These results would be beneficial for future research and programs of development or innovation to effectively promote PWB among breast cancer survivors, especially among the Thai population.

Recommendations

Nursing Practice

Nurses should provide psychological care, particularly for resilience factors, such as delivering a program for breast cancer survivors' participation by organizing activities that develop resilience in life.^{56,57} Because it would help them adapt to illness and have good mental health. Also, social support should be advocated, such as Experience Sharing Groups among breast cancer survivors.^{58,59} Additionally, nurses should assess stress regularly, offer stress management programs support stress relief clinics to alleviate stress in the group of patients, and provide comprehensive and appropriate nursing care, which would lead to better mental health promotion for patients.

Education

The results of this study indicate that the factors that could predict mental health among survivors of breast cancer included stress, social support, and resilience. Therefore, it is necessary to provide nurses with training courses or knowledge about assessing stress levels, promoting social support, and increasing resilience in the care of breast cancer survivors.⁶⁰⁻⁶¹

Future research

Further research should explore unpredictable factors like self-efficacy in the PWB of breast cancer survivors, potentially increasing sample size and development programs to enhance PWB among survivors warrant investigation.⁶² Future studies should extend beyond public hospitals to include private and community hospitals, diverse age groups, and other chronic diseases for comprehensive mental health promotion. Longitudinal designs and follow-up studies are essential to uncover the trajectory of Kumpfer's conceptual theory and understand precise changes in breast cancer survivors' well-being.

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Conflicts of interest

The authors declare no conflict of interest.

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Authors' contributions

NS: general research process, framework of the study, data collection procedure, data analysis, writing-original draft preparation; WT: framework of the study, validation, resources, writing -review and editing, visualization, supervision, project administration; NV: framework of the study, methodology, validation, formal analysis, writing – review, and editing; SK framework of the study, methodology, validation, formal analysis, writing–review, and editing; PKY: writing – review, and editing. All authors read and approved the final manuscript.

Data availability statement

Data is unavailable due to privacy and ethical

restrictions from the Institutional Review Board (IRB) of Mahidol University, Thailand.

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Survey-based Study to Assess the Self-perceived Competency in and Knowledge about Reconstructive Microsurgery among Young Plastic Surgeons

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ABSTRACT

Objective: Microvascular free tissue transfer has become a preferred reconstructive technique for managing complex wounds and defects. The aim of this questionnaire-based study was to assess self-perceived competency in and knowledge about reconstructive microsurgery among plastic surgeons who graduated from the Faculty of Medicine Siriraj Hospital, Mahidol University during 2015-2019.

Materials and Methods: Questionnaire was sent by email elicited information about the amount of microsurgery performed in practice, types of microsurgeries performed, reconstructive methods, types of flaps used, and respondent's opinion about the microsurgery course attended during residency/fellowship training.

Results: The total response rate was 87.5%. Almost all respondents work in a government hospital (90.4%), and responses came from all regions of Thailand. Thirty-eight percent of respondents reported no microsurgery cases, and the majority of those who did perform microsurgery did so less than 20 times/year. Hand reconstruction was the most common type of microsurgical procedure. The factors that negatively influence microsurgery in clinical practice include insufficiency of resources and personnel (29.1%), excessive workload (27.3%), and long operative time (23.6%). Suggestions for improvement of the microsurgical training course include having a good objective method for assessing microsurgical practices (27.7%), increasing the volume of practice on animal model (25.5%), and an appropriate number of microsurgery cases to gain necessary experience (25.5%).

Conclusion: Reconstructive microsurgery was found to be a challenging procedure for many junior-level plastic surgeons. A low volume of cases limits a surgeon's ability to develop needed skills. Important improvements in the microsurgery training course were also recommended.

Keywords: Microsurgery; surgical education; free flap; plastic surgery training; plastic surgeon (Siriraj Med J 2024; 76: 255-261)

INTRODUCTION

Microvascular free tissue transfer has become a preferred reconstructive technique for managing complex wounds and defects, such as limb salvage surgery, breast reconstruction, head and neck reconstruction, and lower extremity reconstruction. The development of meticulous microsurgical skills requires good foundational training, clinical experience, and continuous learning. In order

for plastic surgery residents and fellows to be able to competently and confidently perform microsurgical procedures in routine clinical practice after graduation, they must receive sufficient training and have had adequate hands-on experience in the operating room under the guidance of an experienced instructor.¹⁻⁵

At our center, microsurgical skill is an important area of competency that is assessed among our trainees, and

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more than 100 cases of microsurgery are performed in our division annually.⁶⁻⁹ Our trainees receive reconstructive microsurgery training and experience by both practicing in the microsurgery lab, and by operating on real-life patients in the operating theater for conditions that include replantation, auto-transplantation, revascularization in order to resolve defects arising from tumor ablation, traumatic injuries, and congenital abnormalities.¹⁰⁻¹³ However, we have never assessed the views about, attitudes towards, reflections of, and experience in reconstructive microsurgery among our plastic surgery trainees after graduation. Accordingly, the aim of this questionnaire-based study was to assess the self-perceived competency in and knowledge about reconstructive microsurgery among plastic surgeons who graduated from the Faculty of Medicine Siriraj Hospital, Mahidol University during 2015-2019.

MATERIALS AND METHODS

Sample selection

All plastic surgeons who graduated from the Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand during 2015 to 2019 were eligible for study enrollment, and all 24 of those surgeons were sent study questionnaires via email. The surgeons that responded were included in the study and the final analysis. The protocol for this study was approved by the Siriraj Institutional Review Board (SIRB) (COA no. 616/2563), and all included subjects provided written informed consent to participate.

Study design and administration

The survey comprised 44 questions that cover various aspects of microsurgery, including the amount of microsurgery performed per year, the types of microsurgeries performed, the specialists responsible for performing microsurgery, the reconstructive methods used, the types of flaps used, and their opinions about the microsurgery course that they took during their residency/fellowship training. There was no imputation for missing data, such as specific questions for which an answer wasn't given. Data management was performed using Microsoft Excel spreadsheet program (Microsoft Corporation, Redmond, WA, USA).

RESULTS

Twenty-one of 24 (87.5%) junior plastic surgeons returned a questionnaire, and 47.6% (10 of 21 respondents) answered all of the 44 questions. Almost all respondents (90.4%) work in a government academic or non-academic hospital. The remaining 9.6% work in the private sector. Questionnaires were received from all geographical regions of Thailand. Most doctors work in the Central region (11 of 21 (52.4%)), followed by the Southern region (19.0%) and the Eastern region (9.5%) (Table 1).

Annual volume of microsurgery cases

The volume of microsurgery cases per year was 0 cases in 38.1% (8 of 21) of respondents, 1 to 3 cases in 23.8% (5 of 21), and 11 to 20 cases in 14.3% (3 of 21). For the overall number of microsurgery cases, 95.2% of

TABLE 1. Employment and location data of young plastic surgeon respondents.

	n	%
Type of hospital		
Ministry of Public Health hospital	12	57.1%
Medical school or university hospital	7	33.3%
Private hospital	2	9.5%
Region		
Central	11	52.4%
South	4	19.0%
East	2	9.5%
West	2	9.5%
North	1	4.8%
Northeast	1	4.8%

respondents performed microsurgical reconstruction less than 20 cases annually (Fig 1).

Regarding the percentage of microsurgery performed at each region of the body, hand reconstruction was the most frequently performed procedure (61.9%, 13 of 21), followed by breast reconstruction in 42.9% (9 of 21) and head and neck reconstruction in 42.9% (9 of 21). Trunk reconstruction was performed least often (14.3%, 3 of 21) (Fig 2).

Responsible surgeons for reconstructive microsurgery at each region of the body

For the head and neck region, plastic surgeons performed reconstruction in 88.2%, and otolaryngologists performed reconstruction in 11.8%. Breast reconstruction was performed by plastic surgeons in 62.5%, and by general surgeons in 37.5%. Hand reconstruction was performed by plastic surgeons in 78.9%, and by orthopedists in 21.1%. Hand replantation was performed by orthopedists in 55.6%, and by plastic surgeons in 44.4%. Lower extremity reconstruction and trunk reconstruction was performed by plastic surgeons in 95% and 88.2% of cases, respectively. Perineum reconstruction was performed by plastic surgeons in 83.3%, and the remaining cases were performed by urologists, gynecologists, or general surgeons (Fig 3).

Preferred choices of reconstruction for each region of the body

Head and neck reconstruction (no cases in 23.8% of respondents)

The loco-regional flap was reported to be the preferred

method for managing head and neck defects (66.7%), with the most commonly used flaps being nasolabial flap (40.0%), paramedian forehead flap (30.0%), and pectoralis major myo-cutaneous flap (25.0%). Free flaps were performed in 27.8% of cases, with the anterolateral thigh free flap, fibular free flap, and radial forearm free flap used in 45.5%, 31.8%, and 22.7% of cases, respectively (Supplementary Fig 1).

Breast reconstruction (no cases in 38.1% of respondents)

Pedicle transverse rectus abdominis myo-cutaneous (TRAM) flap was the most commonly used flap for coverage of a breast defect (performed by 25.0% of respondents), following by pedicled latissimus dorsi (LD) myo-cutaneous flap with silicone implant (13.6%). Free tissue transfer was seldomly performed, but when it was, free TRAM flap and free deep inferior epigastric perforator (DIEP) flap were the reconstructive flaps of choice (4.5% and 2.3%, respectively). Regarding the timing of reconstruction, nearly one-third of respondents preferred delayed breast reconstruction (28.6%). Other reported types of breast reconstruction that were encountered included implant-based reconstruction (22.7%), mastopexy (18.2%), and lipofilling (13.6%) (Supplementary Fig 2).

Hand reconstruction (no cases in 38.1% of respondents)

The most frequently used flaps for soft tissue reconstruction were loco-regional flap (43%) (such as reverse radial forearm free flap, and posterior interosseous artery flap), followed by tissue substitute with skin graft (24%), and distant flap (14%). For replantation, single

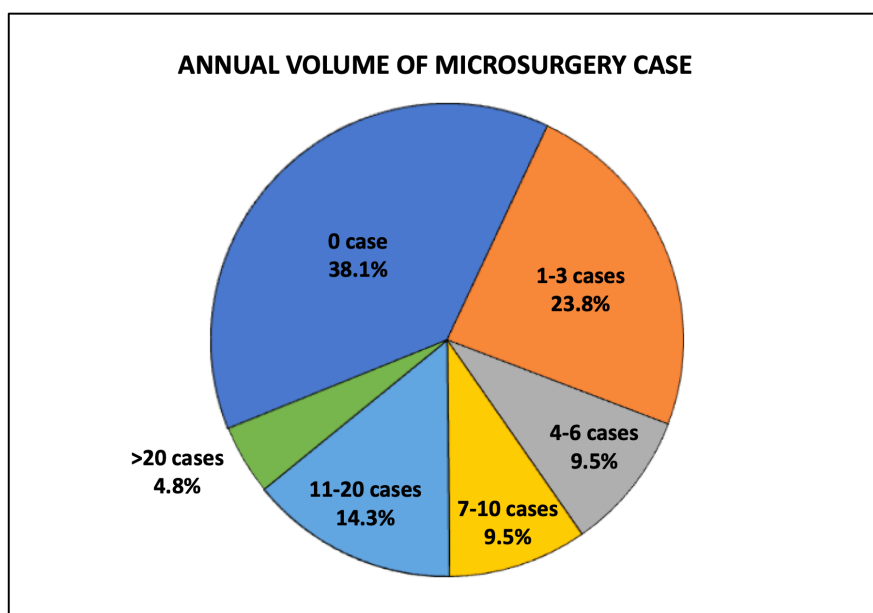


Fig 1. Volume of microsurgery cases per year among our respondent cohort.

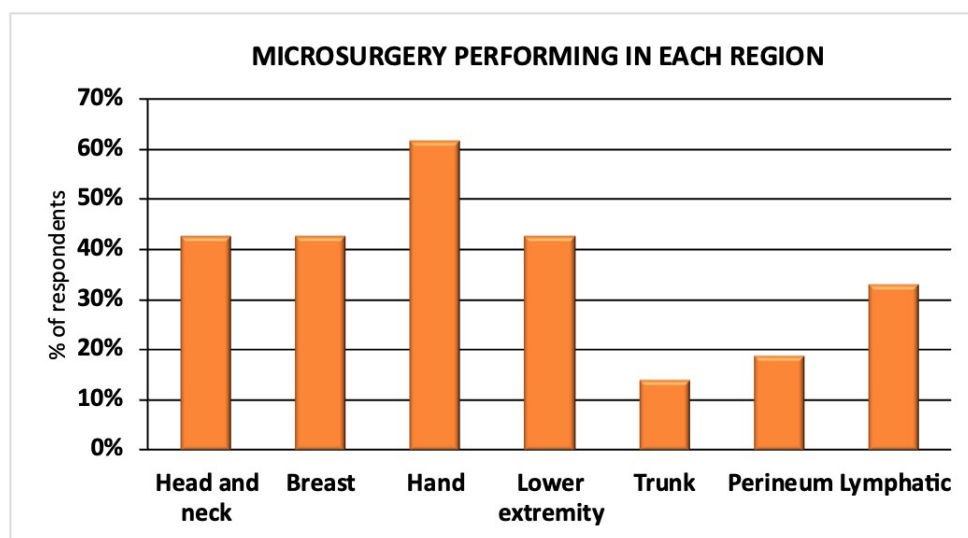


Fig 2. The percentage of respondents who performed microsurgical procedures compared among different regions of reconstruction.

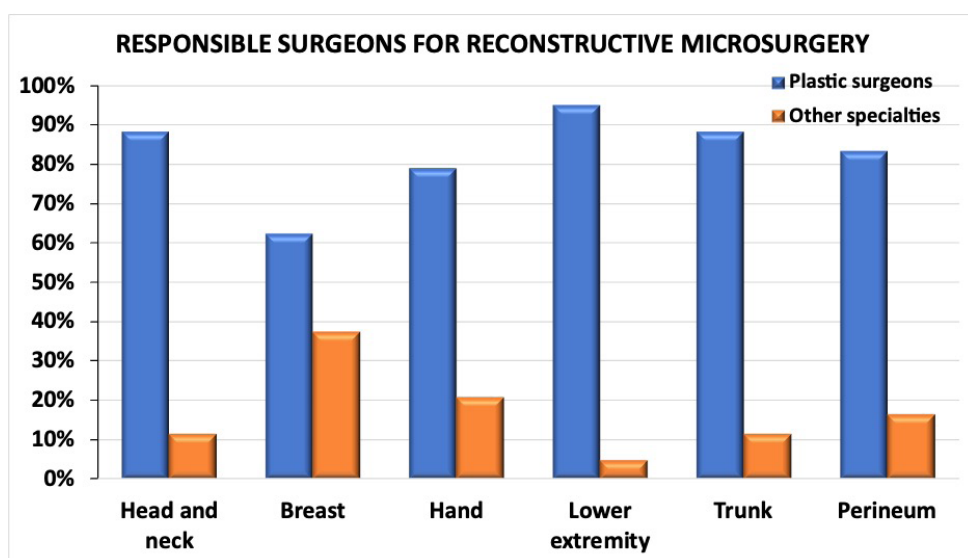


Fig 3. Surgeon responsible for performing microsurgical reconstruction between plastic surgeons and other specialties compared among different regions of reconstruction

axial K-wire was the most commonly used method for bony fixation (78.9%). During the postoperative period, most respondents (89.5%) reported the use of nail plate removal and stab incision at the nail bed if blood-letting was required (Supplementary Fig 3).

Lower extremity reconstruction (no cases in 4.8% of respondents)

For the repair of lower limb defects, the reported methods of choice were loco-regional flap (40%) and skin graft (35%). Free flap surgery was performed in only 10% of cases, and the ALT free flap was used in 53.3%. Perforator/propeller flap was used in 15% of lower extremity cases (Supplementary Fig 4).

Trunk reconstruction (no cases in 42.9% of respondents)

Loco-regional flaps, such as the rectus abdominis myo-cutaneous flap, the omental flap, and the internal oblique muscle flap, were reported to be preferred reconstruction techniques (46.7%), followed by skin grafting (33.3%). Free flap (flap of choice was the ALT free flap) and keystone/propeller flap were both used in 6.7% of cases. About 6.7% of respondents performed laparoscopy-assisted component separation (LACS) for abdominal wall reconstruction (Supplementary Fig 5).

Perineum reconstruction (no cases in 42.9% of respondents)

Most cases were performed by plastic surgeons

(83.3%), and loco-regional flap was the reconstructive method of choice (64.3%), followed by skin grafting (35.7%) (Supplementary Fig 6).

Lymphatic reconstruction (no cases in 66.7% of respondents)

The number of lymphatic reconstruction cases per year among our respondents was 0 cases in 66.7%, 1 to 3 cases in 14.3%, and 7 to 10 cases in 14.3%. The majority of cases (66.7%) were performed using non-microsurgical techniques, such as Charles procedure or liposuction. The methods most commonly used for investigation and diagnosis of lymphedema were of circumferential measurement of the affected limb (44.8%), lymphoscintigraphy (27.6%), and indocyanine green (ICG) lymphography with infrared camera (17.2%) (Supplementary Fig 7).

Microsurgical learning experience during the residency/fellowship training program

During their 3 years learning in our division, about half of trainees participated in more than 30 microsurgical reconstruction cases (31 to 50 cases [28.6%], and more than 50 cases in 23.8%). Regarding the replantation procedure, most trainees had experience with more than 5 cases [6 to 10 cases (38.1%), 11 to 15 cases (19%), and 16 to 20 cases (19%), respectively] (Supplementary Fig 8).

Most respondents reported that the microsurgical reconstruction training and experience that they received at our center positively influenced their real-life practices

and surgical outcomes (moderate positive influence in 57.1%, and marked positive influence in 33.3%). In contrast, the factors that were reported to negatively influence having to perform microsurgery in routine clinical practice included insufficiency of resources and personnel (29.1%), excessive workload (27.3%), and long operative time (23.6%) (Fig 4).

In the final part of the survey, our respondents were given an opportunity to suggest ways that the microsurgical learning experience can be improved in terms of take-aways that can be used improve skills for real-life clinical practice after graduation. Those suggestions included having a good objective method for assessing microsurgical practices (27.7%), increasing the volume of practice on animal model (25.5%), and an appropriate number of microsurgery cases to gain necessary experience (25.5%) (Fig 5).

DISCUSSION

Thailand has approximately ten medical schools that train and graduate about 25 plastic surgeons each year. Our center is Thailand's largest medical school, and we normally graduate 5 plastic surgeons each year or about one-quarter of all plastic surgeons that graduate each year in Thailand. Data from our questionnaire revealed that more than ninety percent of our graduates that completed their plastic surgery training during the study period work in academic or non-academic government hospitals. The questionnaire response rate in this study was a high 87.5%, and nearly half of those (47.6%) answered all of the questions. So, the outcomes of this study might

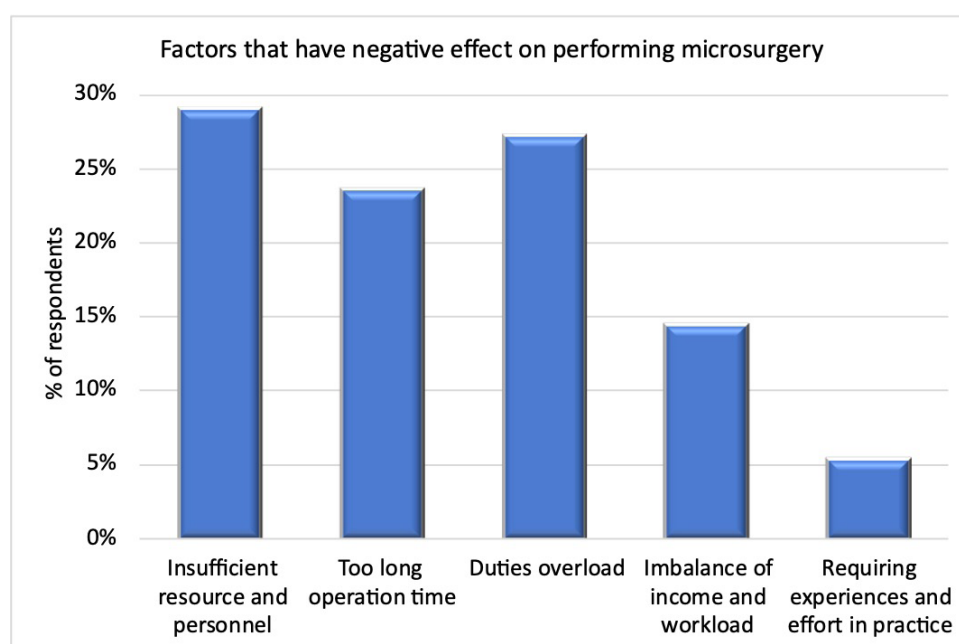


Fig 4. Factors that negatively influence having to perform microsurgery in routine clinical practice

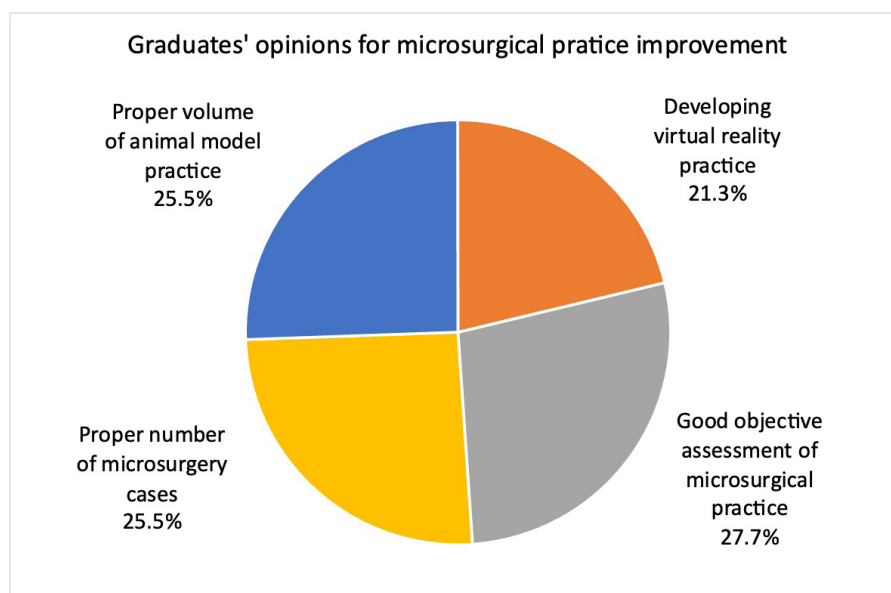


Fig 5. Suggested ways to improve the microsurgical learning experience during the plastic surgery training program

be thought to reflect the current situation relative to reconstructive surgery and reconstructive microsurgery among junior plastic surgeons in Thailand.

Our results showed that approximately 82.7% of all kinds of surgical reconstructions were performed by plastic surgeons, and that the 3 most frequent regions requiring reconstruction were lower extremity region (95.0%), head and neck region (88.2%), and trunk region (88.2%) (Fig 3). This data might guide us in how we can improve training so that our graduates will be better prepared for the real-life requirements that Thai plastic surgeons most often need after graduation from training.

The questionnaire data also revealed insufficient resources and personnel (29.1%), excessive workload (27.3%), and long operative time (23.6%) as the factors that most negatively influence having to perform microsurgical reconstruction. Moreover, 38% of our respondents reported having no microsurgery cases, and 95.2% of those who did perform microsurgery did so less than 20 times per year. The finding of our respondents having to perform no or minimal microsurgical procedures adversely influences the development of experience that is needed to obtain a high level of competence in microsurgical reconstruction.

About 90% of respondents reported that the experience gained in reconstructive microsurgery during residency/fellowship training had a substantial positive impact on their real-life practices and surgical outcomes. Our respondents also suggested the following ways that we might improve the microsurgery training: having a good objective method for assessing microsurgical practices (27.7%), increasing the volume of practice on animal model

(25.5%), and participating in an appropriate number of microsurgery cases to gain necessary experience (25.5%). Even though our survey may have some limitations, such as recall bias and the generalizability of the data, we believe this data provides a foundation from which we can begin a process of improvement in microsurgical reconstruction training for plastic surgery residents and fellows at our center. Moreover, knowing the regions of the body most operated upon may guide us in providing more specific training for high prevalence procedures. Importantly, these data also provide some insights into other types of challenges that plastic surgeons face after they enter clinical practice in the Thai public healthcare system. Lastly, in addition to this data benefiting the Division of Plastic Surgery, Department of Surgery, Faculty of Medicine Siriraj Hospital, Mahidol University, this data may also be of some benefit to the Society of Plastic and Reconstructive Surgery of Thailand and the Thailand Ministry of Public Health relative to the challenges that junior plastic surgeons encounter during the early period of their career path.

CONCLUSION

Reconstructive microsurgery was found to be a challenging procedure for many junior-level plastic surgeons that graduated from our center. No microsurgery cases or a low volume of cases limits a surgeon's ability to develop needed skills. Important improvements in the microsurgery training course were also recommended. Enhancements in the microsurgery training course taken by residents and fellows may improve surgeon confidence, skill, and experience for performing microsurgical reconstruction.

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Conflict of interest declaration

The authors declare no personal or professional conflicts of interest relating to any aspect of this study.

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This was an unfunded study.

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Validity and Reliability of the Thai version of the International Consultation on Incontinence Questionnaire – Female Lower Urinary Tract Symptoms Long Form (ICIQ-FLUTS LF) and Its Correlation with the IPSS

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ABSTRACT

Objective: Incontinence Modular Questionnaire on Female Lower Urinary Tract Symptoms Long form (ICIQ-FLUTS LF) is a robust psychometric tool to assess the severity of lower urinary tract symptoms (LUTS) in women. A Thai language version of the ICIQ-FLUTS LF is available, but it had not been validated yet. This study aimed to validate the ICIQ-FLUTS LF questionnaire in Thai and to identify the correlation between the ICIQ-FLUTS LF and the IPSS.

Materials and Methods: We recruited 130 females, 50 with LUTS were recruited from patients visiting the Urology Clinic to assess the test with known group validity. They completed the ICIQ-FLUTS LF twice, two weeks apart, and the IPSS once. Meanwhile, 80 without LUTS (control group) were recruited from relatives of the patients to increase the consistency of the statistical analysis, completed the ICIQ-FLUTS LF. Then validity and reliability were determined using statistical analysis.

Results: Convergent validity showed a moderate correlation between ICIQ-FLUTS LF and IPSS for both storage and voiding symptoms, with Pearson's correlation coefficient 0.49, 0.66; $P < 0.001$, respectively. Construct validity, using the Wilcoxon signed-rank test, demonstrated statistically significant difference between the target group and the control group ($P < 0.001$). The Thai version of the ICIQ-FLUTS LF showed good internal consistency, with Cronbach's alpha coefficients 0.76-0.79 and Test-retest reliability strong, with weighted kappa values 0.63 to 0.90.

Conclusion: The Thai version of the ICIQ-FLUTS LF shows good validity and reliable measures of females with LUTS, and it is simple to use. This questionnaire in the Thai version can be used in clinical practice and academic research.

Keywords: Lower urinary tract symptoms; Female LUTS; ICIQ-FLUTS LF; validate questionnaire (Siriraj Med J 2024; 76: 262-271)

INTRODUCTION

The International Continence Society (ICS) defined lower urinary tract symptoms (LUTS) as symptoms related to the lower urinary tract. The symptoms may originate from the bladder, urethra, prostate (men) and/

or adjacent pelvic floor or pelvic organs, or from similarly innervated anatomy, e.g., lower ureter.¹ LUTS commonly occur in patients who have pathological lower urinary tract organs, which include storage symptoms, voiding symptoms and post-micturition symptoms. LUTS are

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not life-threatening but can negatively affect quality of life, leading patients to seek treatment. Sometimes, if found together with red flag signs such as hematuria, LUTS can be symptoms of dangerous diseases like bladder cancer.² Physicians should investigate the causes of the symptoms because various pathologies, for example, overactive bladder or vesical stone, can cause LUTS in women. Many tools have been developed to help physicians diagnose the disease, assess LUTS severity, and guide appropriate treatment, but they have some limitations for use in daily clinical practice and research. The International Prostate Symptoms Score (IPSS) is one of those tools. It is a questionnaire which is widely used to assess the severity of LUTS in both males and females. However, the IPSS was originally developed to assess LUTS in men with benign prostatic hyperplasia and does not have a module about incontinence which is an important and the most bothersome symptom.² Moreover, some important questions for evaluating female LUTS are not included in the IPSS. Therefore, in the past, urologists lacked of good questionnaire to assess all varieties of aspects of LUTS in females.

The International Consultation on Incontinence (ICI), which is sponsored by the WHO, developed a fully validated international standard questionnaire for lower urinary tract dysfunction. It includes modules to assess pelvic problems, is applicable to clinical practice and to research, and allows cross-comparisons.³ Furthermore, the questionnaires for assessing LUTS have been designed with consideration for gender differentiation.

The International Consultation on Incontinence Modular Questionnaire on Female Lower Urinary Tract Symptoms long form (ICIQ-FLUTS LF) is a high-quality robust questionnaire of the ICIQ series. It was created to evaluate the severity of LUTS in women, and it can be used throughout the world for both clinical practice and research. The questions are simple, easy to understand, and can be self-completed by the patient. ICIQ-FLUTS LF has been translated and validated in various languages, for example, Tamil and Sinhala. In Thailand, sixty-six million people use Thai for daily life and as the official language.⁴ Recently, patients with LUTS in Thailand either receive an overestimated or underestimated evaluation of severity due to lacking of a standardized tool to help guide the clinical practitioner in accurate diagnosis and such a tool has not been realized yet. Moreover, Thai urologists lack of well-validated questionnaires in Thai for evaluating LUTS specifically tailored for females. Leading to inadequate assessment of the severity, causes, and efficacy of the treatment of LUTS in Thai women. To date, the ICIQ-FLUTS LF is available in Thai but it

has not been validated yet. This study aimed to validate the ICIQ-FLUTS LF questionnaire in the Thai language and to identify the correlation between ICIQ-FLUTS LF and IPSS. We have chosen the IPSS as the comparative questionnaire due to its widely and long-standing usage, simplicity, and has been validated in Thai (21). Moreover, IPSS consists of questions concerning storage, voiding, and postmicturition symptoms, which are somewhat similar to those in the ICIQ-FLUTS LF, albeit with less detail compared to the latter.

MATERIALS AND METHODS

This is a prospective study to evaluate the validity and reliability of the ICIQ-FLUTS long form questionnaire. Permission was granted from the ICIQ Development Group, Bristol Urological Institute to translate into Thai and adapt the questionnaire. The Research Ethics Committee of the Faculty of Medicine, Thammasat University approved the experiment. All participants provided signed informed consent.

Participants

The participants were divided into two groups, the target group and the control group. For questionnaire validation, the optimal number of participants in the target group was 50. During January to December 2023, we recruited 130 female participants, 50 with LUTS for the target group and 80 without relevant symptoms for the control group. Having 80 participants in the control group increased the consistency of the statistical analysis.⁵ To assess the test in a population with known group validity, we recruited females with LUTS from patients visiting the Urology Clinic of Thammasat University Hospital, Pathum Thani, Thailand. The inclusion criteria were (a) age 18 years or older, (b) chief complaint of lower urinary tract symptoms, and (c) ability to read and understand Thai language. The exclusion criteria were (a) unable to answer the questionnaire twice with an interval of two weeks and (b) diagnosed with urinary tract calculi, urinary tract infection or urinary tract cancer.

For the control group, we recruited participants from relatives of the patients at the urology clinic. The inclusion criteria were (a) age 18 years or older, (b) no history of lower urinary tract symptoms, (c) no history of lower urinary tract disease, and (d) ability to read and understand Thai language.

We took note of the potential of bias in recruiting the population. In control group, the participants were recruited from the relative of the visiting patients in outpatient department. Usually, the caretaker or relative

accompanying patients were younger of age than patients themselves. But overall the method of recruiting still be able to achieve randomization to eliminate the potential occurrence of bias.

Instrument

ICIQ-FLUTS LF is an instrument to evaluate in females the severity of symptoms and the quality of life associated with LUTS. The questionnaire has 18 items with two questions in each item. The first question asks about the severity of LUTS using a Likert scale (with 0 being the least and 4 the most severe). The other questions allow participants to rate their quality of life between 0-10, where 0 means “not bothersome at all” and 10 means “very bothersome.”

This study also uses the International Prostate Symptom Score (IPSS) for comparison to determine the validity of the ICIQ-FLUTS LF. The IPSS consists of 7 questions related to lower urinary tract symptoms. The IPSS is a validated, reproducible scoring system which has long been used worldwide to assess disease severity. Both questionnaires are self-completed by subjects.

Procedure

All participants completed their questionnaires at Thammasat University Hospital and provided their ages as demographic data. Participants in the target group completed both the ICIQ-FLUTS LF and the IPSS questionnaires. Participants in the control group

completed only the ICIQ-FLUTS LF. For test-retest reliability, all participants in the target group completed the questionnaires again after two weeks (Fig 1).

Statistical analysis

The convergent validity (how closely a test is related to other tests that measure the same or similar constructs) was determined by comparing the ICIQ-FLUTS LF scores of the target group with a known validated questionnaire. In this study we used the International Prostate Symptom Score (IPSS) as the comparison test. The comparisons were performed using Pearson’s correlation.

The construct validity (a parameter that defines how well a test measures what it is intended to measure) was determined by comparing the ICIQ-FLUTS LF scores of the target group with the ICIQ-FLUTS LF scores of the control group. In order to easily compare between the target group and the control group, we organized the questions in the questionnaire into six subscales which were storage, voiding, incontinence, bladder pain, post micturition, and ability to stop voiding. The comparisons were performed using the Wilcoxon signed-rank test.

The internal consistency (a parameter that verifies correlations between items within a subscale or domain) was assessed by using Cronbach’s alpha coefficients. The assessment was done in each domain of the instrument. If Cronbach’s alpha coefficients were between 0.7 and 0.95, the instrument was considered to have good internal consistency.

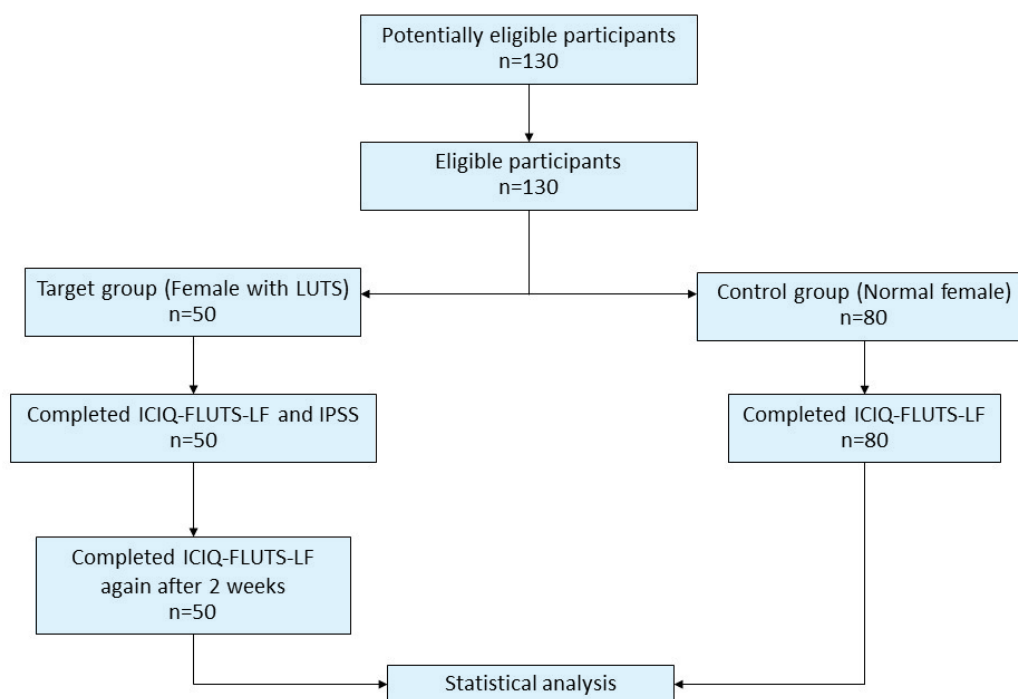


Fig 1. Flow of participants through the study

The test–retest reliability (a property of producing repeated measurements that are consistent) was verified by having the participants of the target group answer the questionnaire twice with an interval of 2 weeks between the evaluations. We calculated test-retest reliability by using weighted kappa (κ).

STATA statistical Software Version 15 (StataCorp, College Station, Texas) was used for data analysis, with P-value of 0.05 considered statistically significant.

RESULTS

Demographic data

The mean age was 54.9 years in the LUTS group and 40.4 years in the control group. The difference was statistically significant, as shown in [Table 1](#).

For the three most common diagnosis in the LUTS group, overactive bladder was the highest at 30 (60%), followed by nocturnal polyuria at 7 (14%), and pelvic organ prolapse at 5 (10%).

Construct validity

The differences between the median ICIQ-FLUTS LF scores of the LUTS group and those of the control group were statistically significant ($p < 0.001$) for all six subscales, as shown in [Table 1](#).

Convergent validity

Convergent validity between ICIQ-FLUTS LF and IPSS was evaluated with voiding symptoms and with storage symptoms. The Pearson's correlation coefficient

for voiding symptoms was 0.66 ($P < 0.001$) (moderate correlation) ([Fig 2](#)), and for storage symptoms it was 0.49 ($P < 0.001$) (moderate correlation) ([Fig 3](#)).

Reliability

Internal consistency

Internal consistency was assessed using Cronbach's coefficient alpha score, which ranged from 0.76 to 0.79 for the 18 questions ([Table 2](#)).

Test–retest reliability

Test–retest reliability was assessed by using weighted kappa, which ranged from 0.63 to 0.90 for the 18 questions ([Table 2](#)).

Correlation between each of questions in each module (storage, voiding, and incontinence)

For the correlation between each of questions about storage symptoms, each of questions in this module showed weak to moderate correlation. Nocturia has a moderate correlation with urgency ($r = 0.44$) but weak correlation with the frequency (0.24) as shown in [Table 3](#). For voiding symptoms, hesitancy demonstrated moderate correlation with straining to void ($r = 0.53$) but weak correlation with others. Also, intermittency showed moderate correlation with dysuria ($r = 0.58$) whereas showed weak correlation with others ([Table 4](#)). For incontinence symptoms, most of the questions in this group demonstrated moderate to good correlation between each other ($r = 0.41-0.63$) as shown in [Table 5](#).

TABLE 1. Construct validity between females with LUTS and the control group.

ICIQ-FLUTS	Control group (N=80)	LUTS group (N=50)	p-value
Age, year, mean (SD)	40.4 (15.8)	54.9 (15.2)	< 0.001
Storage score, median (IQR)	2 (1-3)	5 (4-8)	<0.001
Voiding score, median (IQR)	0 (0-2)	4.5 (2-7)	< 0.001
Incontinence score, median (IQR)	0 (0-2)	4 (1-6)	<0.001
Bladder pain score, median (IQR)	0 (0-1)	1 (0-2)	<0.001
Post-micturition score, median (IQR)	0 (0-1)	1 (0-2)	<0.001
Ability to stop urine flow score, median (IQR)	0 (0)	1 (0-2)	0.028

Abbreviation: N, number; SD, standard deviation; IQR, interquartile range

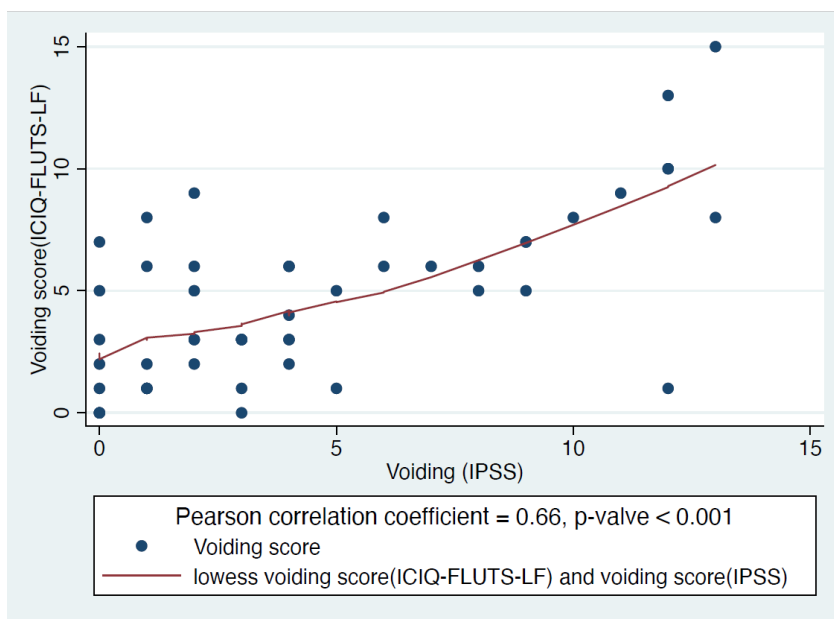


Fig 2. Convergent validity demonstrated in the Pearson’s correlation coefficient between ICIQ-FLUTS LF and IPSS in voiding symptoms score.

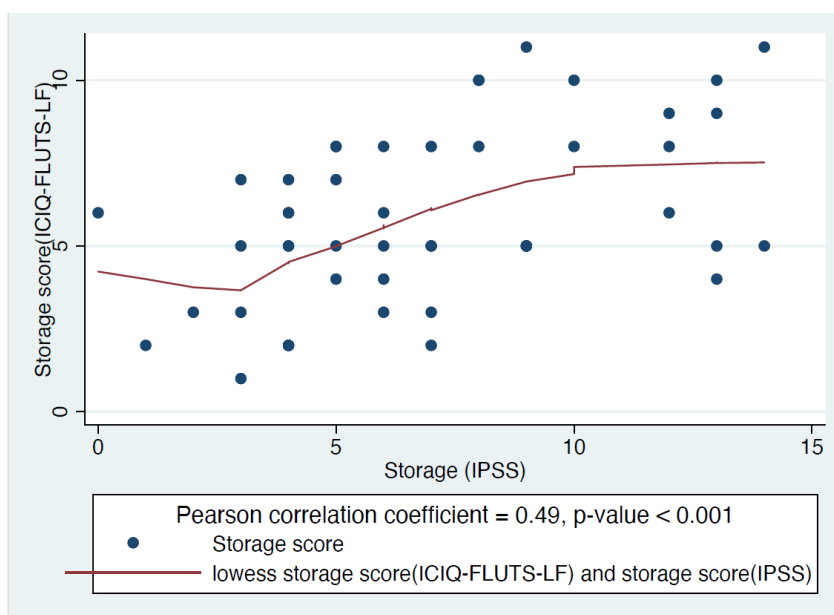


Fig 3. Convergent validity demonstrated in the Pearson’s correlation coefficient between ICIQ-FLUTS LF and IPSS in storage symptoms score.

DISCUSSION

Symptoms caused by urinary tract diseases are common in females of all ages. The EPIC study demonstrated a high prevalence of LUTS in women; 59.2% of women had storage symptoms, 19.5% had voiding symptoms, and 14.2% had post-micturition symptoms. The prevalence of symptoms increased with age.⁶ Specific co-morbidities such as history of vaginal delivery or hysterectomy, post-menopausal status, high BMI, arthritis, depression, hypertension, and neurological conditions are also associated with female LUTS.⁸ Women experience lower urinary tract pain more than men. Many patients seek treatment for LUTS, but current management cannot improve the symptoms.⁷ The most reported risk factor for LUTS in both males and females is increasing age, which this study demonstrated as well. Most previous

studies examining prevalence, risk factors, and comorbid conditions associated with LUTS used the Bristol Female LUTS (BFLUTS) questionnaire for women. A more expansive view, including a broader collection of symptoms would improve clinical recognition and management of LUTS.⁹ Female LUTS have been significantly associated with reduced work productivity (OR 1.11), presenteeism (OR 1.10), and activity impairment (OR 1.11).¹⁰

Although several questionnaires have been developed to measure varying aspects of LUTS, no symptom index has been generally accepted, and no single tool can evaluate all aspects of LUTS in women. An ideal questionnaire should determine the cause of the problem, the frequency and extent of symptoms, and the impact on patient’s activities and well-being. It should be inexpensive. It should not require invasive studies. It should track treatment

TABLE 2. Internal consistency (demonstrated in Cronbach's coefficient alpha score) and Test-retest reliability (demonstrated in weighted kappa value) in females with LUTS.

The question in an original version (English)	The question in Thai version	Cronbach's coefficient alpha scores (N=50)	Weighted kappa (κ) (N=50)
2. How often do you pass urine during the day?	ในแต่ละวัน คุณถ่ายปัสสาวะบ่อยแค่ไหน	0.79	0.75
3. During the night, how many times do you have to get up to urinate, on average?	ในตอนกลางคืน คุณจำเป็นต้องลุกขึ้นมาถ่ายปัสสาวะโดยเฉลี่ยเป็นจำนวนกี่ครั้ง	0.77 0.78	0.89 0.80
4. Do you have a sudden need to rush to the toilet to urinate?	คุณจำเป็นต้องรีบวิ่งเข้าห้องน้ำเพื่อไปปัสสาวะหรือไม่		
5. Does urine leak before you can get to the toilet?	คุณมีอาการปัสสาวะเล็ดก่อนที่จะไปถึงห้องน้ำหรือไม่	0.78	0.79
6. Do you have pain in your bladder?	คุณมีอาการปวดกระเพาะปัสสาวะหรือไม่	0.77	0.90
7. How often do you leak urine?	คุณปัสสาวะเล็ดบ่อยแค่ไหน	0.77	0.78
8. Does urine leak when you are physically active, exert yourself, cough or sneeze?	คุณมีอาการปัสสาวะเล็ดในเวลาที่มีการเคลื่อนไหว ขยับร่างกาย, ออกแรง, ไอหรือจามบ้างหรือไม่	0.76	0.90
9. Do you ever leak urine for no obvious reason and without feeling that you want to go?	คุณมีอาการปัสสาวะเล็ดโดยไม่มีสาเหตุที่แน่ชัด และโดยที่ไม่รู้สึกปวดปัสสาวะบ้างหรือไม่	0.76	0.63
10. How much urinary leakage occurs?	คุณมีปัสสาวะเล็ดในปริมาณเท่าใด	0.77	0.79
11. Is there a delay before you can start to urinate?	มีการหน่วงเวลาก่อนที่คุณจะเริ่มถ่ายปัสสาวะหรือไม่	0.76	0.78
12. Do you have to strain to start urinating?	คุณต้องเบ่งเพื่อที่จะถ่ายปัสสาวะหรือไม่	0.76	0.80
13. Do you stop and start more than once while you urinate?	ในขณะที่คุณถ่ายปัสสาวะ คุณต้องหยุดและเริ่มใหม่มากกว่าหนึ่งครั้งหรือไม่	0.76	0.80
14. Do you leak urine when you are asleep?	คุณมีปัสสาวะเล็ดขณะนอนหลับหรือไม่	0.77	0.80
15. Would you say that the strength of your urinary stream is...	คุณคิดว่าความแรงในการถ่ายปัสสาวะของระบบทางเดินปัสสาวะของคุณนั้น...	0.78	0.74
16. Have you ever blocked up completely so that you could not urinate at all and had to have a catheter to drain the bladder?	คุณเคยมีอาการทางเดินปัสสาวะถูกอุดกั้นอย่างสิ้นเชิงจนไม่สามารถปัสสาวะได้เลย และต้องมีการเสียบสายสวนเพื่อระบายปัสสาวะจากกระเพาะปัสสาวะหรือไม่	0.79	0.78
17. Do you have a burning feeling when you urinate?	คุณมีอาการปวดแสบปวดร้อนเวลาปัสสาวะหรือไม่	0.77	0.89
18. How often do you feel that your bladder has not emptied properly after you have urinated?	คุณรู้สึกว่าปัสสาวะไม่หมดหลังจากที่คุณถ่ายปัสสาวะบ่อยครั้งแค่ไหน	0.78	0.78
19. Can you stop the flow of urine if you try while you are urinating?	คุณสามารถหยุดการไหลของปัสสาวะในระหว่างที่คุณกำลังปัสสาวะได้หรือไม่	0.77	0.83

TABLE 3. The correlation matrix demonstrated in the Pearson’s correlation coefficient values between each of questions about the storage symptoms.

	Question 2	Question 3	Question 4
Question 2	1		
Question 3	0.2488	1	
Question 4	0.2081	0.4416	1

TABLE 4. The correlation matrix demonstrated in the Pearson’s correlation coefficient values between each of questions about the voiding symptoms.

	Question 11	Question 12	Question 13	Question 15	Question 16	Question 17
Question 11	1					
Question 12	0.5312	1				
Question 13	0.372	0.2728	1			
Question 15	0.3012	0.492	0.1431	1		
Question 16	0.2008	0.4468	0.2024	0.3536	1	
Question 17	0.2798	0.2731	0.5815	0.1398	0.0922	1

TABLE 5. The correlation matrix demonstrated in the Pearson’s correlation coefficient values between each of questions about the incontinence symptoms.

	Question 5	Question 7	Question 8	Question 9	Question 10	Question 14
Question 5	1					
Question 7	0.3089	1				
Question 8	0.4174	0.4649	1			
Question 9	0.3836	0.2435	0.6366	1		
Question 10	0.3786	0.2992	0.6143	0.2583	1	
Question 14	0.2481	0.3516	0.6102	0.6333	0.2236	1

outcome. It should be easy for the general population to use. And it should be relevant to clinical practice. Paul Abrams stated four characteristics of good symptom questionnaires “ (1) The questionnaire should be facile; (2) Each item of the questionnaire should have a known causal relationship to the condition being measured; (3) The score should help determine appropriate therapeutic options; (4) Use of the questionnaire should directly improve patient management, and this effect should be demonstrable”.¹¹

The International Prostate Symptom Score (IPSS) is a screening tool commonly used by urologists to evaluate and monitor LUTS in both males and females; however, it was originally developed and validated to assess treatment efficacy in men with benign prostatic hyperplasia. Lower urinary tract pathology differs between males and females, particularly incontinence and urgency. The IPSS excludes urinary incontinence from the questionnaire. Advantages of IPSS are that it is simple to use, is short, and has severity cut-off levels. However, some important questions for evaluating female LUTS are not included in the IPSS, so supplementary questionnaires such as LUTS tool, BFLUTS, etc. were created to better assess female LUTS.¹²

A population study used the ICIQ-FLUTS (short form) to investigate the prevalence of LUTS in nulligravid women. This helped researchers understand how women not seeking care for LUTS respond to the questions. Good tools are necessary for high quality research regarding epidemiology, diagnosis and management of LUTS.¹³ In comparison to recent validation of the study of ICIQ-FLUTS short form (22), this questionnaire has 12 items instead of 18 items from ICIQ-FLUTS long form. One of its strengths is the ability to be completed within a short period of time, making it less burdensome to complete compared to the long form. Though the study itself mentioned that its lack of the ability to detect changes of clinical status is the one such limitation that the study has.

The ICIQ-FLUTS LF consists of the 18 items that evaluate frequency, nocturia, nocturnal enuresis, urgency, urge urinary incontinence, frequency of urinary incontinence, stress incontinence, unexplained urinary incontinence, amount of urinary leakage, hesitancy, straining to start urination, intermittency, nocturnal enuresis, strength of stream, urinary retention, dysuria, incomplete emptying, ability to stop urine flow, and bladder pain. All of these topics are relevant to lower urinary tract symptoms and causes of LUTS in women.³

This is the first study to assess the validity and reliability of ICIQ-FLUTS long form in the Thai language.

We demonstrated a moderate correlation between ICIQ-FLUTS LF and IPSS. Both questionnaires evaluate lower urinary tract symptoms, but they have different subdomains, especially in the domains of urinary incontinence and bladder pain. Therefore, their results should correlate to some degree, i.e., they should share the same general concept but not be identical. For reliability, we found good internal consistency for the ICIQ-FLUTS LF; Cronbach alpha ranged 0.76-0.79, which was similar to previous studies. For test-retest reliability, kappa values for individual items ranged from 0.63 to 0.90, indicating adequate reliability, which was also similar to previous studies.¹⁴⁻²⁰ The Cronbach alpha and kappa values in our study were lower than in some previous studies. This might be because some previous studies collected data in specific populations; for example, the Tamil version collected data in pelvic organ prolapse and incontinence patients. LUTS in these groups would differ more from their control groups than in our study, which tested general female LUTS patients.

The clinical significance of the observed correlations and reliability measures in this study may be exemplified by the specific characteristics of the target group participants experiencing LUTS. Among them, 30 were diagnosed with overactive bladder, 7 exhibited nocturnal polyuria, and 5 presented with pelvic organ prolapse.

A limitation of our study was lack of other demographic data such as parity, menopausal status, pelvic organ prolapses, underlying diseases, education status, etc., which would yield more clarity and information regarding both groups. Further studies should include this demographic data and a wide range of ages and education levels of participants to provide more accurate information.

Another limitation was this study recruited the participants from women experiencing LUTS who visited the Urology clinic to conduct a known group validity test and recruited the relative of patients as the control group. This haphazard sampling might cause some selection bias and may affect the study's findings. For example, the majority of participants in the control group were younger compared to those in the target group, resulting in a lower score of LUTS than observed in the target group.

The correlation coefficients observed between each question in this study demonstrated a range from weak to moderate correlation. It could be because the questions in the ICIQ-FLUTS LF covering all aspects of the female LUTS. Meanwhile, this study recruited participants who present with LUTS from various diagnosis, such as overactive bladder and stress incontinence. Consequently, this broader spectrum of conditions might lead to lower

correlation values between questions compared to studies focusing on specific patient groups. Therefore, future research aimed at further validating these questionnaires should consider recruiting larger participant cohorts and focusing on specific groups of Lower Urinary Tract Symptoms, such as overactive bladder or stress urinary incontinence. This targeted approach will enhance the applicability and effectiveness of these instruments.

CONCLUSION

Assessing Lower Urinary Tract Symptoms can be challenging, but specialized tools can facilitate in accurate diagnosis and guide appropriate treatment decisions. This is particularly crucial in the context of the Thai population, where access to foreign language versions may be limited. The findings of this study affirm that the ICIQ-FLUTS LF in Thai can be aid in diagnosis and treatment LUTS for Thai women. The Thai version of the ICIQ-LUTS LF is a valid and reliable measure of female LUTS, and it is simple to use. The Thai version of this questionnaire can be used in clinical practice and academic research. Using this questionnaire as a standard tool for initial assessment in outpatient department enables patients to easily self-complete it, facilitating clinical practitioners in selecting personalized and optimal treatment approaches for each individual.

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Author contribution

Both authors are involved in the idea of the study, conceptualization of hypothesis, research operation, research design, data collection, data analysis, statistical analysis, data interpretation, discussion of the results, writing the article, critical revision of the article, contribution in manuscript preparation and editing, final approval of the article.

Ethics

All volunteers signed the consent form. The research was approved by the Human Research Ethics Committee of Thammasat University (Medicine): 067/2566. The protocol number MTU-EC-SU-0-002/66.

Conflict of interest

Both authors have no conflict of interest.

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Emotion Regulation Mediates Functional Impairment in Thai Children with Attention-deficit/hyperactivity Disorder: A Cross-Sectional Study

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ABSTRACT

Objective: The study investigated the potential mediating effects of emotion regulation and emotion lability/negativity in the relationship between attention-deficit/hyperactivity disorder (ADHD) symptoms and functional impairment while also examining the associations between ADHD symptoms, emotion regulation, and impaired functioning in different life domains among children with ADHD.

Materials and Methods: The clinical sample comprised 118 children diagnosed with ADHD aged 6–12 years. Primary caregivers completed parent reports on symptom severity using the Thai ADHD Screening Scale–Parent Version, assessed emotion regulation and lability/negativity via the Emotion Regulation Checklist, and evaluated functional impairment using the Weiss Functional Impairment Rating Scale–Parent Version.

Results: ADHD symptoms correlated negatively with overall emotion regulation ($r = -0.515, p < 0.01$) and positively with lability/negativity ($r = 0.583, p < 0.01$). Functional impairment exhibited a negative correlation with emotion regulation ($r = -0.649, p < 0.01$) and a positive correlation with lability/negativity ($r = 0.701, p < 0.01$). Elevated ADHD symptoms were linked with increased functional impairment ($r = 0.639, p < 0.01$). The parallel mediational model showed that emotion lability/negativity partially mediated the association between ADHD symptoms and functional impairment ($\beta = 0.282, p < 0.001$), suggesting that ADHD symptoms and emotion lability/negativity indirectly accentuate functional impairment. Thus, heightened ADHD symptoms may exacerbate emotion lability/negativity, contributing to increased functional impairments.

Conclusion: Emotion regulation difficulties, particularly emotion lability/negativity, may serve as significant risk factors. Regular monitoring and targeting these challenges hold promise in alleviating adverse functional outcomes co-occurring with elevated ADHD symptoms.

Keywords: Attention-deficit/hyperactivity disorder; emotion regulation; emotion lability; functional impairments; children (Siriraj Med J 2024; 76: 272-281)

INTRODUCTION

Attention-deficit/hyperactivity disorder (ADHD) is a highly prevalent neurodevelopmental disorder emerging in childhood, with an estimated worldwide prevalence of 5-7% among school-aged children.¹ Its primary features

include a persistent pattern of inattention and hyperactivity/impulsivity that frequently disrupt academic, occupational, and social settings. While symptoms may change with age, approximately 60-85% of individuals continue to experience some residual symptoms in adolescence and

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adulthood.^{2,3} Etiologically, emerging research underscores neuropsychological theories, emphasizing impairments in executive functioning processes and inhibitory control involving emotion self-regulation. This highlights emotion dysregulation as an additional core feature of ADHD that significantly contributes to impaired daily functioning and psychosocial maladjustment.⁴ Emotion regulation deficits have been proposed as potential mediating mechanisms through which ADHD symptoms contribute to various functional issues, ranging from interpersonal relationship problems to an increased risk of developing psychiatric comorbidities if not properly treated.^{5,6}

Difficulties in regulating emotions arise when individuals struggle to control emotional experiences and expressions to optimize functioning effectively, adapt to daily environments, and foster behaviors conducive to achieving their goals.⁷ The literature on ADHD greatly supports the theoretical model linking emotion regulation challenges to deficits in executive inhibitory control and dysregulated attention extending to emotions.⁸ Therefore, children with ADHD experience greater difficulty controlling shifts in emotion (lability), regulating negative emotional responses, recognizing and allocating attention to emotional stimuli, which are often linked with behavioral problems such as frustration, temper outbursts, or reactive aggression.⁹ Additionally, those struggling with emotional regulation often exhibited fewer prosocial behaviors, encountered higher rates of peer rejection, and had an increased the risk of developing negative self-concept, low self-esteem, and self-destructive behaviors.¹⁰ Recognizing transdiagnostic nature of emotion regulation deficits may play a crucial role in understanding the functional consequences suffered by children with ADHD, extending beyond traditional symptoms.⁸

Given the limited research on the underlying mechanistic relationship between ADHD symptoms and functional impairment, exploring these pathways may shed light on emotion regulation processes that could interfere with developing adaptive regulatory strategies for a healthy emotional adjustment, impacting symptom remission and functional improvement throughout treatment interventions. Therefore, in an effort to identify transdiagnostic targets for treatment and facilitate interventions, our primary objectives were to investigate the associations between ADHD symptoms, emotion regulation, and functional impairment in ADHD children. We also aimed to explore how the specific dimension of emotion regulation may mediate the relationship, using a parallel mediational design to simultaneously examine the indirect effects of emotion regulation and emotion lability/negativity.

MATERIALS AND METHODS

Study design and sample

A sample of 121 participants consisted of children aged 6-12 years diagnosed with ADHD. The clinical diagnosis of each participant was assessed by child and adolescent psychiatrists using the criteria specified in the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5).¹ The exclusion criteria included children with severe medical conditions, individuals with caregivers not serving as the primary caregivers for more than 6 months and those unable to complete the questionnaires. The initial assessment included data from 121 participants; however, reported descriptive information and statistical models refer to the 118 participants remaining after the identification and removal of outliers.

Procedures

This cross-sectional study was conducted at the Child and Adolescent Psychiatry outpatient clinic, Department of Psychiatry, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand, between June and July 2023. Participants and primary caregivers were recruited during a regular follow-up visit. All caregivers provided written informed consent and assent to participate was obtained from the children. All questionnaires were completed by caregivers. Medical records were reviewed for patient clinical characteristics. The study protocol was approved by the Siriraj Institutional Review Board (COA no. Si 328/2023).

Measures

Demographic questionnaire

Demographic information including gender, age, and highest education level was collected for the participants. Primary caregivers' demographic data included age, gender, highest education level, monthly household income and marital status.

ADHD symptoms

ADHD symptoms were assessed using the Thai ADHD Screening Scale-Parent Version (THASS) for children aged 6-12, comprising 30 items. The symptoms are encompassed in two primary subsets: hyperactivity/impulsivity (e.g., difficulty controlling behaviors and persistent overactivity, 15 items) and inattentiveness (e.g., difficulty paying attention and sustaining focus, 15 items). Symptom frequency was reported using a 5-point scale, ranging from 0 (never) to 4 (very often). Interpretation was performed using the T-scores with designated thresholds for varying levels of severity. The

questionnaire has good psychometric qualities, including a robust internal consistency ($\alpha = 0.96$), content validity index ≥ 0.80 , and good test-retest reliability ($r = 0.80-0.9$).¹¹ Internal consistency for total symptom severity ($\alpha = 0.91$), hyperactivity/impulsivity ($\alpha = 0.89$), and inattentive subscales ($\alpha = 0.90$) ranged from good to excellent for the current sample.

Emotion regulation

Parents completed the Emotion Regulation Checklist (ERC)¹², a 24-item instrument that evaluates processes integral to adaptive regulation in children aged between 6–12 by capturing two dimensions of emotion regulation: (1) *Emotion regulation subscale (ERC-ER, 8 items)*, which refers to socially appropriate affective displays, emotional self-awareness, empathy, and (2) *Emotion lability/negativity subscale (ERC-LN, 15 items)*, which refers to emotional inflexibility and reactivity, dysregulated negative affect, and mood lability. Items assessing the frequency of developmentally appropriate behaviors in individuals are measured on a Likert scale ranging from 1 (never) to 4 (almost always). Higher composite scores indicate superior overall emotion regulation, with higher scores in the *ER* subscale reflecting greater congruence in affective displays and optimal regulation of emotion arousal within the environments. Higher scores on the *LN* subscale indicate more significant emotion dysregulation and socially incongruent affective displays. The ERC (Thai version) demonstrated adequate internal consistency for both the *ER* subscale ($\alpha = 0.73$) and the *LN* subscale ($\alpha = 0.82$) in a study involving a Thai clinical sample.¹³ The internal consistency for the *ERC* composite ($\alpha = 0.79$), *ER* subscale ($\alpha = 0.67$), and *LN* subscale ($\alpha = 0.78$) ranged from acceptable to good for the current sample.

Functional impairment

The Weiss Functional Impairment Rating Scale–Parent Report (WFIRS–P) is a 50-item parent-rated scale that assesses functional impairment in various domains, including family, academic, life skills, self-concept, social, and risky activities.¹⁴ Each item is measured using a 4-point scale, ranging from 0 (never or not at all) to 4 (very often or very much). Higher total scores equate to greater overall functional impairment, ranging from mild to extreme impaired levels. The psychometric properties of the WFIRS–P (Thai version) have been translated and cross-culturally validated, with excellent internal consistency ($\alpha = 0.98$) and good test-retest reliability ($r = 0.88$) for total and domain scores.¹⁵ The internal consistency was strong in the current sample ($\alpha = 0.90$).

Data analyses

Descriptive statistics, including Pearson's correlation coefficients, were used to describe clinical characteristics and explore relationships among study variables. Partial correlation analyses were additionally performed to examine these relationships while controlling for the potential confounding factors associated with caregivers' characteristics, including age, gender, and highest education. Prior to conducting the mediation analysis, the assumption of independent values was validated with a Durbin–Watson value of 1.85, below the threshold of 2.5. Multicollinearity was assessed using variance inflation factors (VIF) ≤ 10 and tolerance values ≥ 0.10 , and through ensuring that all correlations remained below 0.8. The current study revealed no evidence of multicollinearity, as indicated by diagnostic measures: VIF ranging from 1.13 to 1.68 and tolerance ranging from 0.59 to 0.88.

A parallel mediation analysis was examined, utilizing scores from the emotion regulation subscale and the emotion lability/negativity subscale as mediators and total functional impairment as the independent variable. Additionally, a bootstrapping method of 5,000 bootstrapped resamples was constructed empirically to determine the statistical significance of the total and specific indirect effects (calculated as the product of the regression coefficients for a_1b_1 and a_2b_2 ; Table 4). These mediating indirect effects are considered statistically significant if the upper and lower bounds of the 95% confidence intervals (BootCIs) are entirely above zero.¹⁶

RESULTS

Sample characteristics

The average age of the children was 9.49 years (standard deviation [SD] ± 1.782). Male participants comprised a larger proportion (81.4%) than female participants (18.6%), with most falling into the elementary year category (90.7%). A high percentage of the participants had psychiatric comorbidities (51.7%). All participants received pharmacological treatment for ADHD, with the majority (76.8%) using a single medication (methylphenidate) and a subset using additional medications, including alpha-2 agonists, second-generation antipsychotics, and selective serotonin reuptake inhibitors (Table 1).

Descriptive statistics

Tables 2 & 3 show the descriptive statistics and correlations for all study variables. On average, the sample had a total ADHD symptom score of 59.4 (SD = 7.73), indicating mild symptoms according to age and

TABLE 1. Demographic and clinical characteristics of participants and demographic of primary caregivers.

Demographic characteristic	<i>n</i> (%)
Children	
Age, Mean (SD)	9.59 (1.782)
Gender	
Female	22 (18.6%)
Male	96 (81.4%)
Education level	
Kindergarten	1 (0.8%)
Elementary	107 (90.7%)
Junior high school	10 (8.5%)
Diagnosis	
Pure ADHD	57 (48.3%)
ADHD + comorbidity	61 (51.7%)
Medication status	
Methylphenidate (MPH)	118 (79.2%)
MPH + Alpha-2 Agonists (α 2-AR)	4 (2.7%)
MPH + Selective Serotonin Reuptake Inhibitors (SSRI)	3 (2%)
MPH + Second-Generation Antipsychotics (SGAs)	24 (16.1%)
Caregivers	
Age, Mean (SD)	41.92 (9.05)
Gender	
Female	103 (87.3%)
Male	15 (12.7%)
Highest education	
Below Bachelor	60 (50.8%)
Bachelor	52 (44.1%)
Master	6 (5.1%)
Marital status	
Single	18 (15.3%)
Married	84 (71.2%)
Divorced	12 (10.2%)
Widowed	4 (3.4%)
Monthly Household Income	
< 420 US dollars ⁺	30 (25.4%)
421 – 700 US dollars ⁺	39 (33.1%)
≥ 700 US dollars ⁺	49 (41.5%)

Abbreviation: ADHD = attention-deficit/hyperactivity disorder, ⁺1 US dollar = 35.67 Baht

TABLE 2. Descriptive results of ADHD symptoms, emotion regulation, and functional impairment.

Variable	Mean (SD)
ADHD symptom	
Hyperactive/impulsive	58.01 (8.89)
Inattention	59.13 (7.9)
Total ADHD score	59.4 (7.73)
Severity of ADHD, n (%)	
Symptom not significant	18 (15.3%)
Mild	48 (40.7%)
Moderate	42 (35.6%)
Severe	10 (8.5%)
Total emotion regulation score	64.6 (7.06)
Emotion regulation composite score level, n (%)	
Poor emotion regulation	55 (46.6%)
Good emotion regulation	63 (53.4%)
Emotion regulation score (ER subscale)	24.03 (3.04)
Lability/negativity score (LN subscale)	34.43 (5.42)
Total impairment score	36.53 (15.29)
Impairment level, n (%)	
Mild	59 (50%)
Moderate	28 (23.7%)
Severe	24 (20.3%)
Extreme	7 (6%)

TABLE 3. Mean, standard deviations, observed range, and correlations among study variables (n = 118).

Variable	1	2	3	4	5	6	7
Total ADHD symptom	1.00						
Hyperactive/impulsive symptom	.832**						
Inattentive symptom	.853**	.426**					
Composite ERC	-.515**	-.605**	-.277**				
Emotion regulation (ERC-ER subscale)	-.157	-.201*	-.065	.693**			
Lability/negativity (ERC-LN subscale)	.583**	.676**	.324**	-.914**	-.341**		
Total impairments	.639**	.613**	.469**	-.649**	-.258**	.701**	
Mean	59.40	58.01	59.13	64.60	24.03	34.43	36.53
SD	7.73	8.89	7.90	7.06	3.04	5.42	15.29
Observed range	43-77	33-75	40-77	48-82	18-32	22-50	8-86
Skewness	-.131	-.012	-.061	-.016	.147	.293	.545

*Statistically significant at p-value<.05, **p-value<.01.

TABLE 4. The mediating effects of the parallel mediation model illustrated in Fig 1.

Outcome Model	β	<i>b</i>	SE	<i>p</i>	95%CI		<i>R</i> ²
					LL	UL	
Model without mediators	.639	1.264	.141	<.001	.984	1.544	.4083
Total effect (<i>c</i>)							
X (ADHD) → Y (FI)							
Model with mediators	.351	.695	.149	<.001	.399	.990	.5734
Direct effect (<i>c'</i>)							
X (ADHD) → Y (FI)							
Indirect effect (<i>a</i> ₁ <i>b</i> ₁)	.006	.0116	.015	>.001	-.021	.041	
X (ADHD) → M ₁							
(ER) → Y (FI)							
Indirect effect (<i>a</i> ₂ <i>b</i> ₂)	.282	.558	.051	<.001	.177	.389	
X (ADHD) → M ₂							
(LN) → Y (FI)							
Total indirect effects	.289	.569	.051	<.001	.189	.386	
(<i>a</i> ₁ <i>b</i> ₁ + <i>a</i> ₂ <i>b</i> ₂)							

Abbreviations: *b* = unstandardized coefficient; β = standardized coefficient; SE = standard error; LL = lower limit, UL = upper limit, *R*² = coefficient of determination, X = independent variable; Y = dependent variable; M = mediating variable; ADHD = attention-deficit/hyperactivity disorder, FI = functional impairment, ER = emotion regulation subscale, LN = lability/negativity subscale.

gender norms. The mean score on the emotion regulation composite score was 64.6 (SD = 7.06), suggesting that the sample had good emotion regulation, on average. Furthermore, the emotion regulation subscale showed a mean score of 24.03 (SD = 3.04), and the lability/negativity subscale showed a mean score of 34.43 (SD = 5.42). Overall, the sample had a total functional impairment score of 36.53 (SD = 15.29), indicating moderate impairment in functioning.

Correlations

Pearson's correlations indicated that ADHD symptoms were negatively associated with overall emotion regulation (ERC composite; $r = -0.515, p < 0.01$). Specifically, lability/negativity subscale correlated positively with ADHD symptoms ($r = 0.583, p < 0.01$), while the emotion regulation subscale correlated negatively only with hyperactive/impulsive symptoms ($r = -0.201, p < 0.05$). Functional impairment showed a negative correlation with overall emotion regulation ($r = -0.649, p < 0.01$), and the emotion regulation subscale ($r = -.285, p < 0.1$), and a positive correlation with lability/negativity ($r =$

$0.701, p < 0.01$). Increased ADHD symptoms correlated positively with more significant functional impairment across most domains ($r = 0.639, p < 0.01$), with life skills demonstrating the strongest association with functional impairment, followed by academic and family domains.

After adjusting for caregivers' age, the partial correlation indicated that ADHD symptoms correlated with the lability/negativity ($r = .591, p < 0.01$) and functional impairment ($r = .642, p < 0.01$), while the correlation with the emotion regulation subscale remained insignificant ($r = -.167, p > 0.05$), aligning with observed relationships under caregivers' age. Further investigation showed a negative correlation between emotion regulation subscale and functional impairment ($r = -.260, p < 0.01$), and a positive correlation between lability/negativity and functional impairment ($r = .702, p < 0.01$). Controlling for caregivers' gender, significant correlations persisted between ADHD symptoms and lability/negativity ($r = .590, p < 0.01$) and functional impairment ($r = .640, p < 0.01$), with the emotion regulation subscale correlation remaining insignificant ($r = -.157, p > 0.05$), consistent with observed relationships under caregivers' gender.

The emotion regulation subscale negatively correlated with functional impairment ($r = -.258, p < 0.01$), while the lability/negativity subscale had a positive correlation with functional impairment ($r = .703, p < 0.01$). Similarly, after considering caregivers' highest education, significant correlations were found between ADHD symptoms and the lability/negativity subscale ($r = .582, p < 0.01$) and functional impairment ($r = .643, p < 0.01$). The emotion regulation subscale correlation remained insignificant ($r = -.162, p > 0.05$), in line with observed relationships under caregivers' highest education. The ER subscale negatively correlated with functional impairment ($r = -.286, p < 0.01$), while the lability/negativity subscale had a positive correlation with functional impairment ($r = .705, p < 0.01$). An inspection of zero-order correlations suggested that controlling for caregivers' characteristics, such as age, gender, and education, minimally impacted the relationship strength between these study variables.

Parallel mediation analysis

To identify whether a specific dimension of emotion regulation most accurately explained the relationship between ADHD symptoms and functional impairment, parallel mediational analyses were performed. Initially, we assessed the significance of the indirect effect of ADHD symptoms through emotion regulation and emotion lability/negativity in functional impairment (path a_1b_1 and a_2b_2) (Fig 1). As Table 4 and Fig 1 show, elevated symptoms of ADHD significantly predicted more significant difficulties regulating negative emotions and controlling emotion lability, which, in turn, predicted higher functional impairment. The indirect effects (path $a_2b_2, \beta = 0.282$, Boot 95%CI 0.177, 0.389) from ADHD symptoms to functional impairment through

the mediating effect of the lability/negativity subscale were statistically significant, given that the 95%CIs were entirely above zero. Further, the direct impact of ADHD symptoms on functional impairment (path $c', \beta = 0.3512, p < 0.01$) was significant, suggesting that ADHD children experiencing greater emotional lability and dysregulated negative affects partially mediated the relationship between ADHD symptoms and functional impairment. The direct path had a substantial effect size ($R^2 = 0.4083$), with ADHD symptoms being able to predict 40.83% of the variances in functional impairment. The indirect effect ($R^2 = 0.5734, p < 0.001$) accounted for 57.34% of the variance in both predictors, ADHD symptoms and functional impairment, when mediated by both mediators. However, the relationship between ADHD symptoms and functional impairment was not significantly mediated by the emotion regulation subscale, as specific indirect effects were not statistically significant (path $a_1b_1, \beta = 0.006$; Boot 95%CI $-0.021, 0.041$).

DISCUSSION

The purpose of this study was to examine the relationships between ADHD symptoms, emotion regulation processes (ERC composite), and functional impairment in children with ADHD. As predicted, higher levels of ADHD symptoms were significantly and positively correlated with more impairments in functioning. Specifically, the symptoms of ADHD had a strong positive relationship with impairments in life skills, academic performance, and family functioning. These findings align with existing research showing that a higher proportion of children with ADHD reported impaired functioning compared with typically developing children. These impairments can be attributed to symptoms related to executive dysfunction,

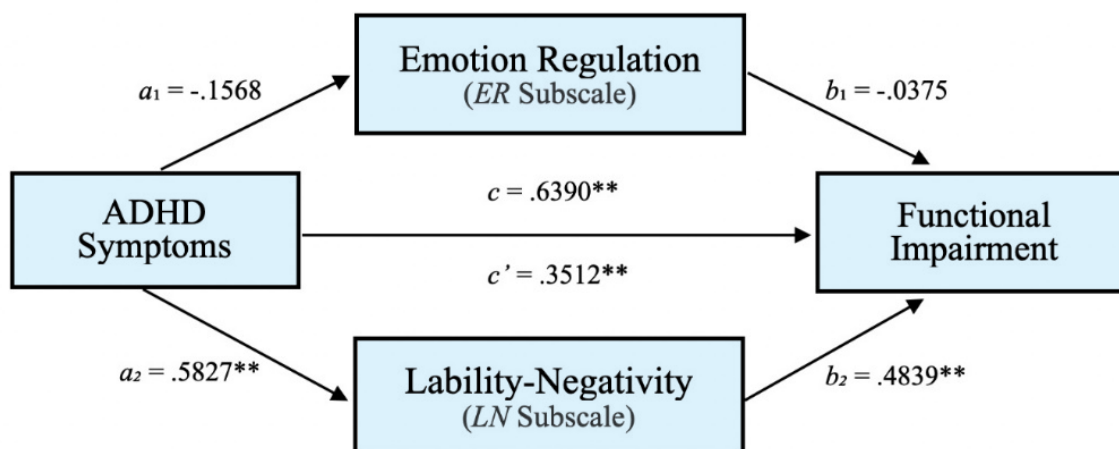


Fig 1. A statistical diagram of ADHD symptoms predicting functional impairment with emotion regulation (ERC-ER subscale) and lability/negativity (ERC-LN subscale) as mediators. ** $p < 0.01$. Coefficients are standardized estimates.

such as deficits in working memory, self-motivation, organization, planning, and time management, and contribute to challenges in acquiring necessary life skills and achieving optimal academic potential, as both areas depend highly on executive functioning.^{17,18}

In our sample, we found a negative correlation between ADHD symptoms and emotion regulation processes (ERC composite). At the same time, lability/negativity displayed a positive association with ADHD symptoms, indicating that heightened ADHD symptoms are linked to greater disinhibition of emotional reactivity and intense shifts in emotional states. These findings might suggest a reciprocal relationship between the tendency to exhibit more ADHD symptoms and challenges in regulating negative emotions or controlling emotional reactivity, which confers a risk of a detrimental impact on functional outcomes. Importantly, even after controlling for potential confounding factors, those correlations remained relatively stable, accentuating the direct impact of ADHD symptoms-particularly those linked with emotion lability/negativity-on functional outcomes in Thai children diagnosed with ADHD.

Notably, parallel mediation analyses examined the causal mechanisms of the emotion regulation and lability/negativity dimensions. They showed that the only significant mediator was the indirect effect of ADHD symptoms on functional impairment through lability/negativity. Thus, children with higher levels of ADHD symptoms may manifest more dysregulated negative, socially incongruent emotions, which, in turn, leads to increased functional deficits. Increased lability/negativity often hinders the inability to sustain a consistent emotional state over time, as this could then be further exacerbated by increasing sensitivity to emotional stimuli. The reduced ability to return to a normal emotional state within a reasonable timeframe can lead to more severe consequences.¹⁹ Based on earlier longitudinal studies, children who are better at managing negative emotions and exhibiting appropriate affective behaviors demonstrate more social competence in peer interactions and prosocial behaviors, ultimately resulting in reduced internalizing symptomatology over time.^{20,21} This perspective underscores the risk associated with difficulties in modulating responses to negative affect, variability of mood lability, and emotional inflexibility, which pose high risks for other problems, including strained parent-child relationships, negative social experiences, and childhood depression.^{20,22,23}

However, contrary to the literature, the indicators of the emotion regulation subscale did not significantly mediate the pathway in our study, which could be partly explained by measurement differences. Our analysis

focused only on appropriate positive emotion expressions, socially congruent behaviors, and empathy toward others as indicators of adaptive emotion regulation. Future research could incorporate more multifaceted aspects of emotion regulation (e.g., emotion recognition and awareness), using diverse instruments and observational measures to better understand a child's emotion regulation processes as manifested in various patterns of difficulty. The present findings underscore the importance of interventions targeting the improvement of emotion regulation deficits in alleviating functional impairment in ADHD children. Evidence-based cognitive behavioral interventions and parent management training have been shown to enhance emotional competence and adaptability in children. These multimodal approaches incorporate emotion-focused coping skills, promoting awareness, understanding, and managing of emotional responses through mindful parenting styles, maternal guidance, modeling positive expressiveness, and cognitive reframing of emotions.^{24,25} Emotion regulation interventions, such as the "Checking the Facts" or "Opposite Action" from Dialectical Behavior Therapy (DBT) skill training²⁶, may specifically target emotion lability and negativity by intentionally identifying emotions that may or may not align with the facts, counteracting action urges with more productive learned options and rehearsing alternative solutions. Acquiring and practicing these set of specific skills can ameliorate a child's emotional dysregulation in response to emotionally triggered situations while also facilitating adaptive, goal-directed behaviors.²⁷

Limitations

A primary limitation of the current study is that the data was derived from a single center and may not fully represent larger patient populations, thus limiting the generalizability of the findings. Future research should incorporate data from multiple centers to ensure a more diverse and representative sample. Second, our study focused on the ongoing effects of difficulties in emotion regulation and functional outcomes among participants who received various pharmacological treatments and interventions and did not capture the initial baseline conditions reflecting the acute effects before treatment. Thirdly, given that all assessments were parental reports and potentially subjected to the possibility of (positive) attributional bias, future research should ensure that correlation analyses between study variables are adjusted, accounting for parental characteristics. Therefore, a multi-informant perspective would be critical for capturing symptoms and conditions in different settings.

CONCLUSION

Understanding the underlying mechanisms linking ADHD symptoms and functional impairment may play a critical role in developing interventions that can effectively target functional challenges in children with ADHD. Our findings suggest that emotion lability/ negativity partially mediated the link between ADHD symptoms and functional impairment ($\beta = 0.282, p < 0.001$), with ADHD symptoms and lability/ negativity indirectly accentuating functional impairment. These findings are consistent with previous research that demonstrated that managing core ADHD symptoms and reducing emotion lability/negativity can play protective roles in reducing the adverse effects of impaired functioning. Therefore, regular monitoring and targeted therapeutic interventions for emotion lability/negativity may be significant priorities in the ongoing effort to improve functional outcomes among Thai children with elevated ADHD symptoms in this age group.

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Conflicts of interest

All authors declare no potential conflicts of interest.

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Role of Resilience in the Relationship between Adverse Childhood Experiences and Behavior Problems among Thai Adolescents in a Province of Southern Thailand: A School-Based Cross-Sectional Study

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ABSTRACT

Objective: This study aimed to investigate the relationship between adverse childhood experiences (ACEs), behavior problems, and resilience among adolescents in Southern Thailand, with a particular focus on the role of resilience in mediating the relationship between ACEs and behavior problems.

Materials and Methods: A paper-and-pencil questionnaire, covering participants' general information, Thai Version of the Adverse Childhood Experiences Questionnaire (ACEs questionnaire), Adolescent Risk Behavior Inventory-12 Items, and Thai Version of the Connor–Davidson Resilience Scale (25-Item CD-RISC), was distributed to 383 senior high school students in a province in Southern Thailand. The data was analyzed using descriptive statistics, correlation analysis, and path analysis.

Results: Out of the 383 students the questionnaire was distributed to, 374 completed the questionnaire, resulting in a response rate of 97.65%. Alarming, 59.36% of the respondents reported experiencing at least one type of ACE. Correlation analysis revealed a significant positive association between ACEs and behavior problems ($r = 0.17, p < 0.01$) and a negative correlation with resilience ($r = -0.19, p < 0.01$). Path analysis demonstrated that ACEs directly influenced behavior problems ($\beta = 0.23, p < 0.01$) and resilience ($\beta = -0.24, p < 0.01$). However, the analysis did not support the hypothesis that resilience mediates the relationship between ACEs and behavior problems.

Conclusion: The findings indicate a troubling prevalence of ACEs among senior high school students in Thailand, likely contributing to current adolescent behavior problems. Although the study's path analysis did not align with prior research, it emphasizes the critical role of resilience in mitigating the adverse effects of ACEs. Therefore, resilience remains a necessary skill in helping adolescents cope with the consequences of ACEs.

Keywords: Adolescent; adverse childhood experiences; behavior problems; resilience (Siriraj Med J 2024; 76: 282-292)

INTRODUCTION

The Centers for Disease Control and Prevention (CDC) in the United States (US) defines adverse childhood experiences (ACEs) as traumatic events or circumstances that can cause lasting emotional harm to children. These events typically occur between birth and age 17¹ and

are categorized into 10 types: emotional abuse, physical abuse, sexual abuse, emotional neglect, physical neglect, household physical violence, household substance abuse, household mental illness, parental separation/divorce, and an incarcerated household member.² Studies have shown that individuals who have experienced ACEs are

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at an increased risk of substance abuse, mental health issues, and even physical illnesses, including heart disease and cancer.³

Research conducted in the US from 2011 to 2014 effectively underscores the extensive nature of this issue, revealing that a substantial 61.55% of individuals aged 18 years old and older in the US had encountered at least one ACE.⁴ Furthermore, scholarly inquiries in East Asian nations, including in locations such as Singapore,⁵ China,⁶ and Thailand,^{7,8} have consistently revealed congruent patterns. These findings provide compelling evidence that the prevalence of ACEs shows a remarkable degree of uniformity across a diverse array of cultural contexts.

In addition to the ACEs that exhibit associations with physical and mental health concerns, these experiences often demonstrate a pronounced link to behavior problems in adolescents, notably within the subset of children subjected to violent or abusive parental environments.⁹ Substantiating this connection, empirical research has highlighted that individuals who have endured ACEs are predisposed to a heightened likelihood of involvement in delinquent activities.¹⁰ An international study, encompassing data from teenagers aged 18 to 20 years old across a diverse array of countries, including Thailand, further underscored the nuanced impact of certain forms of household dysfunction in precipitating the emergence of behavior problems among adolescents. It is noteworthy also that the extent of this influence is contingent upon various factors, including gender and the level of social well-being.¹¹

Adolescent delinquency presents a pressing concern in the Thai context, demanding both careful attention and the formulation of pragmatic, evidence-based solutions. This issue is notably exacerbated by the participation of a significant proportion of adolescents in various criminal activities.¹² Empirical investigations conducted with adolescents in Bangkok have brought to light a discernible correlation between behavior problems, with a particular emphasis on drug use, and the occurrence of ACEs. Furthermore, these studies have revealed that over half of the participating adolescents had encountered ACEs, thus underscoring the pervasive nature of this problem among the youth in Thailand.^{7,8} These documented findings align coherently with analogous research conducted across different countries, emphasizing the global dimension of the challenges presented by ACEs and their associated ramifications.

Nonetheless, it is essential to acknowledge that not all children exposed to ACEs necessarily will manifest behavior problems. Some children demonstrate a capacity for effective adjustment and possess elevated psychological

resilience, which enables them to develop successful coping strategies. In this context, resilience represents a psychological attribute indicative of one's ability to adeptly navigate adverse circumstances. This multifaceted concept encompasses the adept adaptation to challenging situations, the shaping of one's worldview, the acquisition of adequate social support, and the implementation of more suitable problem-solving strategies.¹³

Supporting this perspective, prior research has emphasized that resilience is a skill that can be cultivated and enhanced.¹⁴ Additionally, resilience plays a pivotal role as a psychological attribute that can serve as a protective factor against the adverse consequences of ACEs, particularly concerning emotional and behavioral issues. For example, a study involving high school students aged 14 to 19 in Turkey revealed that resilience and self-esteem can collectively act as mediators in the relationship between exposure to child abuse and the development of emotional and behavioral challenges.¹⁵

Adolescence is a crucial period characterized by the emergence of behavior problems as individuals transition from childhood to adulthood. This developmental stage encompasses significant changes across physical, cognitive, emotional, and social dimensions. Notably, the age range of 15 to 18 years old is particularly noteworthy for the increased occurrence of behavior problems and delinquent behaviors.¹⁶

Furthermore, it's important to acknowledge the gap in scholarly research concerning the role of resilience amidst ACEs and their link to behavior problems, especially within Thailand's distinct context. Recognizing this gap, our study focuses specifically on investigating how resilience acts as a mediator between ACEs and behavior problems among adolescents in the southern region of Thailand. The research objectives aim to comprehensively explore the impact of ACEs on adolescent behavior. Firstly, the study delves into understanding how resilience mediates the connection between ACEs and behavior problems in adolescents. Secondly, it seeks to clarify the direct relationship between ACEs and adolescent behavior problems, shedding light on its nature and scope. Lastly, the study aims to assess the prevalence rates of ACEs, behavior problems, and resilience among adolescents, providing valuable insights into their co-occurrence. Through these objectives, the research endeavors to deepen our understanding of how ACEs, resilience, and behavioral outcomes interact among adolescents.

The collection of empirical data from this specific demographic holds the promise to provide valuable insights that can deepen our understanding and contribute to the prevention and mitigation of the behavioral challenges faced

by young individuals in Southern Thailand. Additionally, the foundations established by this study may serve as a fundamental knowledge base, with potential applications in guiding future research endeavors across diverse geographical areas within the nation.

MATERIALS AND METHODS

Participants

Twenty-two high schools located within a specific province in Southern Thailand were categorized into three groups: small, medium, and large to extra-large schools, according to the criteria set by the Office of the Basic Education Commission. Three high schools were randomly selected from each group. The population consisted of 8,909 students. The sample size, totaling 383 participants, was determined using Taro Yamane's formula. The participants in this study were senior high school students currently enrolled in these selected high schools. In order to be eligible for participation, individuals had to meet the following inclusion criteria: they had to be between 15 and 18 years old, be proficient in the Thai language, not have a history of psychiatric or developmental disorders, and must obtain parental permission and provide informed consent to partake in the research. Students who did not complete the questionnaires or who responded randomly were excluded from the final dataset.

Questionnaire

A paper-pencil-based questionnaire was used in this study and consisted of 4 parts:

1. General Information Questionnaire, which included questions on the participant's gender, age, grade level, co-resident parents, parent's occupation, parent's income, marital status of parents, and medical condition.

2. Thai Version of the Adverse Childhood Experiences Questionnaire (ACEs questionnaire)¹⁷, consisting of 28 items covering 10 different types of ACEs. Participants were requested to complete the questionnaire, and their scores were computed and categorized for each type of ACE. The scale of answers and scoring criteria varied based on the type of ACEs, and the total score ranged from 0–10, representing the number of different types of ACEs encountered. The questionnaire demonstrated good content validity and empirical validity. Internal consistency reliability was 0.79 for the child abuse question, 0.82 for the neglect question, and 0.66 for the household dysfunction question.¹⁸

3. Adolescent Risk Behavior Inventory-12 Items consisting of 12 items covering question about risk of

engaging in violent behaviors, such as "Carrying weapons or objects with the intent to harm others," "Assembling your own weapons," "Providing illegal drugs to others," and "Sexually harassing." Responses measured on a 5-point rating scale from 0 (Never) to 4 (Very often), with the total score ranging from 0–48. Higher scores are indicative of a greater number of behavior problems. The participants were asked to complete the questionnaire by themselves. The overall internal consistency was 0.928.¹⁹

4. Thai Version of the Connor-Davidson Resilience Scale (25-Item CD-RISC), as translated by Nauwarat Imlimtharn and approved by Dr. Jonathan Davidson, one of the scale developers, consisting of 25 items. Responses were measured on a 5-point rating scale from 0 (Not true at all) to 4 (True nearly all the time). Self-reporting was required. The total score ranged from 0–100. Higher scores are indicative of a higher level of resilience. The overall internal consistency was 0.89.²⁰

Data collection

The study received approval from the Human Research Protection Unit at the Faculty of Medicine Siriraj Hospital, Mahidol University, under the COA number Si 069/2023. Data collection occurred during the months of June through August in 2023. Participants who met the inclusion criteria were invited to participate through a face-to-face invitation. These participants were provided with detailed information regarding the research's objectives, data-collection procedures, the expected duration of participation, the potential benefits and risks, data confidentiality, contact information for addressing any procedural concerns, and their right to withdraw from the research at any point. Interested participants received an informational document and a consent form for their parents. Those with parental consent were required to sign their own consent form before starting the questionnaire. After completing the questionnaires, a group relaxation workshop was conducted to mitigate any stress or potential effects that may have arisen during the questionnaire completion process.

Statistical analysis

The collected data were statistically analyzed using SPSS. The analysis was structured into three distinct segments. First, descriptive analysis was performed to present the frequencies and percentages of the main variable scores along with the demographic data, encompassing the respondents' gender, age, grade level, the co-residency of parents, parental occupation, parental income, marital status of parents, and any existing medical conditions. Second, correlation analysis was performed utilizing

the Spearman correlation coefficient (r_s) to assess the relationships between adverse childhood experiences (ACEs), behavior problems, and resilience, encompassing the analysis of the continuous variables. In cases where the relationships involved nominal dichotomous variables and continuous variables, Point Biserial Correlation analysis (r_{pb}) was applied. Additionally, Phi correlation analysis (r_ϕ) was employed to evaluate the relationships between two nominal dichotomous variables. Any unspecified data was considered as missing values. Last, path analysis was conducted, utilizing the mediation model (model 4) from the PROCESS Macro program. This path analysis aimed to investigate the role of resilience as a mediator in the relationship between ACEs and adolescent behavior problems.

RESULTS

Demographic data of the participants

Out of the total 383 participants, 374 completed the questionnaire adequately, for a response rate of 97.65%, resulting in a final sample size of 374 ($n=374$). The majority of participants were female, accounting for 61.2% of the sample. Additionally, a substantial portion of the participants were enrolled in Grade 10 (40.1%). The average age of the participants was 16 years old, with a small standard deviation of 1.02, indicating a relatively homogeneous age distribution. Regarding the participants' living arrangements, more than two-thirds resided with both their father and mother (66.6%), while 25.9% lived with either one parent, and 5.1% lived with their grandparents. In terms of parental occupation, the most common category was Agriculturist (32.4%), followed by Self-employed (24.3%), and Government officer/State enterprise (21.9%). The average monthly income among the parents was 26,684.13 baht, with a relatively high standard deviation of 35,087.41 baht, suggesting large income variability within the sample. However, over half of the parents fell within the income range of 0 to 20,000 baht monthly. A significant majority of the participants reported that their parents were married (73.5%). Notably, the majority of participants (90.1%) did not report any medical conditions, as detailed in [Table 1](#).

Descriptive analysis

The research encompassed three key variables: ACEs, behavior problems, and resilience. Descriptive statistical analysis of these variables revealed specific characteristics. The mean number of ACEs was 1.36 with a standard deviation of 1.66, ranging from 0–8. Behavior problems had a mean score of 1.68 with a

standard deviation of 2.39 and ranged from 0–17. These scores indicate a group not at risk of engaging in violent behaviors. Resilience exhibited an average score of 68.52, with a standard deviation of 15.23, ranging from 19–100.

The data analysis provided insights into the prevalence of ACEs among the participants. Specifically, 40.64% of all participants reported no ACEs, indicating a considerable proportion of participants did not encounter these adverse events during their childhood. In contrast, 59.36% reported experiencing at least one type of ACE, underscoring the prevalence of these experiences within the sample. Among this latter group, 12.03% reported enduring the challenges of four or more ACEs, signifying a significant level of exposure to multiple ACEs.

An examination of the specific types of ACEs reported by the participants revealed that parental separation or divorce was the most commonly reported experience, acknowledged by 31% of the participants. Additionally, emotional neglect was reported by 20.6% of participants, followed by physical neglect (18.7%) and physical abuse (12.8%). These proportions are visually presented in [Table 2](#), offering a comprehensive illustration of the various ACEs prevalent among the study participants.

Relationship between ACEs, behavior problems, resilience, and demographic data

ACEs displayed a low positive correlation with behavior problems ($r_s = 0.17$, $p < 0.01$) and a low negative correlation with resilience ($r_s = -0.19$, $p < 0.01$). Notably, resilience did not exhibit a significant relationship with behavior problems. Moreover, a significant, albeit low, negative relationship was observed between gender and behavior problems ($r_s = 0.12$, $p < 0.05$), indicating that males were more likely to experience behavior problems than females. Additionally, the marital status of parents showed noteworthy associations. Specifically, living with divorced parents was linked to a significantly low positive correlation with ACEs ($r_{pb} = 0.44$, $p < 0.01$) and behavior problems ($r_{pb} = 0.11$, $p < 0.05$), suggesting that children in such family structures had a higher likelihood of both experiencing ACEs and exhibiting elevated behavior problems. Further details are available in [Table 3](#). Moreover, the correlation analysis between the types of ACEs and behavior problems showed low positive associations with SA ($r_{pb} = 0.23$, $p < 0.05$), HS ($r_{pb} = 0.23$, $p < 0.05$), EA ($r_{pb} = 0.17$, $p < 0.05$), IH ($r_{pb} = 0.17$, $p < 0.05$), and PD ($r_{pb} = 0.11$, $p < 0.05$).

Relationship between the number of ACEs, behavior problems, resilience, and medical conditions

Having no ACEs was found to be negatively associated

TABLE 1. Demographic data of the participants (n = 374)

		n	%
Gender	Male	140	37.4
	Female	229	61.2
	Not specified	5	1.3
Age (year)	15	106	28.3
	16	98	26.3
	17	123	32.9
	18	47	12.6
	(M = 16; SD = 1.02)		
Grade level	Grade 10	150	40.1
	Grade 11	95	25.4
	Grade 12	129	34.5
Co-residency of parents	Father and mother	249	66.6
	Father	16	4.3
	Mother	81	21.7
	Grandparents	19	5.1
	Relative	7	1.9
	Others	2	0.5
Parental occupation	Government officer / State enterprise	82	21.9
	Agriculturist	121	32.4
	Self-employed	91	24.3
	Company employee	14	3.7
	Freelance	63	16.8
	Unemployed	2	0.5
	Not specified	1	0.3
Parental income (bath monthly)	0–20,000	218	58.3
	20,000–40,000	92	24.6
	40,000–60,000	33	8.8
	60,000–80,000	5	1.3
	80,000–100,000	5	1.3
	100,000 or more	5	1.3
	Not specified	16	4.3
	(M = 26,684.13; SD = 35,087.41; Min = 0; Max = 500,000)		
Marital status of parents	Married	275	73.5
	Divorced	99	26.5
Medical conditions	No medical condition	337	90.1
	Allergy	24	6.4
	Asthma	6	1.6
	Thalassemia	2	0.5
	G6PD	1	0.3
	Diabetes	1	0.3
	Migraine	1	0.3
	Not specified	2	0.5

TABLE 2. Number and type of ACEs (n = 374).

		n	%
Number of ACEs	0	152	40.64
	1	91	24.33
	2	65	17.38
	3	21	5.62
	4 or more	45	12.03
Type of ACEs	Emotional abuse (EA)	36	9.6
	Physical abuse (PA)	48	12.8
	Sexual abuse (SA)	26	7
	Emotional neglect (EN)	77	20.6
	Physical neglect (PN)	70	18.7
	Household physical violence (HV)	56	15
	Household substance abuse (HS)	20	5.3
	Household mental illness (HM)	30	8
	Parental separation/divorce (PD)	116	31
	Incarcerated household member (IH)	30	8

Note. A participant can have more than one type of ACE.

TABLE 3. Correlation coefficients of the studied variables.

	1	2	3	4	5	6	7	8
Gender	1.00							
Age	0.18**	1.00						
Marital status of parents	0.07	0.02	1.00					
Parent's income	-0.08	-0.28**	-0.10	1.00				
Medical conditions	-0.09	-0.14*	0.13*	-0.04	1.00			
ACEs	0.07	-0.02	0.44**	-0.16**	0.07	(0.53)		
Resilience	-0.09	0.05	-0.09	0.03	-0.06	-0.19**	(0.93)	
Behavior problems	-0.12*	0.10	0.11*	-0.02	-0.007	0.17**	0.04	(0.64)

Note. The numbers in brackets refer to Cronbach's coefficient alpha.
*p < 0.05; **p < 0.01.

with medical conditions ($r_{\phi} = -0.13, p < 0.05$) and behavior problems ($r_{pb} = -0.14, p < 0.01$). In contrast, it displayed a positive association with resilience ($r_{pb} = 0.15, p < 0.01$). This suggests that individuals who reported having no ACEs were more likely to be free from medical conditions, exhibit no behavior problems, and possess higher levels of resilience compared to those who had experienced ACEs. Conversely, having four or more ACEs was positively

associated with behavior problems ($r_{pb} = 0.15, p < 0.01$) and negatively associated with resilience ($r_{pb} = -0.18, p < 0.01$). The specifics of these associations are presented in [Table 4](#), providing a comprehensive overview of the relationships between the number of ACEs and the variables of medical conditions, behavior problems, and resilience.

TABLE 4. Correlation coefficients between the number of ACEs and other variables.

	0	1	2	3	≥ 4
Medical conditions	-0.13*	0.08	-0.01	0.08	0.04
Resilience	0.15**	0.05	-0.07	-0.05	-0.18**
Behavior problems	-0.14**	0.02	0.05	-0.03	0.15**

* p < 0.05; ** p < 0.01.

Mediating effect of resilience on ACEs and behavior problems

ACEs were found to have a significant negative effect on resilience ($\beta = -0.24, SE = 0.47, t = -4.84, p < 0.01, 95\%CI [-3.20, -1.35], R^2 = 0.059$). However, resilience did not significantly impact behavior problems ($\beta = 0.09, SE = 0.008, t = 1.70, p = 0.09, 95\%CI [-0.002, 0.03]$). Additionally, a direct and significant effect of ACEs on behavior problems was observed ($\beta = 0.23, SE = 0.08, t = 4.39, p < 0.01, 95\%CI [0.18, 0.48]$). Furthermore, the results of the Bootstrap Confidence Intervals (CIs) indicated that there was no indirect effect of ACEs on behavior problems that was mediated by resilience ($\beta = -0.02, SE = 0.02, 95\% CI [-0.08, 0.009]$). These findings are presented comprehensively in Table 5 and Fig 1.

DISCUSSION

The study involved a cohort of 374 participants, of whom 40.64% reported having no ACEs, while 59.36% reported the presence of at least one ACE in their lives. A subset of participants, specifically 12.03%, disclosed the challenging experience of enduring four or more ACEs. These findings align with prior studies conducted both on an international scale and within Thailand itself.³⁻⁸ The persistence of a significant prevalence of ACEs over more than two decades of research underscores a concerning trend. This trend may be better understood when viewed through the lens of intergenerational transmission.

A meta-analysis, which primarily focused on studies published between 1975 and 2017 in Western countries, delved into the concept of intergenerational transmission,

TABLE 5. Mediation analysis of resilience on the relationship between ACEs and behavior problems.

	Unstandardized Coefficients		Standardized Coefficients		p	LLCI	ULCI
	B	SE	Beta (β)	t			
Effect of ACEs on resilience (path a)	-2.27	0.47	-0.24	-4.84	0.00	-3.20	-1.35
Effect of resilience on behavior problems (path b)	0.01	0.008	0.09	1.70	0.09	-0.002	0.03
Total effect of ACEs -> Behavior problems (path c)	0.30	0.07	0.21	4.09	0.00	0.15	0.44
Direct effect of ACEs -> Behavior problems (path c')	0.33	0.08	0.23	4.39	0.00	0.18	0.48
	B	Boot SE	Beta (β)	Boot 95% LLCI	Boot 95% ULCI		
Indirect effect of ACEs on behavior problems mediated through resilience	-0.03	0.02	-0.02	-0.08	0.009		

Note. SE = standard error; LLCI = lower level of the 95% confidence intervals; ULCI = upper level of the 95% confidence intervals; Boot = Bootstrap result.

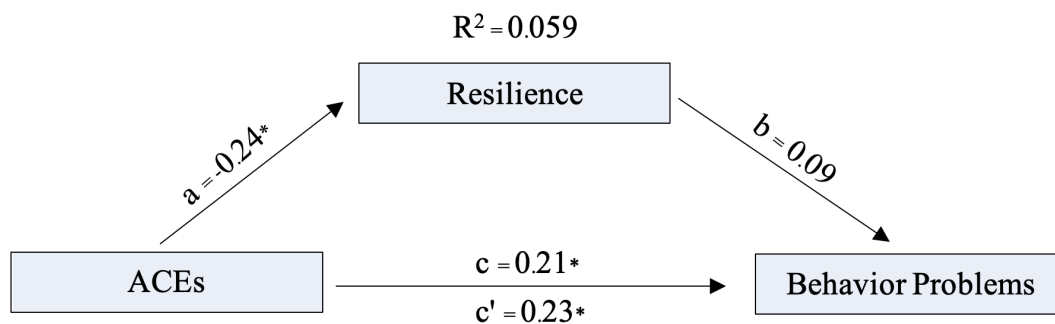


Fig 1. Mediating effect of resilience on ACEs and behavior problems.

revealing that parents who had themselves suffered childhood abuse were at a heightened risk of perpetuating abusive behavior toward their own children. However, it is crucial to emphasize that this transmission of child abuse is not a universal phenomenon; rather, it varies due to multiple contributing factors. These influencing factors encompass the characteristics of families marked by insecure attachment styles, experiences of social isolation among parents, early parenthood, elevated stress levels, economic hardship, parental psychopathology, maternal substance use, and ongoing exposure to parental violence. The meta-analysis ultimately concluded that parents who had endured childhood abuse often carry an ardent desire to shield their own children from similar suffering. Paradoxically, they often lack access to positive parenting role models and have been raised in environments characterized by insecure relationships. Consequently, they face a formidable challenge in cultivating a safe and secure parent–child relationship, inadvertently perpetuating the cycle of child abuse across generations.²¹ This enduring cycle consequently contributes to the continued exposure of a substantial number of children to ACEs. This aligns with research findings where participants reported experiencing family issues, particularly parental divorce, and household violence, indicating an upbringing in an insecure environment. Without adequate psychological support, there's a risk of passing on these emotional or mental challenges to the next generation.

Our findings show that the risk of engaging in violent behaviors is associated with experiences of abuse, household substance abuse, having an incarcerated household member, and parental divorce. These findings, consistent with a prior study, highlight a noteworthy connection between ACEs and behavior problems that emerge during adolescence.^{9,11} This observation corresponds to the foundational tenets of Bandura's social learning theory, which posits that behavior is significantly influenced by observational learning processes. To provide a theoretical

underpinning to this relationship, one can invoke Bandura's classic experiment, which involved exposing children to aggressive models interacting with a Bobo doll. The results of that experiment demonstrated that children who witnessed aggressive behavior directed at the Bobo doll were more inclined to exhibit similar aggressive behaviors when given the opportunity.²² This supports the idea that behavior is shaped through observation and imitation, thereby reinforcing the relevance of social learning theory. As a result, when children find themselves in environments characterized by abuse, insecurity in attachment, violence, substance abuse, or involvement in illegal activities, they are exposed to ample opportunities for observational learning. Consequently, they may imitate behaviors they have witnessed, with the potential culmination being the manifestation of future behavior problems during their adolescent years.

ACEs were found to have a negative association with resilience, suggesting that individuals who have experienced a higher number of ACEs tend to exhibit lower levels of resilience compared to those with fewer such adverse experiences. This finding aligns with prior research studies^{23,24} that have explored the relationship between ACEs and resilience. However, an intriguing perspective has emerged from an in-depth interview study involving individuals aged 50 to 77 years old. The results of that study indicate that individuals with a history of ACEs tended to develop higher levels of resilience. This counterintuitive outcome can be explained by the notion that challenging childhood experiences can, in fact, facilitate learning, self-development, and improved problem-solving abilities, ultimately contributing to greater resilience.²⁵ It is essential to note that the existing body of research on the relationship between ACEs and resilience is limited, and previous findings have been inconclusive. This ambiguity arises from the understanding that resilience is not a fixed personality trait but rather a dynamic quality that can either increase or decrease over time.^{26,27} Furthermore, most research studies define

resilience as a mediating or protective factor against the adverse impact of ACEs,^{28,29} adding complexity to the overall picture of this relationship.

The path analysis conducted in this study revealed that resilience did not function as a mediating variable in the relationship between ACEs and adolescent behavior problems. Moreover, it did not exhibit a direct impact on behavior problems. Interestingly, this result contradicts the findings of a previous study,¹⁵ which demonstrated that resilience, along with self-esteem, played a mediating or protective role in mitigating the influence of childhood abuse on emotional and behavioral problems. This discrepancy implies the existence of additional variables, apart from resilience, that mediate the relationship between ACEs and behavior problems. For instance, these variables might encompass self-esteem¹⁵ and impulsivity,³⁰ both of which have been implicated as contributing factors in prior research.

While this study did not find resilience to be a mediating or protective factor in the relationship between ACEs and behavior problems, it is essential to acknowledge that resilience can play such a role in various other contexts. For instance, research conducted among undergraduate students showed that resilience acted as a protective factor in the relationship between ACEs and depressive symptoms.³¹ Additionally, a study involving homeless individuals demonstrated that resilience served as a protective factor against mental health problems influenced by ACEs.³² These findings underscore the multifaceted nature of resilience and its varying impact in different scenarios. Previous research has demonstrated that resilience can be enhanced.¹⁴ Therefore, it is crucial to prioritize resilience development for children and adolescents through interventions such as mindfulness-based approaches.³³

Limitations of the present study and recommendations for future research

This research's exclusivity to school system participants potentially narrowed the diversity of the dataset, particularly in terms of the behavior problem scores; whereby the behavior problem scores in this dataset exhibited limited variability, with a majority of participants scoring low, and a significant 40.4% reporting no behavioral problems. Consequently, this dataset deviated from a normal distribution, thereby affecting the accuracy of the statistical analysis. Additionally, this study asked participants to self-assess their behavioral problems. Therefore, it may underestimate one's own problems. Different information may be obtained if parents or teachers are the respondents. In future research

endeavors, it is advisable to include behavior problem assessment data from parents or teachers, such as Strengths and Difficulties Questionnaire (SDQ), in the analysis to improve the accuracy of the information gathered. Moreover, future research should expand the scope by incorporating a broader range of population groups. This expansion could include vocational education students, children outside the conventional school system, and even those involved in criminal activities (known groups). The inclusion of such diverse groups could provide a richer spectrum of information and facilitate a deeper understanding of any variations between these groups, effectively overcoming the limitations associated with studying a single homogeneous population.

The generalizability of the research findings is inherently restricted by the study's narrow scope. Data collection was confined to students within a single province in the southern region of Thailand, primarily due to time and staffing constraints. It is imperative to recognize that social and cultural differences exist across various regions, potentially influencing research outcomes. For future research endeavors, extending the study's geographical coverage is advisable. This could involve conducting studies at the regional or even national level, allowing researchers to obtain more comprehensive and representative insights, ultimately enhancing the applicability and generalizability of their findings.

Furthermore, this research exclusively focused on the impact of ACEs on behavior problems, but previous studies have demonstrated that ACEs can have a wide range of effects that extend beyond just behavioral issues. It is therefore imperative that future investigations explore additional variables influenced by ACEs, including emotional problems and mental health concerns.

In addition to considering resilience, it is equally important to investigate other variables that may serve as protective factors against the impact of ACEs. These factors may include aspects such as self-esteem and emotional regulation skills. By examining a more comprehensive set of variables, we can gain a better understanding of the multifaceted effects of ACEs and identify potential avenues for intervention to reduce their impact.

In this research, the Intelligence Quotient (IQ) of participants emerges as a confounding factor that can significantly influence their adaptability and, consequently, their resilience levels. Additionally, psychiatric disorders can affect the severity of behavioral issues such as Conduct Disorder and Oppositional Defiant Disorder, as well as attention and concentration levels, and the ability to cope with adverse situations, such as Attention Deficit Hyperactivity Disorder (ADHD), Depression, and Post-

traumatic Stress Disorder (PTSD). However, the inclusion criteria for this study did not encompass individuals with psychiatric or developmental disorders. This criterion was solely based on self-evaluation by the participants. Therefore, for future research, it is essential to employ screening tests for both IQ and psychiatric disorders to control confounding factors. This may involve selecting groups with similar IQ or excluding those with psychiatric disorders from the study. Alternatively, considering IQ as a variable of interest in our research framework could provide an additional avenue for nuanced exploration.

CONCLUSION

The results of this study shed light on the prevalence of ACEs among senior high school students in Southern Thailand, with a notable presence revealed among those whose parents are divorced. This observation highlights a broader child welfare concern in Thailand, even though the data were specifically collected from students within the school system. This situation raises alarms regarding the potential adverse consequences, particularly behavioral and mental problems, that these children might face in the future. While it is true that resilience was not found to serve as a mediating factor between ACEs and behavior problems in this context, it is important to recognize that resilience is a vital skill that can help mitigate the mental and emotional impacts of stress and life difficulties. As such, there is a compelling need to prioritize the development of resilience in children to equip them for future challenges and reduce the risk of them developing emotional or mental health issues.

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Conflict of interest

The authors have no conflicts of interest to declare.

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Factors Affecting the Mental Health of Thai Medical Staff during the Second and Third Waves of the COVID-19 Pandemic: An Online Cross-sectional Survey

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ABSTRACT

Objective: This comparative study of the second and third waves of the COVID-19 pandemic aimed to: 1) examine the mental health status of hospital staff; 2) describe the associations among various factors that affect mental health; and 3) investigate the impact of COVID-19.

Materials and Methods: Data were collected from Siriraj Hospital staff using online questionnaires including demographics, staff characteristics, health behavior, readiness to handle COVID-19; COVID-19 impact; and the Thai version of the Depression Anxiety Stress Scales–21 (DASS-21).

Results: Depression, anxiety, and stress scores were significantly higher in the third wave. Living in a high-surveillance area, social distancing difficulties, health behaviors, and office work all impacted mental health in both waves. Demographics, infection exposure outside the hospital, awareness of social distancing, and readiness to work from home impacted only the second wave. Direct work with COVID-19 patients impacted only the third wave. The common stressors included living expenses, daily life changes, and disease prevention costs in both waves, with COVID-19 news having a greater impact in the third wave. Main daily life impacts were income, transportation, and disease prevention equipment in both waves, with food becoming more important in the third wave.

Conclusion: Mental health should be prioritized especially in severe waves, focusing on staff at high risk of infection, experiencing social distancing challenges, daily life changes, and having health problems. Disease protection should also be emphasized early on.

Keywords: COVID-19; impact; medical staff; mental health; Thailand (Siriraj Med J 2024; 76: 293-303)

INTRODUCTION

Healthcare professionals are an essential group of people who care for COVID-19 patients. Previous studies have found that frontline healthcare staff are at risk of experiencing depression, anxiety, and insomnia, and can face more desperation than non-frontline staff.¹

However, a previous study showed no difference in scores on anxiety and depression between frontline workers and non-frontline workers.² Furthermore, non-frontline staff experienced more vicarious traumatization than frontline staff.³ As a result, it is critical to consider the mental health of all personnel.

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Siriraj Hospital, part of Mahidol University's Faculty of Medicine, is a tertiary-level medical service institution in Thailand. With the potential to treat patients infected with the novel coronavirus 2019, many people are expected to visit for disease examination and treatment. During the first wave, the Human Resources Department of the Faculty of Medicine Siriraj Hospital surveyed stress, mental health status, and the basic needs of hospital staff. According to the survey, more than 31% of staff were found to have high levels of stress, 43% to have high levels of anxiety, and 46% to have high levels of depression on the Depression, Anxiety, and Stress Scales (DASS-21).

Each wave of the pandemic has a different level of stress exposure. Following a previous study in China, the second wave of the outbreak's fear levels was lower than those for the first. Yet compared to the first wave, depression scores in the second wave were significantly greater.⁴ According to reports from England, anxiety levels in the second wave were much lower than in the first wave. Although there was no significant difference in depression in this study, there was a considerably higher rate of suicide ideation.⁵ Nevertheless, the prior study was conducted among the general population. Studies on the mental health of medical staff in the subsequent wave are still scarce.

Thailand managed the COVID-19 crisis so efficiently during the early phases of the outbreak that it was ranked first in the global COVID-19 Index (GCI).⁶ However, the second wave of the outbreak, which started in January 2021, was primarily from a group of migrant workers in the wet market in Samut Sakhon Province, which led to a new wave of panic among the population. Furthermore, during the third wave of the outbreak in May, a cluster of COVID-19 cases was linked to entertainment venues such as pubs, bars, and nightclubs. This wave of the outbreak was caused by the British strain, which was considered more dangerous due to its ability to spread rapidly. As a result of the increased burden on hospitals to treat COVID-19 patients, understanding the mental health status of hospital staff in the second and third waves is critical.

Furthermore, understanding the factors influencing staff mental health status will allow for more effective targeting assistance. A previous study in China indicated that being a nurse, female, a frontline worker, and working in Wuhan were associated with mental health symptoms.¹ Additionally, compliance with and perceived effectiveness of social distancing measures were also associated with lower levels of stress, anxiety, and depressive symptoms, as evidenced in a study in Hong Kong.⁷ Upon closer

examination at university hospital in southern Thailand, being female, having a physical illness, and perceiving exposure to COVID-19 were identified as risk factors for severe mental health outcomes among university staff.⁸ Therefore, this study focuses on demographic information, staff characteristics, health behavior, and readiness to handle the COVID-19 situation.

The objectives of this comparative study of the second and third waves of the COVID-19 pandemic were to: 1) examine the mental health of the medical staff working in the Faculty of Medicine Siriraj Hospital, Mahidol University; 2) describe the relationships between various factors and the staff's mental health; and 3) investigate the effects of the COVID-19 situation on staff.

MATERIALS AND METHODS

Study design and participants

The participants were the staff of the Faculty of Medicine Siriraj Hospital who voluntarily agreed to complete the online survey. The survey link was promoted on a local social media platform, Siriraj staff group. The data of the second wave were collected between January and February 2021, and data of the third wave collected between May and June of the same year. This study was approved by the Institutional Review Board (IRB), Faculty of Medicine Siriraj Hospital, Mahidol University (COA no. Si 081/2021). Participants were informed about the study's objectives and the use of their responses for research. The participants acknowledged consent by completing the survey.

Measurement

A questionnaire on factors affecting the mental health during COVID-19; regarding demographic information, staff characteristics, health behavior, and readiness to handle the COVID-19 situation. Respondents were asked to choose only one option that applied to them in each item.

Questions about the impact of the COVID-19 pandemic; included lists of factors affecting stress and lists of impacts on daily living. Respondents were asked to choose the factors that had an impact on their lives and were allowed to choose more than one factor.

The Thai version of the Depression Anxiety Stress Scales-21 (DASS-21)⁹ was used to assess the mental health status, which had three subscales (Anxiety, Depression, and Stress). Each subscale consisted of seven items with a 4-point Likert scale ranging from "applied to me very much" to "did not apply at all." Cronbach's alpha coefficient cutoffs for Anxiety, Depression, and Stress were .82, .78, and .69, respectively.

Statistical analysis

All statistical analyses were conducted using SPSS 24. The frequency and percentages were used to calculate descriptive data. As distributions of DASS-21 scores were highly right-skewed, the comparisons of scores on DASS-21 with categorical variables were conducted using the Mann-Whitney U and the Kruskal-Wallis tests. Finally, generalized linear models were used for multivariate analysis, including all significant variables from the univariate analysis. P values <.05 were considered statistically significant in this study.

RESULTS

The mental health status of the Siriraj Hospital staff during the second and the third waves.

The number of participants in the second and the third waves was 3,096 and 1,192. In the second and the third waves, the participants' median scores and Q1-Q3 intervals on the DASS-21 were 10 (3-20) and 8 (2-17), respectively. It was found that the scores on depression, anxiety, and stress in the third wave were significantly higher than those in the second wave (Table 1).

Factors affecting the mental health status of Siriraj Hospital staff in the second and the third waves.

Table 2 showed significant factors in the univariate analysis. After performing a multivariate analysis (Table 3), younger age, longer work hours, a history of external infection exposure, and awareness of social distancing were associated with higher depression, anxiety, and stress scores, only in the second wave. Additionally, readiness to work from home were correlated with higher anxiety and stress, demonstrating significant associations only in the second wave.

Factors significantly associated with all emotional scores in both waves included underlying diseases, sleep issues, alcohol use during stress, lack of exercise, residence

in high-surveillance zones, and social distancing difficulties. Office work was correlated with higher anxiety and stress in both waves, with depression showing association only in the third wave. The lack of potential for self-quarantine at home was associated with higher depression and stress in both waves.

Directly caring for COVID-19 patients was significantly associated with higher depression and anxiety only in the third wave. Less exercise than usual was associated with higher anxiety and stress, with these correlations being significant only in the third wave.

Impact (of COVID-19 pandemic) on Siriraj Hospital staff in the second and the third waves

Table 4 indicated that in the second wave, the top three factors affecting stress were living expenses (57.9%), changes in daily living patterns (53.7%), and the cost of protective equipment (45.6%) (7th in the third wave). In the third wave, the first two factors remained consistent (61.3% and 58.6%, respectively), with news and information about pandemics ranking third (51.1%) (7th in the second wave).

Regarding daily life impacts, the top three in the second wave were income (54.3%), transportation (53.1%), and protective equipment for COVID-19 prevention (33.7%) (4th in the third wave). In the third wave, the first two impacts remained the same (59.5% and 52.0%, respectively), with food ranking third (48.2%) (4th in the second wave).

DISCUSSION

This study aimed to investigate the mental health status of hospital staff, the factors affecting the staff's mental health status, and the impact of the COVID-19 pandemic on the staff of Siriraj Hospital in comparison between the second and the third waves of the pandemic.

TABLE 1. The difference between depression, anxiety, and stress of the second and third waves.

DASS-21	Mean (SD)		Median (Q1-Q3)		P-value
	Wave 2	Wave 3	Wave 2	Wave 3	
Depression	3.74 (4.25)	4.35 (4.58)	2 (0-6)	3 (1-7)	.000
Anxiety	2.82 (3.57)	3.25 (3.85)	1 (0-4)	2(0-5)	.001
Stress	4.72 (4.46)	5.27 (4.66)	4 (1-7)	5(1-8)	.000

TABLE 2. Factors that affect the depression, anxiety and stress of the second and third waves.

Variables	Wave 2						Wave 3									
	n	%	Depression Median (Q1-Q3)	p value	Anxiety Median (Q1-Q3)	p value	Stress Median (Q1-Q3)	p value	n	%	Depression Median (Q1-Q3)	p value	Anxiety Median (Q1-Q3)	p value	Stress Median (Q1-Q3)	p value
Demographic information																
Gender				0.676		0.619		0.641				0.043		0.284		0.010
Female	2568	82.9	2 (0-6)		1 (0-4)		4 (1-7)		1062	89.1	3 (1-7)		2 (0-5)		4 (1-7)	
Male	504	16.3	2 (0-6)		2 (0-4)		4 (1-7)		125	10.5	3 (1-7.5)		2 (0-5)		5 (2-10)	
Age (years)				0.000		0.000		0.000				0.000		0.013		0.002
20 - 30	880	28.4	3 (0-7)		2 (0-5)		4 (1-7)		319	26.8	4 (1-8)		2 (0-6)		5 (2-9)	
31 - 40	920	29.7	3 (1-6)		2 (0-5)		5 (1-8)		319	26.8	4 (1-7)		2 (1-5.5)		5 (2-8)	
41 - 60	1269	41.0	2 (0-5)		1 (0-4)		3 (1-7)		547	45.9	2 (0-6)		2 (0-4)		4 (1-7)	
>60	27	0.9	0 (0-3)		1 (0-1)		1 (0-4)		7	0.6	1 (0-4)		2 (0-6)		2 (0-4)	
Work experience (years)				0.000		0.000		0.000				0.000		0.008		0.001
<5	785	25.4	3 (0-7)		2 (0-5)		4 (1-8)		278	23.3	3 (1-8)		2 (0-5.25)		5 (2-8)	
5 - 10	612	19.8	3 (0-6)		2 (0-4)		4 (1-8)		212	17.8	4 (1-8)		2 (0-7)		5 (1-9)	
11- 20	857	28	3 (0-6)		2 (0-5)		4 (1-7)		299	25.1	3 (1-7)		2 (1-5)		5 (2-8)	
>20	842	27	2 (0-5)		1 (0-3.25)		3 (1-6)		403	33.8	2 (0-5)		1 (0-4)		3 (1-7)	
Working hour (hours)				0.000		0.003		0.000				0.142		0.096		0.210
<8	1257	40.6	2 (0-5)		1 (0-4)		3 (1-7)		541	45.4	3 (0-7)		2 (0-5)		4 (1-7)	
8-9	1420	45.9	3 (0-6)		2 (0-4)		4 (1-7)		536	45.0	3 (1-7)		2 (0-5)		5 (1-8)	
>9	419	13.5	3 (0-7)		2 (0-5)		5 (1-9)		115	9.6	3 (1-7)		3 (0-5)		5 (2-8)	
Staff characteristics																
Working frontline				0.322		0.532		0.691				0.591		0.325		0.563
Yes	630	20.3	3 (0-6)		1 (0-4)		3 (1-7)		259	21.7	3 (1-7)		2 (0-5)		5 (2-8)	
No	2466	79.7	2 (0-6)		1 (0-4)		4 (1-7)		933	78.3	3 (1-7)		2 (0-5)		5 (1-8)	
Working in the office				0.965		0.001		0.003				0.009		0.001		0.002
Yes	775	25.0	2 (0-6)		2 (0-5)		4 (1-8)		255	21.4	3 (1-8)		3 (0-7)		5 (2-10)	
No	2321	75.0	2 (0-6)		1 (0-4)		4 (1-7)		937	78.6	3 (1-6)		2 (0-5)		4 (1-7)	
Working in the lab				0.679		0.875		0.795				0.162		0.034		0.021
Yes	61	2.0	2 (0.5-5)		1 (0-4)		4 (1-7)		22	1.8	4 (2-7.25)		3 (2-5.75)		7 (3.5-12)	
No	3035	98.0	2 (0-6)		1 (0-4)		4 (1-7)		1170	98.2	3 (1-7)		2 (0-5)		5 (1-8)	
Caring for COVID-19 patients directly				0.369		0.527		0.272				0.025		0.016		0.047
Yes	112	3.6	3 (0-6)		2 (0-5)		4 (1-8)		156	13.1	4 (1-8)		3 (0-6)		5 (2-9)	
No	2984	96.4	2 (0-6)		1 (0-4)		4 (1-7)		1036	86.9	3 (1-7)		2 (0-5)		4 (1-8)	
Exposure to infection outside the hospital				0.000		0.000		0.000				0.326		0.203		0.352
Yes	267	8.6	4 (1-7)		3 (0-5)		5 (2-8)		137	11.5	2 (0-7)		1 (0-5)		4 (1-7.5)	
No	2829	91.4	2 (0-6)		1 (0-4)		4 (1-7)		1055	88.5	3 (1-7)		2 (0-5)		5 (1-8)	

TABLE 2. Factors that affect the depression, anxiety and stress of the second and third waves. (Continue)

Variables	Wave 2				Wave 3				Wave 3							
	n	%	Depression Median (Q1-Q3)	p value	Anxiety Median (Q1-Q3)	p value	Stress Median (Q1-Q3)	p value	n	%	Depression Median (Q1-Q3)	p value	Anxiety Median (Q1-Q3)	p value	Stress Median (Q1-Q3)	p value
Living in the highest surveillance area			0.000		0.000		0.000				0.000		0.000		0.000	
Yes	502	16.2	4 (1-7)		3 (1-5)		5.5 (2-9)		253	21.2	4 (1-8)		3 (1-6)		6 (2-9)	
No	2594	83.8	2 (0-5)		1 (0-4)		3 (1-7)		939	78.8	3 (1-6)		2 (0-5)		4 (1-7)	
Health behavior																
Having underlying disease			0.008		0.000		0.000				0.012		0.000		0.003	
Yes	981	31.7	3 (1-6)		2 (0-5)		4 (1-8)		433	36.3	4 (1-7)		3 (0-6)		5 (2-8)	
No	2115	68.3	2 (0-5)		1 (0-4)		3 (1-7)		759	63.7	3 (1-6)		2 (0-4)		4 (1-7)	
Sleep problems				0.000		0.000		0.000				0.000		0.000		0.000
No	1170	37.8	1 (0-3)		0 (0-2)		1 (0-5)		387	32.5	1 (0-4)		1 (0-2)		2 (0-5)	
Yes	1926	62.2	4 (1-7)		3 (1-5)		5 (2-8)		805	67.5	4 (1-8)		3 (1-6)		6 (3-9)	
Physical exercise				0.000		0.000		0.000				0.000		0.000		0.000
Exercise normally	546	17.6	1 (0-5)		1 (0-3)		2 (0-6)		197	16.5	2 (0-5)		1 (0-3.5)		3 (1-6)	
Less exercise than usual	645	20.8	2 (0-5)		1 (0-4)		4 (1-7)		278	23.3	3 (1-7)		2 (0-5)		5 (1-8)	
More exercise than usual	48	1.6	2.5 (0.25-4)		1 (0-3.75)		3.5 (1-6)		21	1.8	4 (0.5-6)		1 (0-5)		4 (1-8.5)	
No exercise at all	1857	60.0	3 (0.5-6)		2 (0-5)		4 (1-7)		696	58.4	3 (1-7)		2 (0-6)		5 (2-8)	
Drinking alcohol when stressed				0.000		0.000		0.000				0.000		0.000		0.000
Yes	199	6.4	4 (1-7)		3 (1-6)		6 (2-9)		60	5.0	9 (2-12)		5 (2-8)		8 (4.25-14)	
No	2897	93.6	2 (0-6)		1 (0-4)		4 (1-7)		1132	95.0	3 (1-6.75)		2 (0-5)		4 (1-7)	
Readiness to handle the COVID-19 situation																
The potential of the residence for quarantine				0.000		0.000		0.000				0.000		0.001		0.000
Yes	1532	49.5	2 (0-5)		1 (0-4)		3 (0-7)		570	47.8	2 (0-6)		1 (0-4)		4 (1-7)	
Not sure	625	20.2	3 (1-6)		2 (0-4)		4 (1-7)		208	17.4	4 (1-7)		2 (0-5)		5 (2-8)	
No	939	30.3	3 (1-6)		2 (0-5)		5 (1-8)		414	34.7	4 (1-7)		2 (0-6)		5 (2-8)	
Readiness to work at home				0.217		0.000		0.036				0.842		0.946		0.636
Yes	1511	48.8	2 (0-6)		2 (0-5)		4 (1-7)		548	46.0	3 (1-7)		2 (0-5)		5 (1-8)	
No	1585	51.2	2 (0-6)		1 (0-4)		4 (1-7)		644	54.0	3 (1-7)		2 (0-5)		5 (2-7)	
Awareness of social distancing				0.000		0.007		0.001				0.773		0.869		0.974
Yes	2671	86.3	2 (0-6)		1 (0-4)		4 (1-7)		1059	88.8	3 (1-7)		2 (0-5)		5 (1-8)	
No	425	13.7	3 (1-7)		2 (0-5)		5 (1-8)		133	11.2	4 (1-6.5)		2 (0-5)		4 (1-8)	
Having difficulty executing social distancing				0.000		0.000		0.000				0.000		0.000		0.000
Yes	711	23.0	4 (1-7.5)		3 (0-6)		5 (2-9)		284	23.8	5 (2-9)		3 (1-7)		6 (2.75-11)	
No	2385	77.0	2 (0-5)		1 (0-4)		3 (1-7)		908	76.2	3 (0-6)		1 (0-4)		4 (1-7)	

TABLE 3. General Linear Regression for Wave 2 and Wave 3.

Depression Attributes	B(95%CI)	Std	Sig.	Anxiety Attributes	B(95%CI)	Std	Sig.	Stress Attributes	B(95%CI)	Std	Sig.
Wave 2											
Age (years)				Age (years)				Age (years)			
<30	0.640 (0.047-1.234)	0.3028	0.034	<30	0.396(-0.114to0.907)	0.2604	0.128	<30	0.460(-0.159to1.079)	0.3158	0.145
31 - 40	0.694 (0.240-1.149)	0.2317	0.003	31 - 40	0.760(0.373to1.148)	0.1977	0.000	31 - 40	0.905(0.435to1.375)	0.2398	0.000
>41 (Ref)				>41 (Ref)				>41 (Ref)			
Working hour (hours)				Working hour (hours)				Working hour (hours)			
<8 (Ref)				<8 (Ref)				<8 (Ref)			
8-9	0.429(0.129-0.729)	0.1531	0.005	8-9	0.130(-0.127to0.386)	0.1307	0.321	8-9	0.248(-0.063to0.558)	0.1586	0.119
>9	0.926(0.489-1.363)	0.2230	0.000	>9	0.730(0.356to1.103)	0.1906	0.000	>9	1.078(0.625to1.531)	0.2312	0.000
Exposure to infection outside the hospital	0.822 (0.327-1.317)	0.2525	0.001	Working in the office	0.457(0.177to0.738)	0.1433	0.001	Working in the office	0.633(0.292to0.974)	0.1738	0.000
Living in the highest surveillance area	0.802(0.424-1.180)	0.1930	0.000	Exposure to infection outside the hospital	0.598(0.174to1.023)	0.2165	0.006	Exposure to infection outside the hospital	0.945(0.430to1.460)	0.2627	0.000
Having underlying disease	0.407(0.094-0.720)	0.1596	0.011	Living in the highest surveillance area	0.604(0.282to0.927)	0.1646	0.000	Living in the highest surveillance area	1.013(0.622to1.405)	0.1997	0.000
Having sleep problems	2.125(1.833-2.418)	0.1491	0.000	Having underlying disease	0.378(0.111to0.644)	0.1360	0.005	Having underlying disease	0.386(0.062to0.709)	0.1649	0.019
Physical exercise				Having sleep problems	1.717(1.468to1.965)	0.1269	0.000	Having sleep problems	2.644(2.342to2.946)	0.1540	0.000
Exercise normally (Ref)				Physical exercise				Physical exercise			
Less exercise than usual	0.289(-0.161-0.740)	0.2298	0.208	Exercise normally (Ref)				Exercise normally (Ref)			
More exercise than usual	0.777(-0.381-1.935)	0.5908	0.189	Less exercise than usual	0.075(-0.309to0.458)	0.1956	0.703	Less exercise than usual	0.336(-0.129to0.801)	0.2373	0.157
No exercise at all	0.678(0.296-1.061)	0.1952	0.001	More exercise than usual	0.898(-0.088to1.884)	0.5029	0.074	More exercise than usual	0.963(-0.233to2.159)	0.6101	0.115
Drinking alcohol when stressed	0.626(0.057-1.194)	0.2899	0.031	No exercise at all	0.352(0.027to0.678)	0.1662	0.034	No exercise at all	0.592(0.197to0.987)	0.2016	0.003
The potential (eligibility) of the residence for quarantine				Drinking alcohol when stressed	0.775(0.292to1.259)	0.2468	0.002	Drinking alcohol when stressed	1.029(0.442to1.616)	0.2994	0.001
Yes	-0.361(-0.684to-0.038)	0.1649	0.029	Readiness to work at home	0.368(0.128to0.607)	0.1223	0.003	The potential (eligibility) of the residence for quarantine			
Not sure	-0.136(-0.535to0.264)	0.2037	0.506	Awareness of social distancing	-0.756(-1.100to-0.412)	0.1755	0.000	Yes	-0.540(0.1713to-0.876)	0.1713	0.002
No (Ref)				Having difficulty doing social distancing	0.944(0.660to1.227)	0.1448	0.000	Not sure	-0.117(0.2104to-0.530)	0.2104	0.577
Awareness of social distancing	-1.093(-1.497to-0.689)	0.2061	0.000					No (Ref)			
Having difficulty doing social distancing	1.372(1.040to1.705)	0.1698	0.000					Readiness to work at home	0.311(0.020to0.601)	0.1484	0.036
								Awareness of social distancing	-1.201(-1.618to-0.783)	0.2130	0.000
								Having difficulty doing social distancing	1.184(0.840to1.528)	0.1756	0.000

TABLE 3. General Linear Regression for Wave 2 and Wave 3. (Continue)

Depression Attributes				Anxiety Attributes				Stress Attributes			
	B(95%CI)	Std	Sig.		B(95%CI)	Std	Sig.		B(95%CI)	Std	Sig.
Wave 3											
Working in the office	1.212(0.617to1.806)	0.3034	0.000	Working in the office	0.943(0.430to1.455)	0.2614	0.000	Working in the office	1.119(0.513to1.725)	0.3093	0.000
Caring for COVID-19 patients directly	0.766(0.057to1.474)	0.3615	0.034	Caring for COVID-19 patients directly	0.835(0.223to1.447)	0.3122	0.007	Living in the highest surveillance area	1.102(0.512to1.691)	0.3006	0.000
Live in the highest surveillance area	1.051(0.473to1.629)	0.2947	0.000	Living in the highest surveillance area	0.627(0.128to1.127)	0.2547	0.014	Having underlying disease	0.829(0.309to1.349)	0.2654	0.002
Having underlying disease	0.637(0.126to1.149)	0.2610	0.015	Having underlying disease	1.025(0.583to1.467)	0.2256	0.000	Having sleep problems	2.584(2.062to3.106)	0.2663	0.000
Having sleep problems	2.324(1.811to2.838)	0.2618	0.000	Having sleep problems	1.854(1.410to2.298)	0.2265	0.000	Physical exercise			
Physical exercise				Physical exercise				Exercise normally (Ref)			
Exercise normally (Ref)				Exercise normally (Ref)				Less exercise than usual	0.975(0.203to1.748)	0.3941	0.013
Less exercise than usual	0.651(-0.107to1.409)	0.3867	0.092	Less exercise than usual	0.548(-0.109to1.204)	0.3348	0.102	More exercise than usual	0.155(-1.724to2.034)	0.9586	0.872
More exercise than usual	0.055(-1.791to1.902)	0.9421	0.953	More exercise than usual	0.037(-1.563to1.636)	0.8161	0.964	No exercise at all	1.004(0.326to1.682)	0.3460	0.004
No exercise at all	0.770(0.104to1.436)	0.3399	0.023	No exercise at all	0.792(0.215to1.370)	0.2945	0.007	Drinking alcohol when stressed	2.553(1.426to3.681)	0.5755	0.000
Drinking alcohol when stressed	3.293(2.187to4.399)	0.5643	0.000	Drinking alcohol when stressed	2.107(1.173to3.042)	0.4769	0.000	The potential (eligibility) of the residence for quarantine			
The potential (eligibility) of the residence for quarantine				Having difficulty doing social distancing	0.929(0.445to1.412)	0.2467	0.000	Yes	-0.603(-1.145to-0.061)	0.2766	0.029
Yes	-0.660(-1.193to-0.127)	0.2721	0.015					Not sure	-0.022(-0.720to0.675)	0.3559	0.950
Not sure	-0.487(-1.173to0.199)	0.3501	0.164					No (Ref)			
No (Ref)								Having difficulty doing social distancing	1.334(0.765to1.904)	0.2906	0.000
Having difficulty doing social distancing	1.468(0.909to2.026)	0.2849	0.000								

TABLE 4. Ranking of the list of factors affecting stress and the list of factors affecting daily life.

Lists	Wave 2		Wave 3	
	N	Percent of Cases	N	Percent of Cases
Factors affecting stress				
Daily expenses	1783	57.9%	730	61.3%
Changes in daily living patterns	1655	53.7%	698	58.6%
Cost of equipment for disease prevention	1405	45.6%	527	44.2%
Health	1402	45.5%	547	45.9%
Changes of work pattern	1296	42.1%	547	45.9%
Rules and regulations during the COVID-19 pandemic	1262	41.0%	471	39.5%
News and information regarding the epidemics	1254	40.7%	609	51.1%
Higher prices of consumer products	1246	40.4%	542	45.5%
Feeling of anger and dissatisfaction towards lawbreakers, illegal immigration, and those who gather in the casino	1168	37.9%	522	43.8%
Relationship with family members	864	28.0%	400	33.6%
Relationship with colleagues	731	23.7%	321	27.0%
Factors affecting daily life				
Income	1614	54.3%	694	59.5%
Transportation	1576	53.1%	607	52.0%
Protective equipment for COVID-19 prevention	1099	37.0%	385	33.0%
Food	1002	33.7%	562	48.2%
Look after family members or children	841	28.3%	359	30.8%
Accommodation for quarantine and on duty during COVID-19 pandemic	344	11.6%	189	16.2%
Lack of information, knowledge, and how to deal with COVID-19 pandemic	147	4.9%	55	4.7%

Mental health status of staff

The staff at Siriraj Hospital scored significantly lower in the second wave than in the third wave across all three subscales. When the data from the human resources department from the first wave were compared, it was discovered that the scores for depression, anxiety, and stress – Mean (SD) = 4.24 (4.08), 3.33 (3.57), 5.52 (4.43), respectively – were higher than those in the second wave. This trend of the scores declining in the second wave but increasing in the third wave contradicted the previous studies' findings that the scores would continuously decline in consecutive waves.^{5,10,11} However, these previous

studies were conducted among the general population, in contrast to this study, which aimed at results among medical staff. It was hypothesized that the score was higher in the third wave than in the second wave, because in the third wave a more life-threatening mutant strain of COVID-19 that originated in the United Kingdom was spreading in Thailand and resulted in more deaths of infected patients. During this period, Siriraj Hospital was heavily burdened with the care of patients infected with COVID-19, which placed a tremendous psychological strain on the medical staff.

Factors affecting the staff's mental health

Demographic information factors showed significant associations only in the second wave. Staff who were younger scored higher on depression, anxiety, and stress than those older. Furthermore, staff who worked longer hours had significantly higher mental health scores in the second wave, consistent with previous research.¹² In the third wave, there was no significant correlation between mental health status and demographic information. It is likely that as the severity of COVID-19 increases (Wave 3), even older staff members and staff with fewer working hours were also emotionally affected.

Health behaviors were significantly associated with mental health status in both waves. Staff with underlying diseases and sleep problems had significantly higher scores for depression, anxiety, and stress than those without such a history in both waves, which was consistent with previous research.^{13,14} Alcohol consumption when under stress also showed association with depression, anxiety, and stress in both waves. This finding is consistent with previous studies reporting that excessive alcohol consumption during lockdown was associated with depression and mental health problems.¹⁵ In addition, this study found that no exercise at all affected all emotion subscales in both waves, while less exercise than usual (less frequency) was associated only with anxiety and stress solely in the third wave. This finding is in line with synthesizing further empirical findings, which found that anxiety, sadness, and depression can be reduced by physical exercise; and that intensity and frequency of exercise can maintain mental health.¹⁶

No significant association was found between frontline work and mental health status in both waves, consistent with previous research.³ Interestingly, this study found that staff who worked in the office had significantly higher anxiety and stress scores in either the second or third waves than staff who did not work in the office. It is possible that the Faculty of Medicine at Siriraj Hospital implemented policies requiring non-patient staff to work from home, resulting in some experiencing social isolation and changing their work patterns. As a consequence, some staff experienced conflict with family members, which led to stressful situations.^{17,18} In terms of depression, there was a significant correlation only in the third wave, when the outbreak was considered more lethal. A previous study in China, gathering data during a severe outbreak, found that staff whose jobs did not involve COVID-19 patients had higher levels of depression and anxiety than those who were involved with COVID-19 patients.² However, only the third wave of the study revealed a significant association between depression and anxiety

and directly caring for COVID-19 patients. During this wave, hospitals were likely overwhelmed with severely infected patients, placing significant physical and mental pressure on staff in direct contact.¹⁹ In both waves, it was also found that staff who resided in the zones with the highest surveillance rates were more likely to have significantly higher emotional scores than staff who did not reside in such areas. These zones were also affected by lockdown measures that made transportation, access to supplies, and treatment of the disease difficult, all of which can affect mental health status.^{20,21} Only in the second wave were staff with a history of infection exposure outside the hospital more likely to have significantly higher scores for depression, anxiety, and stress than those without history. It is possible that the second wave of the pandemic was relatively restricted to certain areas, so the hospital's ability to treat patients was unaffected.

Staff with difficulty executing social distancing were significantly more likely to have higher levels of depression, anxiety, and stress than staff without difficulty in both waves. This is consistent with previous research showing that people who perceive themselves as effective at social distancing have lower levels of depression, anxiety, and stress.⁷ Furthermore, this study discovered that staff whose residences lacked the potential to self-quarantine were more likely to have higher depression and stress levels in both waves. It is interesting to note that factors such as awareness of social distancing and readiness to work from home did not correlate with mental health status in wave 3, in contrast to the results in wave 2, which showed a correlation. This suggests that unawareness of social distancing skills and not being able to work from home can have a negative impact on staff's anxiety and stress during the initial wave.

Impact of the COVID-19 situation

The two most common factors contributing to stress among the staff in both waves were daily expenses and changes in daily living patterns. Staff also reported that income and transportation were the two most important factors affecting daily life in both waves. It is possible that the lockdown affected individual staff finances, restricting travel and shutting down services, including medical services, leading medical staff to cut back on both regular and overtime hours. This resulted in decreased income²² whilst raising expenditures for protective equipment, non-public transportation²³, food delivery, etc. Staff stress was thus impacted by changes in lifestyle to the new normal.²⁴ In the third wave, news and information about the pandemic increased in importance as a factor affecting stress, up to third rank, replacing the cost of

protective equipment that had previously ranked third in the second wave. Given how easily accessible news and information is in the modern era, people with anxiety desired to know what was happening with the pandemic. Previous research has found that news consumption's frequency, duration, and variety of media are all positively correlated with feelings of depression and anxiety.²⁵ Acquiring false information also exacerbates distress.²⁶ For factors affecting daily life, protective equipment for COVID-19 prevention remained important but dropped from third rank (37.0%) in the second wave to fourth rank (33.0%) in the third wave, being replaced by food consumption (33.7% to 48.2%) as food prices had risen during the pandemic's long duration.²⁷ It is worth noting that protective equipment had the greatest impact on daily life, according to data gathered by the Siriraj Hospital Human Resources Department during the first wave of the pandemic because when the outbreak started, there was a shortage of equipment due to limited supply and higher prices driven by high demand. In the COVID-19 situation, protective equipment was crucial for hospital operations.^{28,29}

Implications, Strengths and Limitations, and Suggestions for future study

The practical implications of this study highlight the need for hospital administrators to prioritize and care for staff mental health during a pandemic situation, especially when the outbreak worsens. They should pay special attention to staff members with health problems, at risk of contracting COVID-19, or having difficulties in dealing with preventive measures, notably office staff who would be working remotely. Psychological support channels such as hotlines and educational programs on stress management should be created. Aid for physical health, including promoting quality sleep and exercise is also required. Furthermore, hospital administrators should proactively assist staff and establish support channels to alleviate the impact on their daily lives, including financial challenges. During the early stages of an outbreak, adequate protective equipment and education for staff on disease prevention and social distancing should be prepared. During more serious outbreaks, reliable news sources should be emphasized along with a reasonable level of news consumption.

In terms of the study's strengths and limitations, its strengths include the large number of respondents, the comprehensive examination of various factors, and the effectiveness of the DASS-21 assessment, known for its acceptable quality. However, since this is a newly emerging pandemic, many of the questions used in

this study did not validate the psychometric property. Furthermore, as an online survey advertised via social media and staff group, the inability to calculate the response rate, the possible bias through peer-sharing links with specific groups or duplicate submissions, and the possible limitations in access to the survey link raise concerns regarding the representativeness of the sample. Given the dual roles of staff in university hospitals—providing healthcare services and teaching—it's crucial to exercise caution when applying the study's finding to non-university-based hospitals.

For further study, qualitative research using in-depth interviews should be conducted in order to gain a thorough understanding of the factors affecting medical staff. A longitudinal study tracking the mental health and well-being of medical staff over time could also provide insight into the long-term effects and changes. Additionally, comparative analysis between different healthcare settings could provide valuable understanding of the differences among medical staff in various contexts. However, the findings of this study should be useful in understanding the factors that affect medical staff and as information for planning to support medical staff should other pandemics occur in the future.

CONCLUSION

The mental health of medical staff was more severe in the third, more critical wave. Health behaviour, infection risk, social distancing challenges, and office work were associated with mental health in both waves. Social distancing awareness and work-from-home readiness were correlated only in the initial second wave, whilst caring for COVID-19 patients impacted solely in the more critical third wave. Finance, lifestyle changes, and protective equipment were commonly stressed in both waves. COVID-19 news played a more important role in the severe third wave.

Author contributions

Nattha Saisavoey contributed to the conception, study design, data collection, and essential revision of the manuscript. Rungarun Anupansupsai designed the study, interpreted and analyzed the data; critically reviewed and wrote the manuscript. Suroj Supavekin conceptualized the study and reviewed the manuscript. Woraphat Rattapha, Juthawadee Lortrakul, and Somboon Hataiyusuk also designed the study and reviewed the manuscript. All authors were involved in the final approval of the manuscript and agreed to be accountable for all aspects of the work.

Conflict of interest

No potential conflict of interest with respect to this article was reported.

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The Association between Visceral Adipose Tissue and Coronary Atherosclerosis in Thai Postmortem Cases

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ABSTRACT

Objective: To determine the correlation between visceral adipose tissue (VAT) and degree of coronary artery stenosis in the Thai population.

Materials and Methods: This prospective cross-sectional study was conducted in 220 Thai postmortem cases. Sex, age, weight, height, waist and hip circumferences were recorded for each case. The intra-abdominal VAT weight of each site was assessed during the autopsy procedure, and degrees of stenosis for three coronary arteries (left anterior descending artery (LAD), right coronary artery (RCA) and left circumflex artery (LCX)) were evaluated in histological examination. Descriptive statistics, bivariate correlation, and multivariate linear regression were used to determine the correlations between VAT and degrees of coronary artery stenosis.

Results: There were 108 female and 112 male subjects with a mean age of 45.95 years old. Waist circumference, waist-hip ratio and VAT in the male subjects were significantly higher than in the female subjects ($p < 0.001$). VAT was well correlated with waist circumference and waist-hip ratio ($p < 0.001$). VAT weights were positively correlated with degrees of LAD, RCA and LCX stenosis, with coefficient correlations (r) of 0.561, 0.453 and 0.451, respectively ($p < 0.001$). Mesenteric and peri-renal adipose tissues produced better correlations than the other sites. Multivariate linear regression showed that sex and age were correlated with stenosis in all three coronary arteries ($p < 0.001$), and mesenteric and peri-renal adipose tissues had strong correlations with LAD stenosis ($p < 0.001$).

Conclusion: VAT weights from all sites were correlated with degrees of coronary artery stenosis. Mesenteric and peri-renal adipose tissues produced better correlations than the other sites.

Keywords: Visceral adipose tissue; coronary atherosclerosis; Thai; obesity (Siriraj Med J 2024; 76: 304-312)

INTRODUCTION

Coronary artery disease (CAD) is the leading cause of death in patients who die from sudden cardiac death.¹ Risk factors for CAD were categorized into traditional risk factors, and non-traditional risk factors such as ankle-brachial index, high-sensitivity C-reactive protein level, and coronary artery calcium score.² Traditional risk factors included sex, age, high blood pressure or hypertension,

impaired fasting plasma glucose or diabetes mellitus, high blood lipid profiles, obesity (high body mass index (BMI) and waist circumference), and smoking.³ Some of the traditional risk factors, namely, hypertension, diabetes mellitus, dyslipidemia, and obesity, can be classified as metabolic syndrome. The prevalence of metabolic syndrome as a risk factor for CAD in 107,933 Thai police officers was 39.24%, and males had a higher

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prevalence than females.⁴ This figure indicated that the number of Thai people at risk for CAD was relatively high. Common cardiovascular risk prediction models in clinical practice, such as the Framingham Risk Score (FRS), Systematic Coronary Risk Evaluation (SCORE) and the World Health Organization/International Society of Hypertension (WHO/ISH) models, still use traditional risk factors to evaluate high-risk people.³ One of these risk factors is being overweight or having obesity. Being overweight and having obesity in the Asian population have been defined as a BMI between 23.5-25 kg/m² and greater than 25 kg/m², respectively.³ Being overweight and having obesity leads to increased visceral adipose tissue (VAT), and this VAT could escalate risks of coronary artery stenosis.^{5,6} Previous studies have suggested that VAT secretes some vasoactive substances and adipocytokines that could increase inflammation and alter glucose and lipid metabolism, leading to increased risks of CAD.^{5,6} In clinical practice, BMI, waist circumference, and waist-hip ratio could be used for assessing risks of CAD because these parameters are related to VAT.^{5,6}

Previous studies on the Thai population have suggested that being overweight and having obesity are also associated with increased risks of CAD.^{7,8} However, there is scarce evidence of the association between VAT and CAD in the Thai population. Jongjirasiri S et al. indicated that the volume of VAT, as assessed by computerized tomography (CT) of the whole abdomen, was positively associated with coronary artery calcium scores in Thai living people.⁹ This finding is in accordance with a study on Chinese living people in Singapore by Ei Ei Khaing N et al., which also showed that VAT measured by CT of the whole abdomen was positively correlated with coronary artery calcium scores.¹⁰ There have been some studies that have conducted assessments of VAT and CAD in cadavers. Edston E showed that there was a positive association between the weight of VAT and degree of coronary artery stenosis ($r = 0.31$) in Swedish cadavers.¹¹ A positive correlation between the amount of VAT and degree of coronary artery stenosis was also demonstrated in dead bodies in Brazil, and it was also found that age had an effect on this correlation.¹²

As there is still scarce information about the association between VAT and CAD in Thai people, the authors aim to study the association between VAT and degree of coronary artery stenosis. In addition, the authors also consider the effect of VAT in each area on the degree of coronary artery stenosis to determine the significant area of VAT that principally affects the degree of coronary artery stenosis. This information will be fundamental data for further studies on CAD in the Thai population.

MATERIALS AND METHODS

Study design and data collection

A prospective cross-sectional study was performed for medico-legal cases sent for autopsy at the Department of Forensic Medicine, Siriraj Hospital, Mahidol University. The inclusion criteria were as follows: Deceased Thai people who were at least 18 years old at the time of death and sent for autopsy at the Department of Forensic Medicine, Siriraj Hospital, Mahidol University between February 14, 2023, and November 30, 2023. The exclusion criteria were as follows: decomposed bodies, bodies which presented with abnormal fluid or blood in abdominal cavities, bodies which presented with cardiac injuries, bodies with fractures of lower extremities, bodies with underlying diseases related to metabolic syndrome and bodies with evidence of cardiac surgeries. This study was approved by the Siriraj Institutional Review Board, Faculty of Medicine Siriraj Hospital, Mahidol University (COA no. Si 120/2023, SIRB protocol No. 947/2565 (IRB3)).

Sex, age, weight, height, waist circumference, hip circumference, and cause of death were recorded for each case. All anthropometric measurements were assessed on all cadavers lying on stainless steel autopsy tables without clothes in supine positions. Body weights were measured in kilograms (kg) to one decimal place on a Tiger® digital balance model TI-01SS. Body heights were assessed in centimeters (cm) from vertex to heel using a stainless steel tape measure. Waist and hip circumferences were measured in centimeters (cm) using a non-elastic measuring tape. The landmarks for measurement of waist circumference and hip circumference were at the mid-position between the lowest rib and the iliac crest and at the point of maximum extension of the buttocks, respectively. Body mass index (BMI) was calculated by using weight (kg) divided by height (m) squared, and waist-hip ratio was calculated by dividing waist circumference (cm) by hip circumference (cm).

Evaluation of visceral adipose tissue (VAT)

The autopsy was performed in each case using the Letulle method, or “en masse” evisceration, and all organs were removed as one block.¹³ Briefly, when skin on the anterior trunk was incised by using a Y-incision, the thorax and abdominal cavity were exposed and visceral fat tissue could be examined. First, omentum was removed from the transverse colon. Then, the small bowel and large bowel were removed from the position just distal to the ligament of Treitz to the area between the sigmoid colon and proximal rectum. After the small bowel and large bowel were removed, the transverse and sigmoid mesocolon were removed from the transverse colon and

sigmoid colon. Next, all of the mesentery was removed from the small intestine (Fig 1.1). Then, blunt dissection of both sides of each ureter was performed, and pelvic organs (including the bladder and prostate in males or the bladder and uterus and both ovaries in females) were identified and removed from the pelvic floor together with both ureters. After this procedure was completed, evisceration was performed by removing the tongue out of the floor of the mouth so that all of neck organs could be pulled down. Then, the vessels at the thoracic inlet were incised so that all of the thoracic organs could be pulled down. Next, both diaphragms were cut from the internal surface of the thoraco-abdominal wall. After the liver, spleen, both kidneys, including peri-renal adipose tissue, and abdominal vessels, including inferior vena cava and abdominal aorta, were dissected from all attachments, the organ block could be pulled down to the pelvic cavity and it could be removed from the body by cutting both sides of the internal and external iliac vessels. After the organ block had been removed, it could be dissected separately into a thoracic block, hepato-biliary block and genito-urinary block. In the genito-urinary block, both sides of the peri-renal adipose tissue were dissected and removed from both kidneys (Fig 1.2). Then, all of the organ blocks were dissected by following the standard procedure to determine the cause of death. According to this procedure, the omentum, mesocolon, mesentery and both sides of the perinephric fat tissue could be collected for weighing on a Sunford® digital balance, model FEH5000, which covered weights from 1-5,000 grams. The amount of adipose tissue taken from each site was recorded, and all adipose tissue weights were used in statistical analysis.

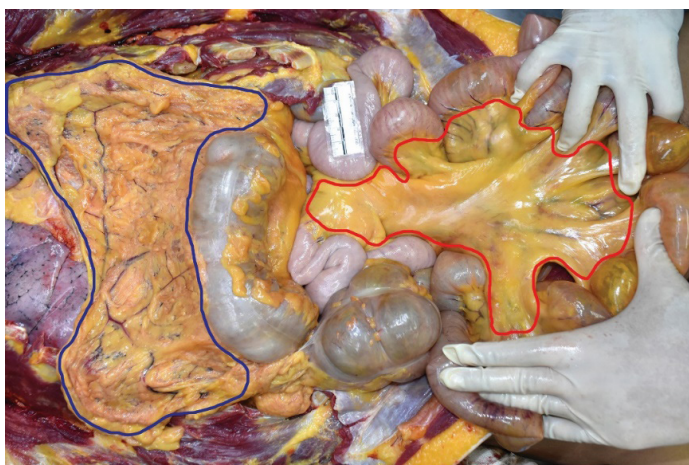


Fig 1.1. Sites for dissection of the omentum (blue circle) and mesentery (red circle).

Fig 1. Assessment of VAT during the autopsy procedure (Fig 1.1 shows the omentum and mesentery, and Fig 1.2 shows the peri-renal adipose tissue.)

Assessment of coronary artery stenosis

Three coronary arteries, which were the left anterior descending artery (LAD), left circumflex artery (LCX) and right coronary artery (RCA), were evaluated as percentage of stenosis according to the serial section of each coronary artery, with around 3-5 millimeters taken from each section. After serial cutting, all of the coronary sections were taken for histology and microscopic evaluation of the percentage of luminal diameter reduction, which was performed on the internal elastic lamina of each side of the coronary artery, was carried out (Fig 2). The maximal point of stenosis of each coronary artery was recorded for statistical analysis.

Statistical analysis

Statistical analysis was performed using IBM SPSS® Statistics for Windows version 25. Descriptive statistics, including the mean, median and standard deviation (SD), were calculated. Kolmogorov-Smirnov test was performed

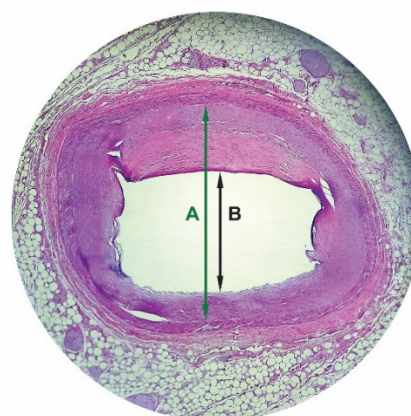


Fig 2. Assessment of degree of coronary artery stenosis in histological examination (degree of coronary artery stenosis = $[(A-B)/A] \times 100$)

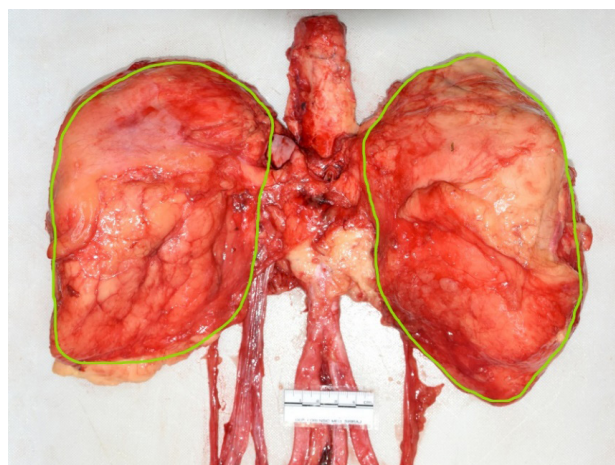


Fig 1.2. Sites for dissection of peri-renal adipose tissue from both kidneys (green circles).

to determine normality testing for descriptive data, anthropometric parameters and degree of coronary artery stenosis and it was found that they were not normally distributed. Thus, comparisons of descriptive data were performed using the Mann-Whitney U test. Correlations between anthropometric parameters and coronary artery stenosis were evaluated by using Spearman's correlation. Multivariate linear regression and multicollinearity testing were performed for anthropometric parameters and VAT levels, with the variance inflation factor (VIF) converged to 1.

RESULTS

There were 220 cases recruited in this study, consisting of 108 females (49.09%) and 112 males (50.91%). The mean age of all subjects was 45.95 years old, whereas the mean ages of female and male subjects were 45.60 and 46.29 years old, respectively. All anthropometric parameters and VAT values were compared between female and male subjects, and results are shown in [Table 1](#). Waist circumference and waist-hip ratio in male subjects were much more statistically significant than

in female subjects ($p < 0.001$). In addition, the amount of VAT in each area and total amount of VAT in male subjects were significantly higher than in female subjects ($p < 0.001$). In addition, male subjects had a higher degree of coronary stenosis than female subjects in all three coronary arteries ($p < 0.001$).

[Table 2](#) shows that both the amount of VAT taken from each site and the total amount of VAT was positively correlated with all of three anthropometric parameters ($p < 0.001$). Looking in detail, it was found that waist circumference generated the highest coefficient correlation (r) with VAT, followed by waist-hip ratio and BMI, respectively, in both genders and all cases except for correlation between peri-renal adipose tissue and anthropometric parameters in male subjects, where the waist-hip ratio produced a higher coefficient correlation (r) than waist circumference and BMI. This finding suggested that waist circumference and waist-hip ratio were better than BMI for indicating VAT amounts.

[Table 3](#) shows the number of subjects who had a degree of coronary artery stenosis $\geq 50\%$, classified by age group. The threshold of 50% was used because this

TABLE 1. Comparison of demographic data in female and male subjects in this study.

Parameters	Female (N = 108)		Male (N = 112)		p-value
	Mean \pm SD	Range	Mean \pm SD	Range	
Age (years)	45.60 \pm 12.92	18-74	46.29 \pm 12.33	21-76	0.753
BMI (kg/m ²)	24.84 \pm 4.11	17.69-36.44	25.98 \pm 3.57	18.17-35.48	0.019
Waist (cm)	82.97 \pm 11.21	62-108	88.46 \pm 8.90	71-112	<0.001
Waist-hip ratio	0.88 \pm 0.06	0.75-0.99	0.94 \pm 0.04	0.83-0.99	<0.001
Omentum (g)	207.44 \pm 148.40	47-972	336.42 \pm 160.02	64-860	<0.001
Mesocolon (g)	111.90 \pm 89.25	20-717	157.95 \pm 94.19	31-553	<0.001
Mesentery (g)	237.26 \pm 153.35	48-764	374.69 \pm 179.18	81-989	<0.001
Peri-renal (g)	264.44 \pm 206.34	43-1294	420.08 \pm 273.64	53-1548	<0.001
Total adipose tissue (g)	821.05 \pm 512.98	195-2886	1289.13 \pm 604.67	289-3053	<0.001
Log (omentum)	2.23 \pm 0.27	1.67-2.99	2.47 \pm 0.23	1.81-2.93	<0.001
Log (mesocolon)	1.95 \pm 0.30	1.30-2.86	2.12 \pm 0.25	1.49-2.74	<0.001
Log (mesentery)	2.29 \pm 0.29	1.68-2.88	2.52 \pm 0.23	1.91-3.00	<0.001
Log (peri-renal)	2.32 \pm 0.30	1.63-3.11	2.53 \pm 0.30	1.72-3.19	<0.001
Log (total adipose)	2.84 \pm 0.26	2.29-3.46	3.06 \pm 0.22	2.46-3.48	<0.001
LAD (% stenosis)	34.14 \pm 26.39	0-92.28	58.40 \pm 27.25	0-92.32	<0.001
RCA (% stenosis)	27.15 \pm 23.70	0-91.86	45.22 \pm 27.22	0-94.67	<0.001
LCX (% stenosis)	18.57 \pm 20.45	0-93.75	34.88 \pm 27.32	0-96.25	<0.001

TABLE 2. Bivariate correlations between VAT and anthropometric parameters.

Parameters		BMI		Waist circumference		Waist-hip ratio	
		r	p-value	r	p-value	r	p-value
Log (omentum)	Female	0.602	<0.001	0.718	<0.001	0.607	<0.001
	Male	0.472	<0.001	0.675	<0.001	0.577	<0.001
	Total	0.550	<0.001	0.723	<0.001	0.676	<0.001
Log (mesocolon)	Female	0.519	<0.001	0.630	<0.001	0.566	<0.001
	Male	0.450	<0.001	0.682	<0.001	0.554	<0.001
	Total	0.506	<0.001	0.679	<0.001	0.613	<0.001
Log (mesentery)	Female	0.625	<0.001	0.711	<0.001	0.551	<0.001
	Male	0.469	<0.001	0.647	<0.001	0.489	<0.001
	Total	0.565	<0.001	0.711	<0.001	0.617	<0.001
Log (peri-renal)	Female	0.619	<0.001	0.688	<0.001	0.526	<0.001
	Male	0.344	<0.001	0.583	<0.001	0.655	<0.001
	Total	0.506	<0.001	0.668	<0.001	0.626	<0.001
Log (total visceral tissue)	Female	0.653	<0.001	0.763	<0.001	0.619	<0.001
	Male	0.469	<0.001	0.715	<0.001	0.660	<0.001
	Total	0.577	<0.001	0.761	<0.001	0.700	<0.001

TABLE 3. Number of subjects with a degree of coronary artery stenosis $\geq 50\%$, classified by age.

Age group	N	LAD $\geq 50\%$ (N)	RCA $\geq 50\%$ (N)	LCX $\geq 50\%$ (N)
<30 years	28	3 (1.4%)	1 (0.5%)	1 (0.5%)
30-39 years	43	13 (5.9%)	9 (4.1%)	5 (2.3%)
40-49 years	52	28 (12.7%)	15 (6.8%)	10 (4.5%)
50-59 years	68	44 (20.0%)	32 (14.5%)	17 (7.7%)
≥ 60 years	29	20 (9.1%)	15 (6.8%)	11 (5.0%)
Total	220	108 (49.2%)	72 (32.7%)	44 (20.0%)

cut-off is still conventionally used to define obstructive coronary artery stenosis in clinical settings.¹⁴ Based on this cut-off, it was found that the number of subjects who had coronary arteries with a degree of stenosis $\geq 50\%$ tended to increase when the ages of subjects in both genders increased until the age of 60 years old. The number of subjects who presented with LAD stenosis $\geq 50\%$ was significantly higher than the number of subjects who had RCA and LCX stenosis $\geq 50\%$ ($p < 0.01$ and $p < 0.01$), respectively.

Correlations between VAT and degree of coronary artery stenosis were analyzed, and the results are shown in Table 4. Virtually all correlations between sites of VAT and the percentage of coronary stenosis were significant positive correlations except for the correlation between the omentum and LCX stenosis in male subjects. Almost all correlations between sites of VAT in female subjects and the degree of coronary stenosis were higher than in male subjects except for the correlation between peri-renal adipose tissue and LAD stenosis. In addition, it

TABLE 4. Bivariate correlations between VAT and degree of coronary artery stenosis.

Parameters		% stenosis					
		LAD	p-value	RCA	p-value	LCX	p-value
Log (omentum)	Female	0.452	<0.001	0.416	<0.001	0.409	<0.001
	Male	0.334	<0.001	0.198	0.036	0.179	0.059
	Total	0.504	<0.001	0.404	<0.001	0.377	<0.001
Log (mesocolon)	Female	0.436	<0.001	0.321	<0.001	0.410	<0.001
	Male	0.327	<0.001	0.210	0.026	0.302	0.001
	Total	0.460	<0.001	0.339	<0.001	0.408	<0.001
Log (mesentery)	Female	0.490	<0.001	0.430	<0.001	0.438	<0.001
	Male	0.375	<0.001	0.253	0.007	0.311	0.001
	Total	0.530	<0.001	0.428	<0.001	0.442	<0.001
Log (peri-renal)	Female	0.443	<0.001	0.443	<0.001	0.387	<0.001
	Male	0.471	<0.001	0.343	<0.001	0.339	<0.001
	Total	0.531	<0.001	0.457	<0.001	0.424	<0.001
Log (total adipose tissue)	Female	0.495	<0.001	0.450	<0.001	0.454	<0.001
	Male	0.446	<0.001	0.292	0.002	0.314	0.001
	Total	0.561	<0.001	0.453	<0.001	0.451	<0.001

was indicated that mesentery and peri-renal adipose tissue produced higher correlations with the degree of coronary stenosis than the other two sites of VAT.

As seen in the aforementioned results, age, sex, waist circumference, waist-hip ratio, and VAT in the mesentery and both kidneys produced higher correlation coefficients compared with other parameters. However, waist circumference and waist-hip ratio produced similar variables to VAT, and this research aimed to concentrate on the effect of VAT on coronary artery stenosis. Thus, age, sex, and mesenteric and peri-renal adipose tissues were considered for multivariate linear regression with

coronary artery stenosis (Table 5). Age and sex showed statistically significant positive correlations with increasing stenosis of all three coronary vessels ($p < 0.001$). However, the mesentery and peri-renal adipose tissue produced only positive correlations with statistical significance with LAD stenosis ($p = 0.026$ and $p = 0.022$, respectively). In addition to such correlations with LAD stenosis, the mesentery produced a positive correlation with statistical significance with increasing stenosis of LCX ($p = 0.046$).

In addition, the cut-off for significant stenosis of coronary vessels as $\geq 70\%$ for indicating disease status in clinical setting was applied to define single LAD disease,

TABLE 5. Multivariate linear regression with statistical significance between age, sex (male), log (mesentery) and log (peri-renal) and degrees of coronary artery stenosis.

Parameters	LAD		RCA		LCX	
	b	p-value	b	p-value	b	p-value
Age (years, 5-unit)	3.934	<0.001	4.206	<0.001	3.552	<0.001
Sex: Male	16.238	<0.001	13.017	<0.001	10.928	<0.001
Log (mesentery)	17.437	0.026	7.259	0.346	14.990	0.046
Log (peri-renal)	16.028	0.022	13.076	0.057	6.570	0.323

single RCA disease, multi-vessel disease and triple vessel disease following the previous guideline.¹⁵ LAD disease and multi-vessel disease were identified as variables that significantly affected the complexity of CAD.¹⁵ Prevalences of single LAD disease, single RCA disease, and multi-vessel disease including triple vessel disease comprised 17.73% (39/220), 4.55% (10/220), 14.09% (31/220), respectively and the overall prevalence of coronary artery disease in this study was 36.36% (80/220). The prevalence of triple vessel disease was separately defined as 5.91% (13/220). However, when age group ≥ 30 and ≥ 35 years old were applied, overall prevalences of coronary artery disease were 40.63% (78/192) and 43.60% (75/172), respectively. Then, mesenteric VAT and peri-renal VAT were compared among those three disease conditions with non-disease group and results were shown in Table 6.

Table 6 shows that mesenteric and peri-renal adipose tissues in all categories of CAD were significantly higher than those in non-disease group. Single LAD disease and multi-vessel disease including triple vessel disease groups produced high statistical significance. However, single RCA disease had less statistical significance compared with single LAD disease and multi-vessel disease both in mesenteric and peri-renal adipose tissues.

DISCUSSION

This study showed that virtually all VAT was significantly correlated with degrees of stenosis in three coronary arteries in both genders of the Thai population.

This finding was consistent with previous studies that indicated correlations between the amount of VAT and severity of coronary atherosclerosis both in non-Asian populations^{11,12} and Asian populations.^{9,16,17} Compared with a previous study of autopsy cases that produced a correlation coefficient (r) of 0.31 between VAT and coronary artery stenosis¹¹, our data had r values of 0.561, 0.453 and 0.451 between the total amount of VAT and LAD, RCA and LCX stenosis, respectively. However, when sex was considered, Thai female subjects had higher correlations between VAT and the degree of coronary artery stenosis than Thai male subjects, and this difference has not been mentioned in any previous studies. Current data only shows that sex hormones, including estrogen and androgens, play an important role in adipose tissue function leading to linkage with metabolic syndrome and might have different effects on the fat distribution and cardiovascular involvement of males and those of females.⁶ In addition, adipocyte characteristics, including low density lipoprotein (LDL) and high density lipoprotein (HDL) particle sizes, in females were different from males.⁶ These two reasons might partially explain the different r-values between Thai females and males. Further study should be conducted to ascertain the effect of gender on correlations between VAT and coronary atherosclerosis in the Thai population.

Of all the sites of VAT, the mesentery and peri-renal adipose tissue were found to have higher significant correlations with degrees of coronary stenosis in all

TABLE 6. Comparison of VAT between different categories of CAD status.

Comparison among different groups			Log (mesentery)	p-value	Log (peri-renal)	p-value
			Mean \pm SD		Mean \pm SD	
1	Non-disease	N=140	2.32 \pm 0.28	<0.001	2.31 \pm 0.29	<0.001
	Single LAD disease	N=39	2.59 \pm 0.22		2.65 \pm 0.27	
2	Non-disease	N=140	2.32 \pm 0.28	0.037	2.31 \pm 0.29	0.007
	Single RCA disease	N=10	2.51 \pm 0.17		2.56 \pm 0.17	
3	Non-disease	N=140	2.32 \pm 0.28	<0.001	2.32 \pm 0.28	<0.001
	Single vessel disease (both LAD and RCA)	N=49	2.57 \pm 0.22		2.63 \pm 0.25	
4	Non-disease	N=140	2.32 \pm 0.28	<0.001	2.31 \pm 0.29	<0.001
	Multi-vessel disease	N=31	2.53 \pm 0.29		2.62 \pm 0.26	
5	Non-disease	N=140	2.32 \pm 0.28	0.002	2.31 \pm 0.29	<0.001
	Triple vessel disease	N=13	2.58 \pm 0.17		2.61 \pm 0.21	

three vessels compared with other sites of VAT. This finding suggested that the mesentery and peri-renal adipose tissue could be practically used for evaluation of VAT correlation with coronary artery stenosis in the Thai population. A previous study showed that VAT that was associated with metabolic syndrome arose from mesothelial cells, which was proven by lineage tracing analysis, and these sites of VAT included the omentum, the mesentery, peri-renal adipose tissue, retroperitoneal fat mass, gonadal adipose tissue and epicardial fat tissue.¹⁸ Regarding mesenteric fat, there has been some evidence indicating that mesenteric adipose tissue is associated with metabolic syndrome leading to cardiovascular risks.^{19,20} Regarding peri-renal adipose tissue, previous studies showed that the amount of peri-renal adipose tissue was correlated with hypertension and dyslipidemia leading to increased cardio-metabolic risks.^{21,22} However, our data from multivariate linear regression only showed that mesenteric and peri-renal adipose tissues had positive correlations with LAD stenosis ($p < 0.001$), whereas the correlations with RCA were not statistically significant ($p > 0.05$), and the correlations with LCX stenosis were statistically significant only with mesenteric adipose tissue ($p = 0.046$). This finding might result from the predominance of LAD stenosis compared with that of RCA and LCX in both genders in this study, as described in Table 3. Another previous study suggested that LAD was affected more by local hemodynamic effects, including turbulent flow and wall shear stress, than RCA and LCX.²³ Thus, LAD was found to be the most prevalent artery for coronary stenosis, and our data was also found to be consistent with this finding. Thus, a larger sample size is required for further study to elucidate the effect of VAT on RCA and LCX stenosis compared with LAD stenosis. When CAD categories based on the previous guideline were applied¹⁵, mesenteric and peri-renal adipose tissues in both single vessel disease (both LAD and RCA) and multi-vessel disease (including triple vessel disease) were significantly higher than those in non-disease group and this finding supported that mesenteric and peri-renal adipose tissues were also associated with CAD in clinical setting. When considering statistical figures, single RCA disease had less statistical significance than single LAD disease and multi-vessel disease. This finding implied that the impact of mesenteric and peri-renal adipose tissues was more prominent on single LAD disease and multi-vessel disease than single RCA disease. However, the number of subjects in single RCA disease group was small and this could affect the statistical analysis. Further study with greater subjects should be conducted to prove the impact of VAT on single RCA disease.

In addition to VAT, increased age and male sex were the other independent factors that had an influence on coronary stenosis, and this effect was statistically significant for all three coronary arteries, as described in Table 5 ($p < 0.001$). Previous studies indicated that increased age and male sex were associated with the presence of coronary atherosclerosis from cardiac imaging.^{9,10,17} In addition, this study showed that waist circumference and waist-hip ratio were more associated with VAT than BMI, and VAT was strongly correlated with the percentage of coronary artery stenosis. Thus, it was suggested that waist circumference and waist-hip ratio might be useful for prediction of coronary artery stenosis, and this finding was consistent with a previous study that used waist circumference for evaluation of metabolic syndrome in Thai police officers.⁴

The main limitation of this study was the reliability of histories of underlying diseases in autopsy cases. Their relatives might not have any information about their underlying diseases because some cases did not have a history of medical check-ups, or they did not recognize their medical conditions. Thus, there might be possible that some subjects who had some underlying diseases and their relatives did not know were included in this study and this might contribute to confounding factors to the statistical analysis. The other limitation was the disproportionate number of subjects in some age groups, particularly in the < 30 years old and ≥ 60 years old groups. Interpretation of coronary artery stenosis in the group aged ≥ 60 years old should be carefully performed.

CONCLUSION

VAT weights from all sites were positively correlated with degrees of coronary artery stenosis, particularly with that of LAD stenosis, and the degrees of significant correlations were higher in female subjects than in male subjects. Of all the sites of VAT, mesenteric and peri-renal adipose tissues produced better correlations with coronary artery stenosis than the other sites and showed significant correlations with the degree of LAD stenosis.

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Conflict of interest

None

Author's contributions

PW and PP contributed to study conceptualization,

literature review and study design. PW contributed to data collection, data analysis, and data interpretation. PW drafted the manuscript and PP performed critical revision. All authors read and approved the final version of this manuscript that was submitted for publication.

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Cancer Immunotherapy: Challenges and Advancements in CAR T Cell Technology

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ABSTRACT

Cancer, characterized by uncontrolled cell proliferation, poses a major global health threat, as evident in the 2022 World Health Organization-International Agency for Research on Cancer report, recording 20 million new cases and 9.7 million deaths worldwide. Thailand alone reported 183,000 new cases and 118,000 fatalities, underscoring the need for tailored prevention, early detection, and treatment strategies. Conventional therapies like surgery, radiation, and chemotherapy, while effective in early stages, face limitations in advanced cases, prompting the development of targeted therapies and immunotherapy, notably chimeric antigen receptor (CAR) T cell therapy. CAR T cell therapy employs genetic engineering to create receptors recognizing cancer-specific antigens. Despite successes in hematological malignancies, challenges such as toxicities, relapse, and high costs persist. Ongoing research, led by the Siriraj Center of Research Excellence for Cancer Immunotherapy (SiCORE-CIT), focuses on advancing fourth- and fifth-generation CAR T cell technologies. SiCORE-CIT's fourth-generation CAR T cells exhibit potent anti-tumor activity against various cancers, surpassing second-generation counterparts. The innovative fifth-generation "Siriraj fifth-generation CAR T cells" secrete anti-PD-L1 scFv, showing potential for diverse cancer applications, highlighting the transformative impact of ongoing research. Successful applications of fifth-generation CAR T cells in B-cell leukemia, lymphoma, and multiple myeloma underscore their transformative potential. This emphasizes the critical role of continuous research in refining therapeutic approaches for both hematologic and solid malignancies. The ongoing exploration and development in this domain have the potential to revolutionize cancer treatment paradigms, significantly contributing to alleviating the global health burden associated with this complex disease.

Keywords: Cancer immunotherapy; Adoptive T-cell transfer; Chimeric antigen receptor (CAR) T cells; Fourth-generation and fifth-generation CAR T cells; Solid tumor application (Siriraj Med J 2024; 76: 313-324)

INTRODUCTION

Cancer, characterized by uncontrolled cell growth and proliferation, poses a substantial global health challenge with intricate biological complexities, including genetic mutations, tumor microenvironment dynamics, and immune system evasion. An epidemiological perspective enables the identification of patterns, recognition of risk factors, and acknowledgment of disparities in cancer occurrence, revealing its extensive impact across diverse

populations. Beyond individual health, cancer brings socio-economic ramifications, including substantial financial burdens, productivity losses, and healthcare access disparities. The World Health Organization's (WHO) cancer agency, the International Agency for Research on Cancer (IARC), has released 2022 estimates, revealing a global cancer burden of 20 million new cases and 9.7 million deaths.¹ Underserved populations bear a disproportionate impact, underscoring the urgent need

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to address global cancer inequities. Lung, breast, and colorectal cancers collectively account for two-thirds of global cases and deaths. Lung cancer tops the list with 2.5 million cases, followed by breast cancer with 2.3 million and colorectal cancers with 1.9 million. The resurgence of lung cancer as the leading cause of cancer death (1.8 million deaths) is linked to persistent tobacco use in Asia. In Thailand, where cancer remains a significant health concern, recent statistics reveal an escalating burden, with an increase in both new cases and cancer-related fatalities in 2022. The prevalence in Thailand was 154.4 age-standardized rate (ASR) per 100,000 persons, with 183,541 new cases diagnosed and 118,829 people succumbing to cancer.²

Cancer, as highlighted by WHO, induces substantial human suffering and places a significant economic burden. The global economic cost of cancer from 2020 to 2050 is estimated at \$25.2 trillion (in constant 2017 prices), equivalent to an annual tax of 0.55% on the global gross domestic product.³ This cost encompasses direct medical expenses, productivity losses due to premature mortality and disability, and strain on healthcare systems. To address this multifaceted issue, a comprehensive approach is imperative, involving public health interventions and policy initiatives. Recognizing and addressing cancer's impact is vital for advancing prevention, early detection, and treatment, contributing to a healthier and more resilient global community, with specific attention to the challenges faced by countries like Thailand.

Current standard cancer treatments, involving surgery, chemotherapy, and radiation therapy, aim to mitigate tumor burden and prevent metastasis. Surgery physically removes tumors, chemotherapy targets rapidly dividing cells, and radiation induces cellular damage. Despite efficacy, these treatments have limitations and adverse effects. Surgery may be constrained by tumor inoperability or risk to vital structures. Chemotherapy leads to systemic toxicity, affecting healthy cells. Radiation faces challenges in delivering high doses while sparing healthy tissues. Resistance mechanisms contribute to treatment failures. The need for personalized, targeted therapies and immunotherapeutic approaches arises in response to current limitations, driving the ongoing quest for more effective and tolerable cancer treatments.

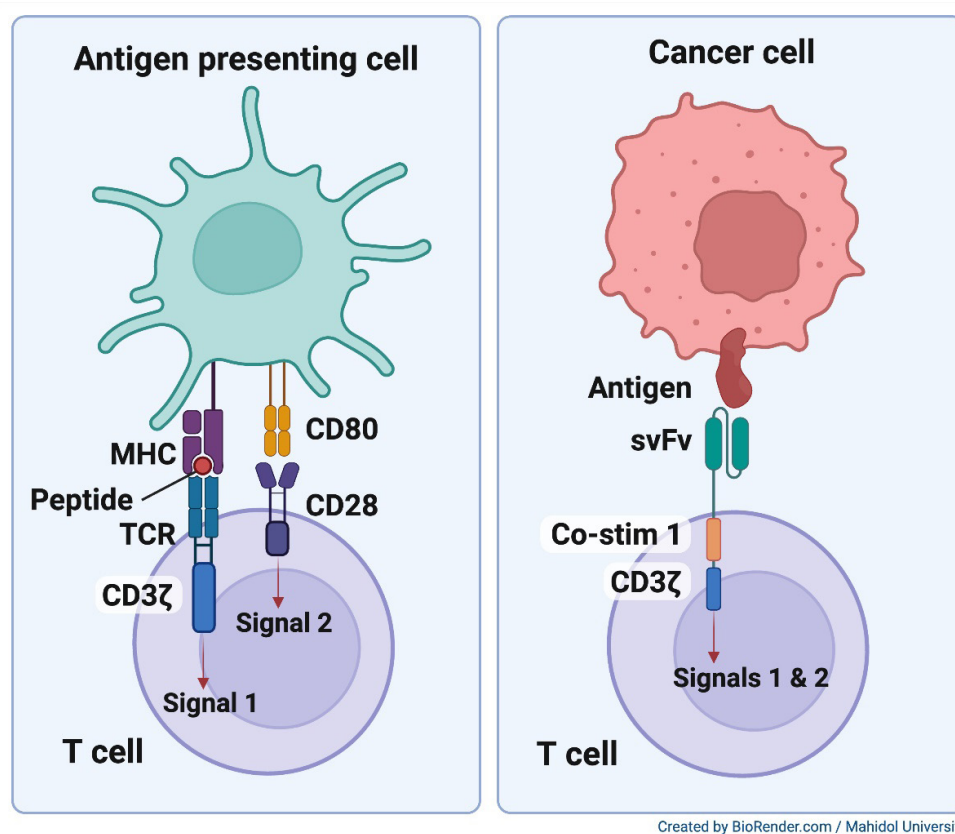
The advancement of cancer therapeutics has witnessed a paradigm shift towards innovative treatment modalities, prominently featuring targeted drug therapy and immunotherapy.⁴ Targeted drug therapy, involving the use of small molecules or monoclonal antibodies, aims to selectively inhibit specific molecular pathways critical to cancer cell proliferation and survival, minimizing

collateral damage to normal cells. Immunotherapy, on the other hand, harnesses the patient's immune system to recognize and eradicate cancer cells by modulating immune responses. An emerging frontier in cancer treatment involves the integration of chimeric antigen receptor (CAR) T cells, a revolutionary form of immunotherapy.⁵ CAR T cell therapy entails the genetic modification of a patient's own T cells to express receptors targeting specific antigens on cancer cells, enabling enhanced and targeted immune responses. This promising approach has demonstrated remarkable success in treating certain hematologic malignancies⁶, heralding a new era in personalized and precise cancer therapeutics. As research continues to unravel the complexities of cancer biology, the integration of these novel strategies holds immense potential for improving treatment efficacy and mitigating the challenges posed by conventional cancer therapies.

Our research team at the Siriraj Center of Research Excellence for Cancer Immunotherapy (SiCORE-CIT) is actively engaged in the exploration of research, development, and innovation in the field of cancer immunotherapy, with a particular focus on advancing CAR T cell technologies. This review article aims to showcase the progress made in our research endeavors, highlighting the innovations in fourth- and fifth-generation CAR T cell therapy. We emphasize the significant potential of these advancements in treating both hematologic and solid malignancies.

Chimeric antigen receptor (CAR) T cell therapy

CAR T cell therapy represents a groundbreaking therapeutic approach within the domain of cancer treatment. Characterized by the genetic engineering of T cells to express artificial receptors, CAR T cells are designed to recognize specific antigens on the surface of cancer cells, thereby enhancing the immune system's targeted response against malignancies. CAR T cells are activated through a unique mechanism compared to normal T cell activation (Fig 1). In the process of normal T cell activation, the T cell receptor (TCR) mediates the recognition of antigens on the surface of infected or cancer cells by interacting with the peptide antigen presented on the major histocompatibility complex (MHC). This interaction triggers a series of signaling events leading to T cell activation. On the other hand, CAR T cells are engineered to express an artificial receptor on their surface, the chimeric antigen receptor (CAR). This receptor combines the antigen-binding domain of an antibody, namely single chain variable fragment (scFv), with signaling domains from TCR (CD3 ζ) and co-stimulatory molecules (such as CD28 or 4-1BB) (Fig 1). When the CAR binds to a specific antigen on the



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Fig 1. Schematic representation of T cell activation pathways comparing normal T cell and chimeric antigen receptor (CAR) T cell responses. In conventional T cell activation (left), the T cell engages with an antigen-presenting cell, initiating signal 1 by the interaction between the T cell receptor (TCR) and the antigen peptide presented on the major histocompatibility complex (MHC) molecule. Signal 2 is facilitated by the binding of a co-stimulatory ligand (e.g., CD80) to the co-stimulatory receptor (e.g., CD28). In CAR T cell activation (right), the engineered CAR molecule, comprising an extracellular single-chain variable fragment (scFv), directly binds to a specific antigen on the cancer cell surface, triggering the simultaneous activation of signals 1 and 2. Notably, CAR T cell activation is MHC independent. Upon activation, CAR T cells undergo proliferation, release cytokines, and exhibit cytotoxic functions, ultimately leading to the elimination of cancer cells.

target cell, it initiates intracellular signaling, bypassing the need for MHC presentation. This direct activation of CAR cells allows for targeted and enhanced immune response against cancer cells or other diseased cells. The salient characteristics of CAR T cells include their capacity for antigen-specific recognition, activation, and proliferation, allowing for a tailored and potent immune response. This innovative therapeutic strategy has demonstrated notable success in the treatment of hematological malignancies, particularly in cases where conventional therapies have shown limited efficacy.

The historical progression of CAR T cells marks a remarkable journey within the realm of immunotherapy. The concept of CAR T cells began to materialize in the late 1980s, culminating in the development of initial, first-generation CAR T cells (Fig 2). However, these early iterations faced limitations due to the absence of co-stimulatory signals, impacting their efficacy. A significant breakthrough occurred in the early 2000s when researchers, notably Carl June from the University of Pennsylvania, USA, successfully pioneered the second

generation of CAR T cells (Fig 2). Carl June played a pivotal role in elevating CAR T cell effectiveness by incorporating a co-stimulatory molecule such as CD28 or CD137/4-1BB into their design.⁷ This innovative step substantially enhanced the activation, proliferation, and persistence of CAR T cells, resulting in more potent and enduring anti-cancer responses. Subsequent advancements led to the development of third-generation CAR T cells, integrating two co-stimulatory domains (e.g., CD28 and CD137/4-1BB) (Fig 2). Recently, our group and others have created fourth-generation CAR T cells, which include three co-stimulatory domains—CD28, CD137/4-1BB, and CD27 (Fig 2) - aimed at further enhancing CAR T cell efficiency and function for the targeted elimination of cancer cells.

Designing CAR molecules and the production of CAR T cells for therapy

The strategic development of a CAR molecule involves a series of crucial steps to ensure its effectiveness and safety. Initially, the careful selection of a target antigen is

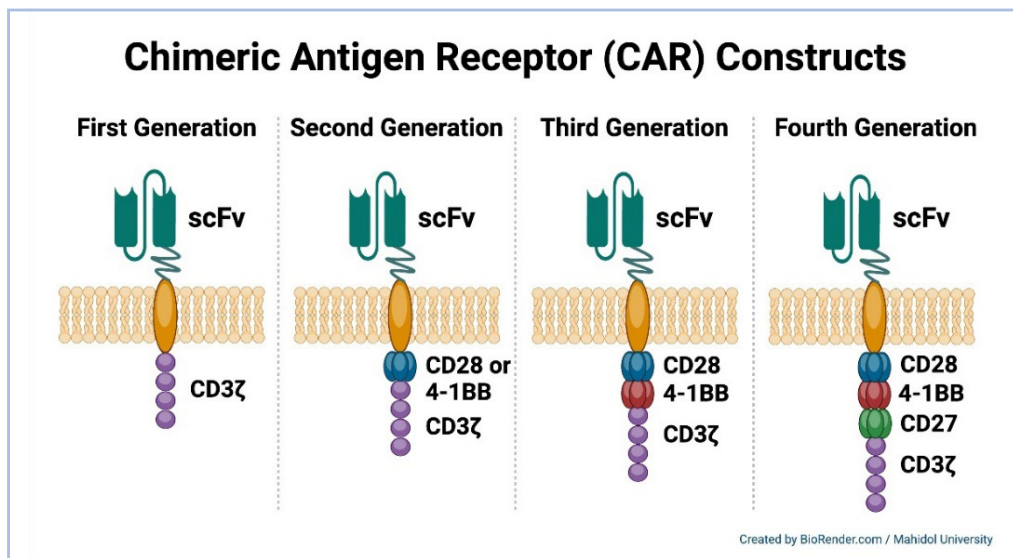


Fig 2. The evolution of CAR T cell generations. The first-generation CAR T cell features a single chain variable fragment (scFv) specific to a target antigen, a transmembrane domain (Tm), and CD3ζ, lacking a co-stimulatory signal. The second-generation CAR T cell includes scFv, Tm, one co-stimulatory molecule (e.g., CD28 or CD137/4-1BB), and CD3ζ. The third-generation CAR T cell is equipped with scFv, Tm, two co-stimulatory domains (e.g., CD28 and CD137/4-1BB), and CD3ζ. In the fourth-generation CAR T cells, scFv, Tm, three co-stimulatory domains (e.g., CD28, CD137/4-1BB, and CD27) are integrated along with CD3ζ.

paramount, focusing on the precise targeting of cancer cells while minimizing the risk of on-target but off-tumor effects. Following this, the meticulous choice of a specific antigen-binding scFv or peptide is essential to facilitate selective binding to the identified target antigen on cancer cells, thereby reducing immunogenicity. The inclusion of the intracellular signaling domain of CD3ζ, essential for generating signal 1, along with co-stimulatory molecules such as CD28, CD137 (4-1BB), or CD27, which contribute to signal 2, constitutes a critical advancement in augmenting the functional capabilities of CAR T cells. Rigorous preclinical validation procedures are then conducted to confirm the expression, functionality, efficiency, and safety of the designed CAR molecule. The conclusive phase involves clinical validation through meticulously designed trials, focusing on the comprehensive assessment of the safety and efficacy of CAR T cell treatment in human subjects. These sequential processes highlight the systematic and rigorous approach necessary for the successful design and implementation of CAR molecules in cancer immunotherapy.

In CAR T cell production, a systematic approach involves identifying and confirming target antigen expression in cell lines and cancer tissues. Subsequently, there is the exploration and selection of a suitable scFv, followed by the design and cloning of the CAR construct into a lentiviral vector. Lentiviruses, engineered to carry the CAR construct that encompasses genes encoding the CD3ζ intracellular signaling domain and co-stimulatory molecules, are

employed for transduction into mammalian cells to assess the expression of the CAR protein. Alternatively, other viral or non-viral vectors may be employed for delivering the CAR construct into the cells. The next step involves extracting lymphocytes from a blood sample and transducing them with lentiviruses carrying the CAR construct. Finally, cultivated CAR T cells undergo expansion, and their phenotypes and functions are assessed to ensure desired therapeutic characteristics. This sequential procedure is essential for the precise development of CAR T cells in cancer immunotherapy.

CAR T cell treatment involves several key steps (Fig 3). First, T cells are collected from the patient through leukapheresis. These T cells are then genetically modified in the laboratory to express a chimeric antigen receptor (CAR) on their surface, enabling them to target specific proteins on cancer cells. The modified CAR T cells are cultured and multiplied to generate a sufficient quantity. Before infusion back into the patient, a conditioning chemotherapy may be administered to enhance the CAR T cells' effectiveness. Once infused, the CAR T cells recognize and bind to the targeted cancer cells, leading to their activation and subsequent destruction. Patients are closely monitored for potential side effects, and follow-up assessments are conducted to evaluate the treatment's long-term efficacy. This innovative immunotherapy has shown promise, particularly in treating certain blood cancers like leukemia and lymphoma.

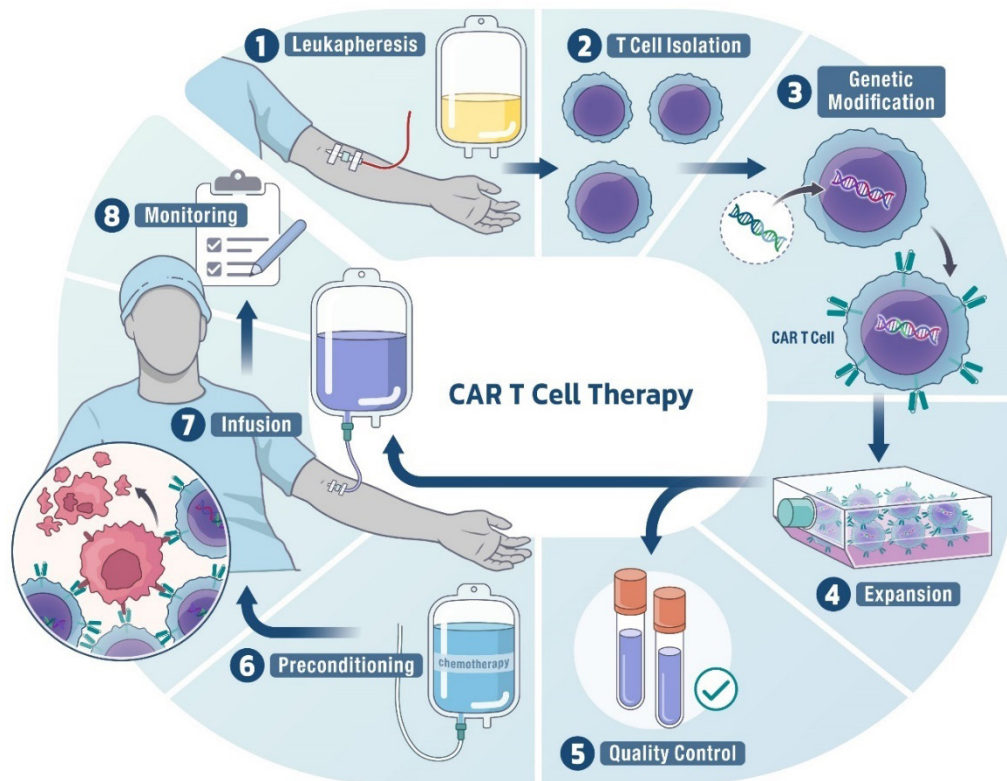


Fig 3. Overview of CAR T cell therapy process. (1) Leukapheresis: White blood cells are collected from the patient. (2) T Cell Isolation: T cells are extracted from the collected sample. (3) Genetic Modification: CAR gene is introduced into T cells, often using viral vectors. (4) Expansion: Modified T cells are multiplied in the laboratory. (5) Quality Control: Modified cells undergo assessment to ensure safety and potency. (6) Preconditioning: Lymphodepleting chemotherapy is administered to the patient. (7) Infusion: CAR T cells are reintroduced into the patient. (8) Monitoring: Regular assessment of the patient's response and management of potential side effects.

FDA-approved CAR T cell therapies for B-cell malignancies in the United States

In 2012, a groundbreaking moment in cancer treatment unfolded with the administration of the first-ever CD19-directed CAR T cell therapy to a 6-year-old pediatric patient suffering from relapsed/refractory B-cell acute lymphoblastic leukemia (r/r B-ALL).⁸ This event marked a significant turning point in cancer therapy. Subsequently, on August 30, 2017, the FDA granted approval for the world's first CAR-T therapy, Tisagenlecleucel, specifically for patients under the age of 25 with r/r B-ALL.⁹ Impressively, the initial patient treated in 2012 has remained cancer-free for over 11 years.⁸ Following this breakthrough, multiple studies showcased outstanding clinical outcomes with CAR-T therapies, resulting in FDA approvals for a total of six CAR T cell products¹⁰, all targeting hematological malignancies (Table 1). While CD19 and B-cell maturation antigen (BCMA) are the only antigens currently approved by the FDA, ongoing research is actively exploring new targets for CAR design. In the realm of acute lymphoblastic leukemia (ALL), CD19-directed CAR T cell treatments like Tisagenlecleucel have demonstrated remarkable response rates. Nevertheless, challenges such as relapse with CD19 antigen loss have

driven investigations into alternative targets like CD22.¹¹ T-cell malignancies present obstacles for CAR T cell therapy due to a lack of appropriate target antigens, but encouraging progress is being made with CAR T cells against CD7 and CD5.¹²

Chronic lymphoblastic leukemia (CLL) poses challenges, including lower success rates and issues with CD19 loss. Research efforts are focused on alternative targets such as CD20, CD23, receptor tyrosine kinase-like orphan receptor 1 (ROR1), and Fc receptor for immunoglobulin M (Fc μ R).¹³ Acute myeloid leukemia (AML) is currently without an FDA-approved CAR-T therapy due to the absence of a specific antigen, but promising targets like CD33, CD123, CD117, and others are actively under investigation.¹⁴ Non-Hodgkin's B-cell lymphoma (NHL) has witnessed remarkable responses to CD19 CAR-T therapies, resulting in FDA approval for multiple products.¹⁵ However, challenges like CD19 antigen loss have prompted exploration of alternative targets like CD20, CD22, CD30, CD33 and CD123.¹⁶ In multiple myeloma (MM), CAR-T therapies targeting BCMA have secured FDA approval¹⁷, while trials targeting non-BCMA antigens like CD38, GPRC5D, SLAMF7, and CD138 are currently underway.¹⁸

TABLE 1. FDA-Approved CAR T Cell Therapies.²²

Brand Name	Generic Name	Target Disease	Target Antigen	Generation and Co-stimulatory Domain	Cost Per Single Dose
Kymriah™	Tisagenlecleucel	Follicular Lymphoma, Diffuse Large B-cell Lymphoma, or Lymphoblastic Leukemia	CD19	Gen 2/4-1BB	\$475,000
Yescarta™	Axicabtagene ciloeucel	Follicular Lymphoma or Diffuse Large B-cell Lymphoma	CD19	Gen 2/CD28	\$373,000
Tecartus™	Brexucabtagene autoleucel	Mantle Cell Lymphoma or Acute Lymphoblastic Leukemia	CD19	Gen 2/CD28	\$373,000
Breyanzi®	Lisocabtagene maraleucel	Large B-cell Lymphoma	CD19	Gen 2/4-1BB	\$410,300
Abecma®	Idecabtagene vicleucel	Relapsed or Refractory Multiple Myeloma	BCMA	Gen 2/4-1BB	\$419,500
Carvykti™	Ciltacabtagene autoleucel	Relapsed or Refractory Multiple Myeloma	BCMA	Gen 2/4-1BB	\$465,000

Despite the successes, CAR T cell therapy confronts various challenges, including common toxicities such as cytokine release syndrome (CRS) and neurotoxicity.¹⁹ Tumor relapse, both antigen-positive and antigen-negative, remains a lingering concern.²⁰ Moreover, the exorbitant cost of the therapy, ranging from \$300,000 to \$500,000 per dose, restricts accessibility.²¹ Ongoing research endeavors aim to tackle these challenges, enhance CAR T cell therapy, and broaden its applicability in hematological malignancies.

Challenges of using CAR T cells in solid tumors

The application of CAR T cells in the context of solid tumors presents a complex set of challenges that significantly hinder their therapeutic efficacy. The physical barriers inherent to solid tumors, characterized by dense stromal tissue, extracellular matrix, and increased interstitial fluid pressure, impede the effective infiltration and distribution of CAR T cells within the tumor microenvironment.²³ Moreover, the immunosuppressive milieu within solid tumors, orchestrated by factors such as regulatory T cells (Treg), myeloid-derived suppressor cells (MDSC), cytokines, and the expression of immune checkpoint proteins like PD-L1 on cancer cells (Fig 4), poses a formidable obstacle to the sustained activity of CAR T cells. This inhibitory

landscape dampens the cytotoxic potential of both native T cells and CAR T cells, compromising their ability to mount an effective anti-tumor response. Overcoming these challenges necessitates innovative strategies, including the engineering of CAR T cells with enhanced tumor-penetrating capabilities, resistance to inhibitory signals, and incorporation of additional functionalities to counteract the suppressive microenvironment. Ongoing research endeavors are focused on unraveling the intricacies of solid tumor biology and tailoring CAR T cell designs to address the unique hurdles posed by these malignancies. As the development of CAR T cells for solid tumors progresses, a comprehensive understanding of these challenges becomes imperative to guide the refinement of therapeutic approaches, ultimately advancing the potential of CAR T cell therapy in the broader spectrum of cancer treatment.²⁴

Challenges inherent in CAR T cell therapy necessitate thoughtful consideration and strategic approaches to address critical concerns. Firstly, there is a pressing need to enhance the efficacy of CAR T cells specifically in the treatment of solid tumors. This prompts exploration into novel methodologies and technologies geared towards augmenting their performance in the context of these challenging malignancies. Secondly, the mitigation of

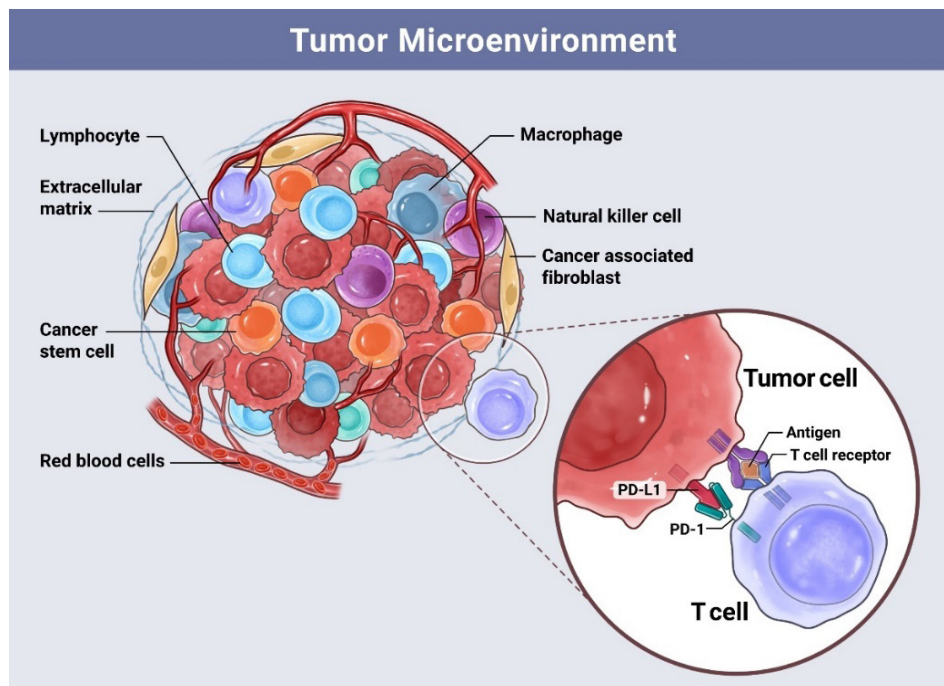


Fig 4. The formidable physical barriers within solid tumors are marked by dense stromal tissue, extracellular matrix, and a tumor microenvironment infiltrated by immunosuppressive cells. Additionally, cancer cells in these tumors express immune checkpoint proteins, such as PD-L1, which interacts with PD-1 to suppress T cell activity.

cytokine release syndrome (CRS), a potentially severe side effect associated with CAR T cell therapy, poses a significant challenge. The development and implementation of effective strategies to minimize CRS constitute a crucial avenue of research and innovation. Thirdly, the formidable hurdles presented by the immunosuppressive tumor microenvironment, marked by the expression of immune checkpoint blockade proteins (such as PD-L1), necessitate innovative approaches to overcome these barriers. Strategies aimed at modulating the microenvironment to favorably impact CAR T cell efficacy are of paramount importance. Lastly, the economic considerations surrounding CAR T cell therapy demand attention, prompting a search for avenues to reduce its cost. Exploring cost-effective technologies, streamlining production processes, and optimizing resource utilization are imperative in addressing this pertinent challenge. In summary, the identified challenges underscore the need for multidisciplinary research and strategic interventions to advance the field of CAR T cell therapy towards enhanced efficacy, safety, and accessibility.

Innovative Fourth-generation CAR T cell therapy for hematologic and solid malignancies

SiCORE-CIT is committed to optimizing CAR T cell therapy, aligning with the global trend of refining designs to overcome challenges in the tumor microenvironment and enhance overall efficacy. Our research group at SiCORE-CIT has pioneered the development of fourth-generation

CAR T cells, aiming to improve functionality, efficiency, and persistence. These advanced cells incorporate three co-stimulatory domains (CD28, CD137/4-1BB, and CD27) fused to CD3 ζ (Fig 5), leading to a significant enhancement of anti-tumor activities, proliferation, and survival. Each co-stimulatory domain offers distinct and shared advantages. CD28 supports T cell proliferation and cytokine production²⁵, providing resistance against activation-induced cell death (AICD).²⁶ CD137/4-1BB not only stimulates T cell proliferation but also enhances T cell survival by inhibiting AICD and boosts cytokine production.²⁷ On the other hand, CD27 fosters T-cell proliferation and facilitates differentiation into effector and memory T cells, positioning it as a potential immune modulatory target for cancer treatment.²⁸ Moreover, we engineered fifth-generation CAR T cells, featuring co-stimulatory domains identical to fourth-generation counterparts and an additional capacity to secrete anti-PD-L1 scFv for inhibiting PD-L1 protein on cancer cells (Fig 5 and subsequent section). Our fourth- and fifth-generation CAR T cells target specific antigens overexpressed in various cancers, such as CD19 in B-cell leukemia and lymphoma; BCMA in multiple myeloma; CD133, MUC1 and integrin $\alpha\beta 6$ in cholangiocarcinoma; and folate receptor α and Trop2 in breast cancer. Table 2 provides a comprehensive compilation of cutting-edge fourth- and fifth-generation CAR T cells meticulously designed by SiCORE-CIT for the treatment of hematologic and solid malignancies.

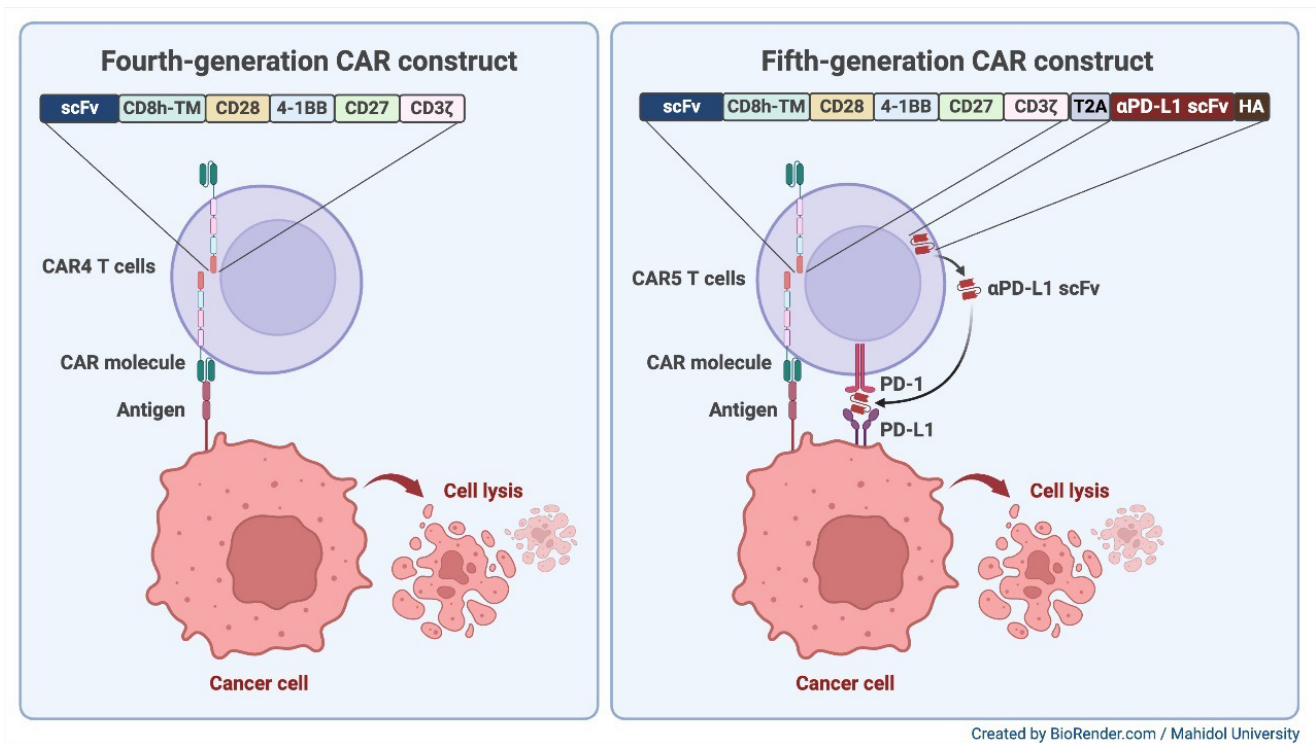


Fig 5. SiCORE-CIT has developed fourth- and fifth-generation CAR T cells. The fourth-generation CAR integrates three co-stimulatory domains (CD28, CD137 or 4-1BB, and CD27) fused to CD3ζ (left). The fifth-generation CAR T cells share similarities with the fourth-generation ones but are additionally engineered to secrete anti-PD-L1 scFv (right).

TABLE 2. Cutting-Edge Fourth- and Fifth-Generation CAR T Cell Therapies for Hematologic and Solid Malignancies.

Fourth-Generation CAR T Cells		
Specific CAR T Cells	Target Cancer	Reference
Anti-CD19 CAR4 T cells	Acute lymphoblastic leukemia (ALL) and B cell lymphomas (BCL)	29
Anti-CD133 CAR4 T cells	Cholangiocarcinoma (CCA)	30
Anti-MUC1 CAR4 T cells	Cholangiocarcinoma (CCA)	31
Anti-Integrin αβ6 CAR4 T cells	Cholangiocarcinoma (CCA)	32
Anti-FRα CAR4 T cells	Breast cancer (BC)	33
Anti-Trop2 CAR4 T cells	Breast cancer (BC)	34
Fifth-Generation CAR T Cells		
Specific CAR T Cells	Target Cancer	Reference
Anti-CD19 CAR5 T cells	Acute lymphoblastic leukemia (ALL) and B cell lymphomas (BCL)	35
Anti-BCMA CAR5 T cells	Multiple myeloma (MM)	36

Fourth-generation anti-CD19 CAR T cells for B-cell malignancies

Autologous T cells expressing CD19-CAR therapy has shown promise for B-cell malignancies. Despite FDA-approved second-generation CD19-CAR T products' clinical efficacy, challenges like adverse effects and cell persistence exist. Fourth-generation CARs (CAR4) containing three co-stimulatory domains (CD28, CD137/4-1BB, and CD27) were developed to address these issues. We generated anti-CD19 CAR4 T cells with fully human scFv (Hu1E7-CAR4) and compared them to murine scFv-based counterparts (mFMC63-CAR4).²⁹ Comparative analyses revealed similar anti-tumor activities and proliferation, with Hu1E7-CAR4 T cells displaying lower cytokine secretion. These findings underscore Hu1E7-CAR4 T cells' clinical viability, warranting further studies and clinical trials.

Fourth-generation anti-CD133 CAR T cells for cholangiocarcinoma

The current treatment paradigm for cholangiocarcinoma (CCA), a lethal bile duct cancer prevalent in the northeast of Thailand, proves ineffective due to the disease's late and advanced stage diagnosis. Urgently required is a novel therapeutic modality, exemplified by the creation of fourth-generation chimeric antigen receptor (CAR4) T cells designed to target CD133, a well-known cancer stem cell marker associated with cancer progression.³⁰ Demonstrating high efficacy against CD133-expressing CCA cells, the anti-CD133-CAR4 T cells induced tumor cell lysis in a dose- and CD133 antigen-dependent manner. Concurrently, significant upregulation of IFN- γ and TNF- α was observed upon tumor treatment. The effectiveness of these anti-CD133-CAR4 T cells extends beyond CD133-expressing CCA, proving beneficial for other CD133-expressing tumors. This study lays the groundwork for future *in vivo* investigations and clinical trials.

Fourth-generation anti-MUC1 CAR T cells for cholangiocarcinoma

Moreover, mucin 1 (MUC1) emerges as an attractive candidate antigen for CCA, given its high expression and association with poor prognosis. Anti-MUC1-CAR4 T cells, evaluated in CCA models³¹, exhibited increased production of TNF- α , IFN- γ , and granzyme B compared to untransduced T cells when exposed to MUC1-expressing KKU-100 and KKU-213A CCA cells. These CAR4 T cells demonstrated specific killing activity against KKU-100 and KKU-213A cells, while showing negligible cytolytic activity against immortal cholangiocytes. Furthermore, anti-MUC1-CAR4 T cells effectively disrupted KKU-

213A spheroids, supporting their development as an adoptive T cell therapeutic strategy for CCA.

Fourth-generation A20 CAR T cells for cholangiocarcinoma

Additionally, integrin $\alpha\beta6$, upregulated in several solid tumors but minimally expressed in normal epithelial cells, emerges as a promising target antigen for CAR T cell immunotherapy in CCA. Investigating integrin $\alpha\beta6$ expression in pathological tissue samples from liver fluke-associated CCA patients revealed overexpression in 23 of 30 (73.3%) cases, with a significant association between high integrin $\alpha\beta6$ expression and shorter survival time.³² Lentiviral constructs encoding CARs targeting integrin $\alpha\beta6$ were engineered, resulting in highly expressed A20-CAR2 and A20-CAR4 in primary human T cells, both exhibiting significant cytotoxicity against integrin $\alpha\beta6$ -positive CCA cells.³² Notably, A20-CAR2 and A20-CAR4 T cells displayed anti-tumor function against integrin $\alpha\beta6$ -positive CCA tumor spheroids. Upon specific antigen recognition, A20-CAR4 T cells produced a slightly lower level of IFN- γ but exhibited higher proliferation than A20-CAR2 T cells, positioning them as a promising adoptive T cell therapy for integrin $\alpha\beta6$ -positive CCA.

Fourth-generation anti-FR α CAR T cells for breast cancer

To address advanced breast cancer (BC), we developed fourth-generation CAR (CAR4) T cells targeting folate receptor alpha (FR α), a BC-associated antigen.³³ These CAR T cells, with FR α -specific scFv and three costimulatory domains (CD28, CD137/4-1BB, and CD27) linked to CD3 ζ , demonstrated potent anti-BC activities. Cocultured with FR α -expressing MDA-MB-231 BC cells, anti-FR α -CAR4 T cells exhibited specific cytotoxicity, with enhanced activity against cells with higher surface FR α expression. This specific cytotoxicity was absent when cocultured with FR α -negative normal breast-like cells (MCF10A). In a 3D spheroid model, anti-FR α -CAR4 T cells effectively reduced spheroid size and induced breakage, highlighting their anti-tumor potential. This proof-of-concept study shows the feasibility and promise of anti-FR α -CAR4 T cells for adoptive T cell therapy in BC, offering a potential strategy for future clinical exploration.

Fourth-generation anti-Trop2 CAR T cells for breast cancer

The overexpressed trophoblast cell surface antigen 2 (Trop2) in BC is a promising immunotherapeutic target. A fourth-generation CAR (CAR4) was developed, featuring

an anti-Trop2 single-chain variable fragment (scFv) with three costimulatory domains CD28/4-1BB/CD27 and CD3 ζ , enhancing BC therapy.³⁴ Anti-Trop2 CAR4 T cells demonstrated heightened cytotoxicity and interferon-gamma (IFN- γ) production against Trop2-expressing MCF-7 cells compared to conventional second-generation CAR (CAR2; CD28). Notably, anti-Trop2 CAR4-T cells exhibited superior long-term cytotoxicity, proliferation, and specific targeting of Trop2-positive BC cells in both two-dimensional (2D) and three-dimensional (3D) cultures. Post-antigen-specific killing, these cells robustly secreted interleukin-2 (IL-2), tumor necrosis factor-alpha (TNF- α), IFN- γ , and Granzyme B compared to non-transduced T cells. This study emphasizes the therapeutic potential of anti-Trop2 CAR4-T cells in adoptive T cell therapy for BC, holding significant promise for advancing BC treatment strategies.

Innovative Fifth-Generation CAR T cell Therapy for Hematologic and Solid Malignancies

In our continuous effort to enhance the effectiveness of fourth-generation CAR T cells against cancers, our research group at SiCORE-CIT introduces a cutting-edge advancement: fifth-generation CAR T cells. These innovative CAR T cells, named ‘*Siriraj fifth-generation CAR T cells*’, are engineered to secrete anti-PD-L1 scFv (Fig 5), distinguishing them from their predecessors. These fifth-generation CAR T cells possess the dual capacity to target and eliminate cancer cells expressing specific antigens while concurrently secreting anti-PD-L1 scFv, inhibiting PD-L1 on cancer cells and augmenting their killing potential. Recent reports highlight successful developments for B-cell leukemia and lymphoma (CD19)³⁵ and multiple myeloma (B-cell maturation antigen or BCMA).³⁶ Ongoing efforts aim to extend this innovation to fifth-generation CAR T cells designed for cholangiocarcinoma, breast cancer, retinoblastoma, and osteosarcoma. In this review, we delve into two fifth-generation CAR T cells: anti-CD19 CAR5 T cells for lymphoma and anti-BCMA CAR5 T cells for multiple myeloma (MM) (Table 2).

Fifth-generation anti-CD19 CAR5 T cells for B cell lymphoma

Lymphomas, predominantly B cell in origin, exhibit varying behaviors from slow growth to high aggression. Despite successful responses to chemotherapy in certain lymphomas, approximately 30–40% of aggressive B cell lymphomas (BCL) like Burkitt lymphoma (BL) and diffuse large B cell lymphoma (DLBCL) fail to respond or relapse after standard treatment. Immunotherapies, including

adoptive T cell therapy with chimeric antigen receptor (CAR) T cells targeting CD19, have shown promise but face challenges in aggressive BCL. We engineered fourth-generation CAR T cells (CAR4-T) with three costimulatory domains targeting CD19 (anti-CD19-CAR4-T). Seeking to enhance their efficacy against PD-L1-positive tumors, we further developed anti-CD19-CAR5-T cells secreting anti-PD-L1 scFv.³⁵ Our study demonstrated that anti-CD19-CAR5-T cells exerted more effective cytotoxicity and superior proliferation compared to anti-CD19-CAR4-T cells. Importantly, the secreted anti-PD-L1 scFv not only promoted self-proliferation of anti-CD19-CAR5-T cells but also restored the cytotoxic effect of anti-CD19-CAR4-T cells inhibited by PD-L1 expression on target cancer cells. Anti-CD19-CAR5-T cells exhibited lower proinflammatory cytokine release and demonstrated cytotoxicity against PD-L1-positive tumors even at lower cell numbers. This study provides substantial evidence for the enhanced antitumor efficiency of anti-CD19-CAR5-T cells, highlighting their potential for further investigation in *in vivo* models and clinical trials against aggressive B cell lymphomas.

Fifth-generation anti-BCMA CAR5 T cells for multiple myeloma

Multiple myeloma (MM), representing 1% of all cancers, necessitates novel therapeutic approaches due to frequent relapses despite advancements in cancer treatments. Chimeric antigen receptor-T (CAR-T) cell therapy targeting B-cell maturation antigen (BCMA) has gained FDA approval for MM, but limitations persist in achieving durable responses. Our research group developed third-generation anti-BCMA CAR T cells with CD28/4-1BB costimulatory domains and demonstrated superior antitumor efficiency. To further enhance CAR T cell persistence, we explored the CD27 costimulatory domain and engineered fourth-generation CAR T cells (CAR4-T) with CD28/4-1BB/CD27, showcasing potent antitumor efficiency across various tumor models. Recognizing programmed death-ligand 1 (PD-L1) as an immune inhibitory factor, we hypothesized that disrupting the PD-1/PD-L1 interaction could enhance CAR-T responses. Our previous work demonstrated that fifth-generation CAR T cells (CAR5-T) secreting anti-PD-L1 scFv mitigate PD-L1-mediated T cell inhibition in B-cell lymphoma.³⁵ In this study, we constructed anti-BCMA-CAR5-T cells capable of secreting anti-PD-L1 scFv.³⁶ Both anti-BCMA-CAR4-T and anti-BCMA-CAR5-T cells exhibited comparable antitumor activity against parental MM cells. However, only anti-BCMA-CAR5-T cells maintained cytolytic activity against PD-L1 high

MM cells, demonstrating their superiority. Anti-BCMA-CAR5-T cells also exhibited increased proliferation, release of cytolytic mediators, and specific cytotoxicity against BCMA-expressing target cells, presenting a potential advancement in MM CAR-T therapy. Further validation through animal models and clinical trials is warranted to assess efficacy and safety comprehensively and facilitate translation into clinical practice.

CONCLUSION

Our research at SiCORE-CIT delves into preclinical studies to thoroughly understand the therapeutic potential, safety, and mechanisms of action inherent in fourth- and fifth-generation CAR T cells. CAR4 T cells, demonstrating heightened cytotoxicity compared to CAR2 T cells, have proven effective against both leukemic and solid cancer cells. Furthermore, CAR4 and CAR5 T cells showed reduced cytokine release, particularly IL-6, suggesting a potential decrease in cytokine release syndrome (CRS) during CAR T therapy. Notably, the secretion of anti-PD-L1 scFv from CAR5 T cells effectively inhibits PD-L1 expressed on cancer cells, enhancing the cytotoxic function and proliferation of CAR5 T cells. Additionally, CAR5-T cells demonstrated efficient cytotoxicity against PD-L1-expressing cancer cells, achieving notable results with fewer cell numbers. Our research trajectory highlights our unwavering commitment to advancing the frontiers of cancer immunotherapy, aiming to translate these innovations into meaningful clinical interventions for the betterment of cancer patients.

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Conflict of interest

The author declares no conflict of interest.

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Lung and Airway Disease Caused by E-Cigarette (Vape): A Systematic Review

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ABSTRACT

Vape use is increasing among the youth and there is a catchphrase that vape is the solution to conventional tobacco smoking. Some case reports show the impact of vape use in the form of lung injury. However, there are no studies that definitively determine how many cases and what kind of problems in the lungs and airways can be caused by the use of vape and this is the purpose of our research. This systematic review article used several databases with the keywords «Vape OR E-cigarette» and «Disease.» We screened and eliminated articles based on the PEOS framework. The included articles were analyzed for risk of bias using the JBI critical appraisal tool. A total of 16 articles were included and involved 313 patients in this review. Several case reports show the incidence of pulmonary infections in vape users, lung damage (EVALI), respiratory failure, burning throat, and various other events associated with vape use. The duration of vape use also varies before the appearance of the disease and the earliest use duration is six months and the longest is up to years. Vape use poses a risk of lung and airway disease and requires further study to accurately determine the degree of risk of the impact of vape use on lung and airway health. In conclusion, vape circulation vigilance needs to be considered because the impacts can cause health issues and interfere with the achievement of health goals for all.

Keywords: Lung disease; e-cigarette; vape (Siriraj Med J 2024; 76: 325-332)

INTRODUCTION

Electronic cigarettes (e-cigarettes), often known as vapes, are gadgets that allow users to vaporize flavors and nicotine solutions instead of burning tobacco leaves as is done with traditional cigarettes.¹ E-cigarettes are now readily available, and their use has skyrocketed all across the world. A 2019 study by Cullen et al.² evaluated the prevalence of e-cigarette usage among teenagers in the United States and found that high school and middle school students were the most likely to report using them; 10.5% of middle school students (from 8837) and an estimated 27.5% of high school students (from

10.097) presently use e-cigarettes. According to a 2020 study by Habib et al., 12.2% (49/401) of medical students reported using e-cigarettes, with men three times more likely to do so than women. The most common reasons in this research for using e-cigarettes were to enjoy the variability in flavors (61.4%), to reduce or quit tobacco smoking (29.5%), and to avert the public smoking ban (13.6%).³

E-cigarettes are actively marketed as a cheaper, healthier, more socially acceptable option, and a tool for quitting smoking.⁴ This may lead to an increase in vape usage, particularly among young individuals. However,

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several studies are starting to demonstrate the negative impacts of vaping on health. In-vitro analysis by Shi et al.³ in 2022 demonstrated that vaping led to a buildup of inflammatory cells in the alveolar space, surrounding the pleura, and in the bronchial lumen. According to this, inhaling vape for four hours may result in respiratory tract irritation. Although reports of cases involving the effects of e-cigarette use on people are starting to rise, there are still few studies that demonstrate the effects on other aspects of health, leaving the public with a low level of knowledge. A systematic review is required to be able to assess the effect of vaping on health comprehensively. This study examined the effects of vaping on health with a particular emphasis on pulmonary and airway conditions. This study is meant to increase public awareness of the negative effects that vaping can have on health.

MATERIALS AND METHODS

Data sources and search strategy

For reporting in systematic reviews, we used Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and synthesis without meta-

analysis. PubMed, Science Direct, Epistemonikos, and Google Scholar were all databases we used to search for articles. We used keywords such as “E-Cigarette OR Vape OR Vaping” AND “Pulmonary OR Disease OR Injury”. We incorporate all research: (1) Full text, (2) English or Indonesian Language, (3) last 10 years and we exclude review articles. The search strategies are described in full in Fig 1. Unpublished data and duplicate research were disregarded. This systematic review is registered at PROSPERO with number ID: CRD42023434514.

Study Selection

Four researchers (AMS, MERP, NAP, and AH) independently evaluated eligibility based on titles and abstracts using the PEOS framework (Population = Human; Exposure = E-Cigarette OR Vape; Outcome = Pulmonary OR Airway Disease; Study = Case Report OR Observational Study OR Clinical Trial). The consensus was reached between investigators to resolve disagreements, or supervisors (SS, IES) were involved when consensus could not be reached.

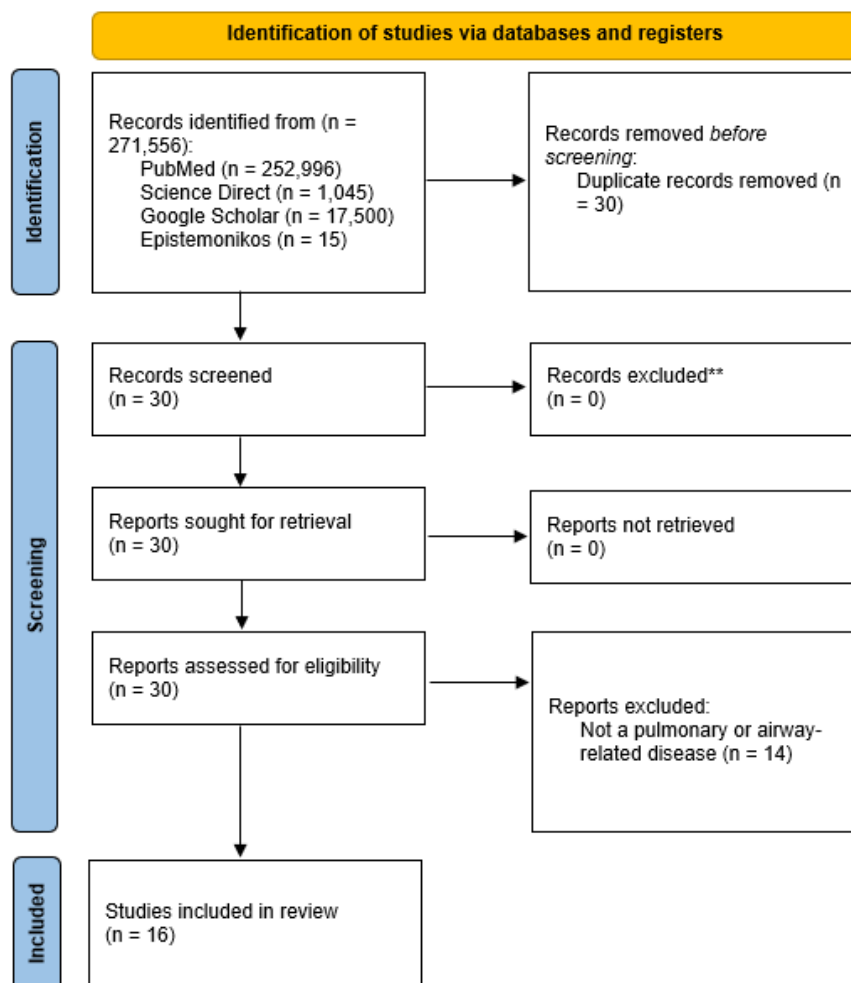


Fig 1. Flow Diagram of Included Studies Based on PRISMA Flow Chart

Data Extraction and Risk of Bias

From each included study, data were taken on : (1) First author's name, (2) Year of study, (3) Study design, (4) Country, (5) Sample size, (6) Age, (7) Gender, (8) Historical disease, (9) Dual/Single User, (10) Ingredients of E-liquid, (11) Imaging/Radiology, and (12) Diagnosis. A dual user is someone who smokes conventional cigarettes and also vapes and a single user is a vape user only without smoking other conventional cigarettes. The primary outcome was to determine pulmonary and airway diseases caused by e-cigarettes (Vape) and categorize the diagnosis we received from articles.

According to the type of articles received, AMS, MERP, NAP, and AH examined full-text articles using the Joanna Briggs Institute Critical Appraisal Tool (jbi.global/critical-appraisal-tools). We count each "yes" from the tools and make it in the form of a score. If the score for each article is below 75% it is considered a "high risk of bias," Consensus was reached to resolve the disagreements, or when consensus could not be established, supervisors (SS, IES) were involved.

RESULTS

Study selection

A total of 271.556 articles were identified from the research database (Fig 1). After removing the duplicate

articles, 30 articles were screened and assessed for eligibility. A total of 16 studies were included in the review, after excluding 14 studies due to out-of-scope based on inclusion criteria.

Characteristics of included studies

Table 1 shows a resume of the characteristics of the articles we included. Of the articles we included, most had a case report design and some were RCTs. The articles we received were mostly from the US and a few from Belgium, Italy, and Canada. In the case of a disease caused by vape, this was suffered by a variety of ages from 17 years old at the youngest and 54 years old at the oldest found in this data compilation. The effects were gender agnostic and some were reported to have a diverse medical history, which was collected in this review to see if there was any influence of this medical history on e-cigarette-related illnesses.

Pulmonary and Airways Disease Caused by E-Cigarette (Vape)

Table 2 shows a collection of lung and airway diseases caused by e-cigarettes (vaping). This table is grouped according to agreed disease categories such as airway infection, E-Vaping Acute Lung Injury (EVALI), respiratory failure, and others that have various diseases.

TABLE 1. Characteristics of included studies.

Study, Year	Design	Country	N	Age (year)	Gender	Historical Disease
Savage, 2023 ⁷	Case Report	America	1	17	M	CAP
Kooragayalu, 2020 ²³	Case Report	America	1	26	F	Scizoaffective
Massey, 2021 ²⁴	Case Report	America	1	33	M	Dental Infection
Chen, 2021 ⁸	Case Report	America	3	18,19,34	1F,2M	Asthma
Chaumont, 2019 ²⁵	RCT	Belgium	25	23±0.4*	7F, 18M	NA
Roman, 2021 ⁹	Case Report	America	1	31	M	Paroxysmal Atrial Fibrillation
Aftab, 2019 ²⁶	Case Report	America	1	26	F	Asthma
Drabkin, 2020 ⁶	Case Report	America	1	19	M	NA
Fryman, 2020 ¹⁰	Case Report	America	5	29,34,24,54,27	2F, 3M	NA
Lin, 2020 ²⁷	Case Report	America	1	34	F	Low-Grade Carcinoid Tumor
Edmonds, 2020 ²⁸	Case Report	America	1	31	F	Untreated Hepatitis C
Grech, 2022 ²⁹	Case Report	America	1	52	F	Obesity
Lucchiari, 2019 ³⁰	RCT	Italy	210	62.8±4.58*	98F, 132M	NA
Chaumont, 2019 ³¹	RCT	Belgium	30	38±2*	M	NA

Abbreviations: CAP: Community-Acquired Pneumonia, F: Female, M: Male, NA: Not Available

*: Mean±SD

TABLE 2. Pulmonary and airway disease caused by E-Cigarette (Vape).

Study, Year	Dual/Single User	Ingredients of E-Liquid	Duration of Vaping	Imaging	Result	Diagnosis
Lung Physiology Impairment						
Chaumont, 2019 ²⁵	S	Nicotine	During Experiment	CT-Scan	Extensive Bilateral Alveolar Infiltrates	Lung Inflammation
Pulmonary Infection						
Savage, 2023 ⁷	S	Nicotine	Every day for 5 years	X-Ray	Right lung pleural effusion	Empyema (Streptococcus)
Kooragayalu, 2020 ²³	S	Tobacco and Marijuana	NA	X-Ray	Bilateral Patchy Opacities	EVALI + Pneumonia (<i>Mycoplasma pneumoniae</i>)
Massey, 2021 ²⁴	D	Marijuana	1 – 2x/day (1 year)	X-Ray	Bilateral Pulmonary Vascular Congestion	<i>Actinomyces odontolyticus</i> infection
Chen, 2021 ⁸	D/S	Nicotine, THC, dabbing, and Cannabinoid	6 months	CT-Scan	5x9cm Cavity	Non-Tuberculous Mycobacteria
EVALI						
Roman, 2021 ⁹	D	Cannabis Oil	3-5x/day	CT-Scan	Bilateral Alveolar Opacities	EVALI
Aftab, 2019 ²⁶	S	Nicotine and Marijuana	NA	CT-Scan	Consolidation and ground-glass opacity	EVALI
Drabkin, 2020 ⁶	S	Nicotine and Marijuana	NA	CT-Scan	Bilateral ground-glass opacities	EVALI
Fryman, 2020 ¹⁰	S	Nicotine and Marijuana	NA	CT-Scan	Ground glass opacities	Acute Respiratory Failure
	S	Marijuana	Several years	CT-Scan	Consolidation	Acute Respiratory Failure
	S	Marijuana	NA	CT-Scan	Bilateral diffuse nodular opacities	Acute Respiratory Failure
	S	Marijuana	2x/week	CT-Scan	Patchy, bilateral ground glass opacities	Acute Respiratory Failure
S	Marijuana	2 months	CT-Scan	Reticulonodular opacities	Acute Respiratory Failure	
Others						
Lin, 2020 ²⁷	D	NA	Everyday	CT-Scan	Nodular Ground Glass Opacities	Pulmonary Granulomatous
Edmonds, 2020 ²⁸	S	Cinnamon and Nicotine	Every day	CT-Scan	Consolidation	Diffuse alveolar Hemorrhage
Grech, 2022 ²⁹	D	Nicotine	1 year	NA		Extreme Carboxyhaemoglobinemia
Lucchiari, 2019 ³⁰	S	Nicotine	6 months			Burning Throat

Abbreviations: D: Dual, D/S: few participants dual users, few are single users, EVALI: E-Vaping causing Acute Lung Injury, Gly: Glycerol, NA: Not Available, PG: Propylene glycol, S: Single, THC: Tetrahydrocannabinol

It was found that the diversity of users in the data was dual users and single users and was dominated by single users. The content of E-liquid is very difficult to know for sure because vape users can use various liquids with a variety of different contents. Some liquids contain nicotine and some that do not contain nicotine. In Table 2, the E-liquid content reported in the study has been compiled and it can be seen that there is a diversity of liquid content. Some E-liquids only contain nicotine, some contain mixed marijuana content, and others do.⁶⁻⁹

Table 2 also collected data on the duration of e-cigarette use. What is different between tobacco smoking and e-cigarette is the Brinkman Index which can determine the severity of smoking that correlates with disease (number of cigarettes per day x duration of smoking (years)). As e-cigarettes do not have such an index, the data collected are the reported duration and have their diversity. From this study, some durations that can be said to be very short can cause a lung problem with a duration of six months, and even some during the experimental period in the RCT have problems due to the use of e-cigarettes. The results of lung imaging also varied, such as diffuse ground-glass infiltrates, pleural effusion, pulmonary congestion, and others. Diagnostically, there was diversity such as non-tuberculous mycobacteria, empyema, and a combination of EVALI with pneumonia. The incidence of EVALI is well-known but Fryman's study showed that it lasted until respiratory failure. Other uncategorized events include asthma, burning throat, and carboxyhemoglobinemia.¹⁰

Risk of Bias

Fig 2 displays the risk of bias score of each article included using the JBI Critical Appraisal tool. The average

JBI score for all articles was 83.63% with the lowest score being 75%. No article was found to have a score below 75%.

DISCUSSION

Summary and interpretation of findings

The use of e-cigarettes that are predicted to be safe and not cause harm to health can be questioned. This review found various incidents of pulmonary and airway diseases that could potentially be caused by vape. There are several events such as lung infections, burning throat, asthma, and EVALI related to respiratory failure. This is certainly dangerous and has the potential to injure human health. No studies have been found regarding the impact on a person exposed to smoke from e-cigarettes, and this study only focused on direct users of these devices. The potential health problems caused to people who are around e-cigarette users are very possible but there are no studies that show this. This review can be interpreted as the use of e-cigarettes can cause various lung and respiratory diseases and related research is also still very minimal so the use of e-cigarettes must be monitored for its impact on health and also its circulation.

Potential damaging content and mechanism of lung and airway damage caused by E-cigarette (VAPE)

Electronic cigarettes are very different from traditional cigarettes in terms of their chemical makeup. The chemical-filled liquid is heated in electronic cigarettes and turned into vapor. When you take into account the chemical makeup and how it affects the body of the user, it's not hard to say that electronic cigarettes are just as toxic as traditional cigarettes.

Electronic cigarette liquid can have a variety of

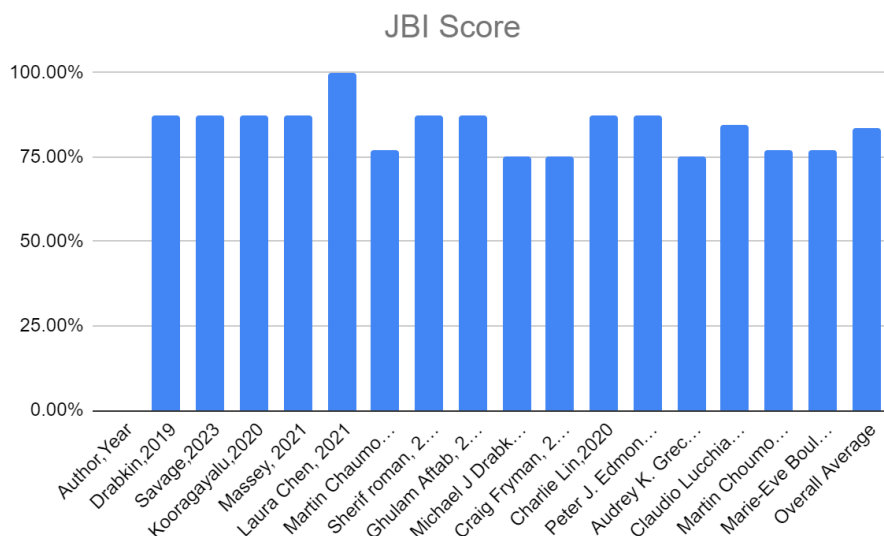


Fig 2. Risk of Bias Score with JBI Critical Appraisal Tools

chemical makeup. Common butter flavoring ingredients in e-cigarette liquids include diethyl and 2, 3-pentanedione, which can harm the respiratory epithelium's cilia activity and impair lung function.⁴ Diacetyl in electronic cigarettes is also thought to contribute to fibrosis and destruction of the respiratory epithelium, which results in bronchiolitis obliterans.⁵ Formaldehyde displays toxicity that can cause oxidative stress, endoplasmic reticulum stress, mitochondrial malfunction, and inflammation as a result of its interaction with proteins and DNA.⁵ The primary components of e-cigarette liquid, propylene glycol, and glycerin, have been shown to disturb the homeostasis of lung immune cells, leading to inflammation. This is one of the many mechanisms that are still not fully understood in terms of the possibility of EVALI occurring in electronic cigarette users.⁵

According to other research, users who inhale the vitamin E included in e-cigarette liquid may experience cytotoxicity that results in acute lung damage.⁶ In the meantime, smoking increases the creation of mucus, slows down cell division, and, due to a persistently reduced inflammatory response, raises the risk of respiratory viral infections.⁷

The tastes included in the liquid used in electronic cigarettes are another way they are distinguished. Plethysmography and flexion lung function tests were done in a study employing a mouse model, and the findings revealed that a combination of vegetable glycerin or propylene glycol with vanilla flavoring reduced lung function metrics.⁸ The combination of these components also had an impact on immunoglobulin levels, markedly raising IgG1 levels. Additionally, lipid mediator levels were raised by vegetable glycerin or propylene glycol.⁸ Some studies suggest that lung disease is not only caused by the liquid content, but also by coil power, coil resistance, coil heat, and even nicotine and PG/Gly levels in the liquid. Differences in levels and settings in electric tokens can change the size of smoke particles that can settle in the alveoli of the lungs.⁹

Several studies have tested vapes and taken samples from the airways of those affected by lung disease. The examination found the presence of Vitamin E Acetate (VEA). This VEA is a thick clear liquid used as an additive in vape products that contain tetrahydrocannabinol (THC).¹⁰ VEA (or vitamin A, retinoic acid) is used as an additive to dissolve/dilute (cutting agent) THC oils alongside minerals, coconut oil, and triglyceride medium chain oils, and is also used as a thickening agent for other non-THC e-liquids. This VEA is safe in food, but harmful when inhaled as it can cause oxidative stress and inflammatory responses.¹¹ THC itself is one of the

active substances that provide psychic effects due to the content of psychoactive molecules.¹² This mixture of VEA and THC has been used and traded since the spring of 2019. When VEA is heated to a certain temperature, it breaks down into Ketene gas, alkene, and benzene, which are highly toxic.^{10,13} When tested in animals, VEA caused acute lung injury when inhaled from e-cigarettes.¹⁰ Vitamin E acetate is attracting increasing attention as a potential culprit in the pathophysiology of EVALI outbreaks. Vitamin E acetate was found in 94% of LAB samples collected from EVALI patients.¹³

In contrast to e-liquid constituents, lipid derivatives from “endogenous” sources such as epithelial lining fluid (ELF) and/or lung surfactant and its constituents, namely phospholipids, including *dipalmitoylphosphatidylcholine* (DPPC), may also be associated with the innate immune cell inflammatory response of Electronic Nicotine Delivery Systems (ENDS) users. Therefore, dysregulation of airway lipids may also contribute to ENDS in the presence of an associated inflammatory response and may also be involved in EVALI. This not only leads to EVALI but also to the development of other comorbid conditions involving cardiomyopathy.¹¹

The epithelium is the initial barrier in the lungs, but exposure to e-cigarette aerosols not only sloughs off epithelial cells but also disrupts the integrity of the epithelial barrier. Inhalation of VEA causes pulmonary edema, neutrophilia, epithelial cell death, and lymphocyte-dominant perivascular inflammation, as well as reduced production of surfactant protein A. In addition, vaping also disrupts mucociliary clearance, which is very important for airway protection from toxic substances, making it easier for infection, colonization, and growth of pathogenic bacteria which, coupled with the presence of nicotine contained in the liquid, also reduces phagocytosis and decreases bactericidal activity. Vape also reduces the frequency of ciliary surfaces with decreased ATP production resulting from disorganized mitochondria. Exposure to e-cigarette vapor reduces airway surface fluid hydration and increases mucus viscosity.¹⁴

Several physiological mechanisms, including pulmonary surfactant, mucociliary clearance, and phagocytosis of inhaled particulates, are critical in maintaining airway homeostasis. Airway epithelial cells (AEC), including alveolar type I (AT-I) and type II (AT-II) cells, alveolar macrophages (AM), and granulocytes or polymorphonuclear cells (PMN) are the innate immune cells of the airway. This physiological function is one of the first responses after exposure to aerosol/vape ENDS. AMs are resident professional phagocytes that digest and degrade various inhaled irritants, pathogens, and apoptotic cells by

“efferocytosis” to help reduce the inflammatory response in damaged tissues. Vape exposure will cause changes in the phenotype and function of AMs that will suppress their efferocytic activity which helps reduce inflammation.¹⁵

E-cigarettes cause adverse health effects through direct contact of aerosols with tissues or cells of the oral cavity and lungs or through systemic effects on multiple organs including the heart, brain, eyes, and kidneys. Damage to organs other than the lungs is caused by injury to the lungs. This lung damage can occur because e-cigarette exposure induces the secretion of proinflammatory cytokines, including interleukins (IL-1, IL-6, IL-8) and Tumor Necrotic Factor (TNF- α) from epithelial cells and immune cells in the upper airway, and lungs. Some studies have also reported the discovery of specific patterns of detectable neutrophil signaling. In the sputum of e-cigarette users, the neutrophilic granule proteins neutrophil elastase, proteinase 3, leukocidin 1, and myeloperoxidase were significantly increased, indicating neutrophil activation through e-cigarette exposure which markedly increased the expression of CD11b and CD66b which play an important role in neutrophil activation. Furthermore, exposure to e-cigarette vapor extract caused an increase in IL-8 and protease activity, including neutrophil elastase and matrix metalloproteinase. Increased proteases can damage the lung basement membrane and extracellular matrix, causing emphysema.¹⁴

Differences in electronic devices and wattage applied affect the particle size of the vapor that can settle in the pulmonary alveoli and cause changes in many cytokines within the airways and lung parenchyma. Vaping produces an increase in reactive aldehyde species leading to cellular accumulation of 4-hydroxynonenal, which induces apoptosis, mitochondrial dysfunction, and protein inactivation. E-cigarette exposure also directly induces cellular damage by promoting increased oxidative stress and DNA damage, leading to an increased risk of lung cancer.^{9,14}

Limitation, strength, and future research direction

The weakness of this study is that it only collects data on diseases potentially caused by e-cigarettes. This study has not been able to determine exactly whether the disease is caused by vaping directly or whether there are other factors that a health problem to arise in humans. However, the concept is clear that chemical compounds that enter the respiratory tract that are not commonly inhaled by humans have the potential to cause problems in the future. The strength of this study is to gather evidence of current health problems that can be caused by e-cigarette users. Thus, it can invalidate the justification

for using e-cigarettes because it is safer than conventional smoking.

Directions for future research are to find means to determine the severity of vape use such as the Brinkman index for conventional cigarette users. The Brinkman index uses the number of cigarette butts used per day multiplied by how many years the patient smokes. This certainly cannot be used in the case of e-cigarettes because what is used is E-liquid in milliliters (mL). Possibly it could be measured by how many mL of E-liquid are used in one month or how many bottles of E-liquid are used and multiplied by the duration of the year of e-cigarette use. However, this requires further research, especially the limits of mild, moderate, and severe degrees.

For future research, it is also necessary to pay attention if there are health problems in vape users whether the patient is a dual or single user because the use of conventional cigarettes has the potential to react to cause a disease. Other research is also needed to determine the risk of disease directly caused by vape.

CONCLUSION

The use of e-cigarettes (Vape) has the potential to cause pulmonary and airway diseases, so it is necessary to break the justification that e-cigarettes are safe to use. With its users increasingly angry, especially among teenagers, the circulation of vape needs to be concerned because of its impact on health and interfering with the success of achieving joint health. Today, the use of conventional cigarettes (tobacco smoking and others) has become a global problem because it has health impacts not only on the users but the surroundings of those living with cigarette smoke. The use of e-cigarettes will potentially be the same if uncontrolled circulation and research on the impact on health is carried out as well as minimal education of the dangers of future use of e-cigarettes.

Conflict of interest

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