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Research Article

Decision Self-Efficacy and Decisional Conflict on Reintubation among Surrogates of Ventilated Patients Undergoing Planned Extubation

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ABSTRACT

Purpose: Although the medical decision-making process can be overwhelming for some surrogates, there is a lack of understanding regarding their experiences. The objectives of this study were to examine the decision self-efficacy and decisional conflict experienced by surrogates in intensive care units (ICUs) when faced with the decision of whether to reintubate patients with respiratory failure after a planned extubation. In addition, predictors and mediators influencing these decision-making processes were identified.

Methods: This study utilized a cross-sectional design to investigate the decision-making processes of 174 surrogates who were faced with the decision of whether to reintubate patients with respiratory failure after a planned extubation in the internal ICU of a medical center between August 2021 and February 2022. Structured questionnaires were administered to collect data on the surrogates' background information, decision self-efficacy, decisional conflict, and positive and negative affect. The patients' background information was also collected. Univariate and multivariate analyses were performed to model the data.

Results: The mean decision self-efficacy score of the surrogates was 82.41 points, and 20.7% surrogates had decisional conflict scores exceeding 37.5 points, suggesting that they faced challenges in the decision-making process. Surrogates' employment status and negative affect significantly predicted their decision self-efficacy. In addition, patients' activities of daily living prior to hospitalization and the decision self-efficacy of the surrogate significantly predicted surrogate decisional conflict. The impact of surrogates' negative affect on decisional conflict was fully mediated by decision self-efficacy.

Conclusions: Surrogate decision self-efficacy mediates the relationship between negative affect and decisional conflict. Providing clinical care interventions that focus on enhancing surrogate self-efficacy and reducing negative affect can help alleviate decisional conflict in this population.

Introduction

Critically ill patients often experience delirium and are administered sedatives that may affect their cognitive state, which can impair their ability to express their thoughts and make medical decisions [1]. In such cases, surrogates are responsible for making medical decisions by navigating various treatment options for their loved ones within a limited timeframe and under considerable pressure [2]. Surrogates of patients in the final six months of their lives face high levels of decisional conflict [3]. Decision regret is reported to be common among surrogates of adult patients in the intensive care unit (ICU). Approximately 20% of surrogates experienced moderate to solid regret about end-of-life or life-support decisions made in the last six months of a patient's life [4].

Surrogates of critically ill patients often experience negative emotions, such as fear, anger, and depression, as a result of sleep deprivation and cognitive blunting, which further impedes their decision-making abilities [5,6]. When faced with medical decision-

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making, individuals often experience decisional conflict, which can lead to uncertainty about choices and personal values, ultimately resulting in delayed decision-making [7]. Identifying surrogate decisional conflict in the ICU contributes to the further development of intervention plans, promotion of communication between healthcare providers and families, and prevention of conflict [8].

Making medical decisions for patients is a multifaceted process that requires consideration of both the patient's benefits and the surrogate's own needs and preferences [9]. Among the various medical decisions made by surrogates on behalf of patients, those related to major surgery and life support are considered the most challenging [10]. Reintubation decisions for patients with respiratory failure are particularly critical as they directly impact the lives of critically ill patients and can be challenging for surrogates. When an intubated patient requiring mechanical ventilation to assist respiration passes the spontaneous breathing trial (SBT) test, the patient meets the criteria for extubation. However, after extubation, a medical decision regarding whether to reintubate may be required for these patients [11]. In a previous study, patients who failed planned extubation and required reintubation presented a statistically more significant incidence of tracheostomy than those who were successfully extubated [12]. In Taiwan, the percentage of patients who elect to undergo tracheostomy is approximately 2.7% in the ICU [13], which is substantially lower than the 40.6% reported for Iran [14] and the mean of 10.7% reported for 12 other countries [15]. Intubated patients who opt against reintubation after planned extubation may prefer to avoid invasive medical treatment. In such cases, noninvasive ventilation options, such as noninvasive positive-pressure ventilators or high-flow nasal cannulas, can be used. However, if these devices fail to support adequate oxygenation, there is a risk of death [16,17]. When physicians ask the surrogates of critically ill patients whether to reintubate, the decision is linked to the possibility of tracheostomy or death. To date, limited research has been conducted on the decision self-efficacy of surrogates in the ICU when participating in medical decision-making. Although the medical decision-making process can be overwhelming for some surrogates, there is a lack of understanding regarding their experiences.

The Ottawa Decision Support Framework is a theoretical paradigm that provides guidance for evaluating the needs and outcomes of individuals engaged in the decision-making process. This framework comprises three key elements: (1) decisional needs, which pertain to understanding the difficulties that decision-makers may encounter during the decision-making process, such as decisional conflict and low decision self-efficacy; (2) decisional outcomes, which involve assessing the results or consequences of the decision-making process; and (3) decision support, which encompasses providing information and assistance to decision-makers during the decision-making process, including offering advice, decision tools, and emotional support. The provision of decisional support holds the potential to improve decisional outcomes, such as reducing decisional conflict [18].

The self-efficacy theory emphasizes that self-efficacy refers to an individual's self-confidence or belief in their ability to modify behavior or adopt a new self-care activity to achieve his or her goal [19,20]. Decision self-efficacy refers to an individual's self-confidence or belief in his or her ability to make decisions, including the ability to participate in shared decision-making [21]. The individual's self-efficacy is affected by various factors, such as performance accomplishments, emotional arousal, verbal persuasion, and performance accomplishments [19,20]. This study based on the Ottawa Decision Support Framework [18] and self-efficacy theory [19] is aimed to investigate decision needs (decision self-efficacy and decisional conflict) faced by surrogates when deciding whether to reintubate critically ill patients after planned extubation, which is a life-sustaining decision. By examining the surrogates' decision self-efficacy and decisional conflict and identifying related influencing factors, including patient and surrogate background information, surrogates' positive and negative affect were evaluated (Figure 1). The main hypotheses posit significant

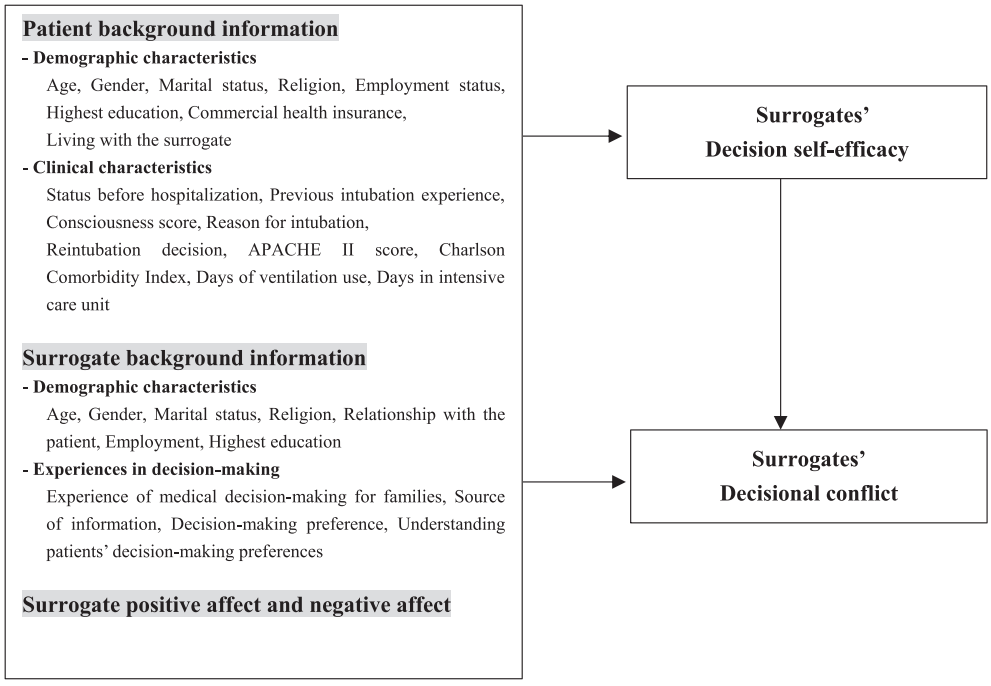

Figure 1. Conceptual Framework for Research

relationships among the following: (1) there is a statistically significant relationship between patient background information and surrogate decision self-efficacy/decisional conflict; (2) there is a statistically significant relationship between surrogate background information and decision self-efficacy/decisional conflict; (3) there is a statistically significant relationship between surrogates' positive/negative affect and their decision self-efficacy/decisional conflict; (4) there was a statistically significant relationship between surrogates' decision self-efficacy and their decisional conflict; and (5) there is a mediation effect of surrogates' decision self-efficacy on the relationship between their positive/negative affect and decisional conflict.

Methods

Design and setting

A cross-sectional research design was used to survey surrogates responsible for deciding whether to reintubate critically ill patients following planned extubation in the internal medicine ICU of a medical center located in northern Taiwan between August 2021 and February 2022. Structured questionnaires were used for data collection.

Participants and sample size

In this study, the surrogate was defined as the person who signed the consent form for reintubation or opted out of reintubation for the patient. The inclusion criteria for this study were as follows: (1) surrogates of intubated patients connected to a ventilator who passed the SBT, (2) surrogates aged ≥20 years, and (3) surrogates who had the ability to understand the content of the questionnaire and to complete it. The exclusion criteria were as follows: (1) surrogates of intubated patients who were connected to a ventilator due to surgery and (2) surrogates of patients who required a tracheostomy tube connected to a ventilator.

The sample size required for this study was estimated using G-Power 3.1.9.4 software (Faul, F. Kiel University, Germany). Based on a correlation of −.39 between decision self-efficacy and decisional conflict reported in a previous study [22] and assuming a type I error rate of .05 and a type II error rate of .8, an effect size of $f^2 = .1794$ was expected. The estimated required sample size was 165, with 32 independent variables in the study. To satisfy this requirement, 174 sets of participant data were collected and analyzed. During the recruitment period, 210 surrogates met the inclusion criteria, and 185 of them were invited to participate. Of these, 182 agreed to participate, and three declined owing to time constraints. Of the 182 questionnaires returned, two were incomplete, and six were excluded owing to changes in the patient's condition, resulting in no extubation. Ultimately, 174 questionnaires were obtained.

Instruments

Background information

The background information questionnaire consisted of 17 items for the critically ill patients and 11 items for the surrogates (Tables 1 and 2). Content validity was tested by five experts, and the content validity index ranged from .8 to 1.0 for patients' and surrogates' background items. Furthermore, as the study was conducted during the coronavirus disease 2019 (COVID-19) pandemic, the number of new confirmed COVID-19 cases in Taiwan on the days when surrogates filled out the questionnaire was also recorded [23].

Decisional Self-Efficacy Scale (DSES)

The DSES developed by Bunn and O'Connor [21] is used to measure an individual's self-confidence or belief in medical decision-making, including participation in shared decision-making. The DSES consists of 11 questions, each rated on a five-point Likert scale ranging from “0” indicating no confidence at all to “4” indicating very confident. The total score is calculated by summing the scores of all items, dividing by 11, and then multiplying by 25. The scores range from 0 to 100, with higher scores indicating better decision self-efficacy [24]. The English version of the DSES has a value of Cronbach's α of 0.96, and an exploratory factor analysis showed that the scale was a unidimensional construct that could explain 81% of the variance [25]. The Chinese version of the DSES, based on a translation by Taiwanese scholars, has a value of Cronbach's α of 0.93 and a content validity index of .98 [26]. Cronbach's α for the DSES was 0.94 in this study.

Decisional Conflict Scale (DCS)

The DCS includes 16 items that are further divided into five subscales: uninformed, values clarity, support, uncertainty, and effective decision. The DCS is scored on a five-point Likert scale where “0” indicates complete agreement and “4” indicates complete disagreement. The total score is obtained by adding all subscale scores, dividing the sum by 16, and multiplying by 25. The scores range from 0 to 100 [27]. Scores <25 suggest a firm decision, while scores ≥37.5 suggest delayed or uncertain decision-making [28,29].

The original English version of the DCS has a value of Cronbach's α ranging from 0.78–0.92 for the overall scale and from 0.58–0.92 for the subscales. The test-retest reliability coefficient at two-week intervals was .81, indicating good stability and discriminant validity [7]. In a previous study involving 472 surrogates in the ICU of a medical center, the DCS demonstrated good reliability and validity, with a value of Cronbach's α ranging from 0.75–0.85, factor loadings in confirmatory factor analysis ranging from .58–.96, and a normed-fit index >.95 [30]. The version of the DCS translated into Chinese has the same construct validity as the original scale, with a value of Cronbach's α ranging from 0.74–0.92 [31]. In this study, Cronbach's α for the DCS was 0.97.

Positive and Negative Affect Schedule (PANAS)

This study used the Chinese version of the PANAS [32], which was translated and revised by Fang [33]and includes 10 items each for positive and negative affect. Questionnaires used a four-point Likert scale (ranging from 1 to 4), with “1” indicating “slightly,” “2” indicating “sometimes,” “3” indicating “often,” and “4” indicating “very often.” The total score ranges from 10 to 40 points, with higher scores indicating higher levels of positive or negative affect. A higher score for positive affect indicates a better mood, whereas a higher score for negative affect indicates a worse mood [33].

The Chinese version of the PANAS [33] has demonstrated good internal consistency, with Cronbach's α values of 0.89 and 0.85 for positive and negative affect, respectively. Exploratory factor analysis showed that positive and negative affect accounted for 29.88% and 21.65% of the variance, respectively. Confirmatory factor analysis showed a χ^2/df ratio of 2.46, a goodness fit index of .91, a normed fit index of .95, and a non-normed fit index of .96. All indicators met the expected levels and indicated good construct validity for the scale [33]. Cronbach's α was 0.88 for both the positive and negative affect subscales in this study.

Data collection

This study obtained a list of patients undergoing the SBT from the REDCap database of the internal medicine ICU of the study

Table 1 *Patient Background Information and Associations with Surrogates' Decision Self-Efficacy and Decisional Conflict.*

Variable	*n* (%)	Decision Self-efficacy		Decisional Conflict			
		Mean ± SD	*t/F*	≤37.5 *n* (%)	>37.5 *n* (%)	*B* (SE)	*OR*
Gender			0.23				
Woman	63 (36.2)	82.79 ± 17.16		51 (37.0)	12 (33.3)		
Man	111 (63.8)	82.18 ± 16.18		87 (63.0)	24 (66.7)	0.16 (0.40)	1.17
Marital status			0.57				
Married/Widowed	138 (79.3)	82.81 ± 16.86		111 (80.4)	27 (75.0)		
Single/Divorced	36 (20.7)	81.87 ± 15.14		27 (19.6)	9 (25.0)	0.32 (0.44)	0.73
Religion			−0.14				
None	88 (50.8)	82.23 ± 16.48		70 (50.7)	18 (50.0)		
Yes	86 (49.4)	82.58 ± 16.60		68 (49.3)	18 (50.0)	0.03 (0.37)	1.03
Employment status			−1.01				
Unemployed/Retired	129 (74.1)	81.66 ± 17.35		70 (50.7)	18 (50.0)		
Employed	45 (25.9)	84.54 ± 13.71		68 (49.3)	18 (50.0)	0.03 (0.37)	1.03
Highest education			−0.31				
High school or lower	110 (63.2)	82.10 ± 17.09		84 (60.9)	26 (72.2)		
College or above	64 (36.8)	82.91 ± 15.54		54 (39.1)	10 (27.8)	−0.51 (0.41)	0.60
Status before hospitalization			0.45				
Independent	114 (65.5)	82.82 ± 15.15		97 (70.3)	17 (47.2)		
Assistance needed	60 (34.5)	81.63 ± 18.91		41 (29.7)	19 (52.8)	0.97 (0.38)	2.64*
Previous intubation experience			0.90				
Yes	48 (27.6)	84.23 ± 16.27		37 (26.8)	11 (30.6)		
No	126 (72.4)	81.71 ± 16.59		101 (73.2)	25 (69.4)	−0.18 (0.41)	0.83
Commercial health insurance			0.48				
Yes	71 (40.8)	83.13 ± 15.34		60 (43.5)	11 (30.6)		
No	103 (59.2)	81.91 ± 17.31		78 (56.5)	25 (69.4)	0.56 (0.40)	1.75
Living with the surrogate			0.99				
Yes	107 (61.5)	83.39 ± 15.22		87 (63.0)	20 (55.6)		
No	67 (38.5)	80.83 ± 18.36		51 (37.0)	16 (44.4)	0.31 (0.38)	1.36
Consciousness score[a]			−0.12				
GCS ≥8	162 (93.1)	82.36 ± 16.44		128 (92.8)	34 (94.4)		
GCS <8	12 (6.9)	82.95 ± 17.93		10 (7.2)	2 (5.6)	−0.28 (0.80)	0.75
Reason for intubation			2.07				
Respiratory issues	108 (62.1)	80.45 ± 17.56		83 (60.1)	25 (69.4)		
Heart-related issues	50 (28.7)	85.95 ± 13.41		41 (29.7)	9 (25.0)	−0.31 (0.43)	0.73
Other	16 (9.2)	84.51 ± 16.66		14 (10.1)	2 (5.6)	−0.75 (0.79)	0.47
Reintubation decision			−0.49				
Reintubation	31 (17.8)	81.08 ± 17.53		27 (19.6)	4 (11.1)		
Successful extubation	143 (82.2)	82.69 ± 16.31		111 (80.4)	32 (88.9)	0.67 (0.57)	1.95
	Mean ± SD		*r.*			*B (SE)*	*OR*
Age	68.69 ± 15.55		.04			0.01 (0.01)	1.01
APACHE II score	23.18 ± 8.25		.02			0.11 (0.07)	1.12
Charlson Comorbidity Index	5.87 ± 2.87		.11			−0.03 (0.02)	0.97
Days of ventilation use	9.89 ± 7.56		−.04			0.01 (0.02)	1.01
Days in intensive care unit	14.55 ± 11.08		−.12			<0.01 (0.02)	1.00

Note. [a]Consciousness score on the day of the questionnaire survey; APACHE II = Acute Physiology and Chronic Health Evaluation II; GCS = Glasgow Coma Scale; OR = Odds Ratio; SD = Standard Deviation; SE = Standard Error.
*$p < .05$.

hospital. The respiratory therapists of the unit updated this database daily with information about patients who were undergoing SBT training that day and were expected to have their endotracheal tubes removed. The investigator arranged one-on-one talks with potential surrogates who met the inclusion criteria between 11:00 am and 12:00 pm, which were the daily patient visiting hours in the ICU. They were informed that it would take approximately 10–15 min to complete the questionnaire and were given the option to participate. To avoid interference due to family visits, the surrogate was asked to sit in a private place after visitation hours to complete the consent form and questionnaire. The investigator provided explanations to the participants who had questions about the questionnaire. Upon completion, participants were offered a small gift as a token of gratitude.

Ethical considerations

The study protocol was approved by the National Taiwan University Hospital Research Ethics Committee (Approval no. 202106085RINC). The investigators provided potential participants with an explanation of the purpose and procedures of the study and distributed consent forms prior to completing the questionnaire. Data were uniformly coded in place of patient names to protect the rights and privacy of the participants. Diagnoses and clinical records as well as participant identities were kept confidential, even in published research results. The research materials were used solely for academic purposes. We received permission to use the Chinese version of the PANAS [33]in this study. The freely available Chinese versions of the DSES [24] and DCS [27] provided by the Ottawa Hospital Research Institute were also employed.

Data analysis

After the completed questionnaires were collected, data filing and statistical analysis were performed using IBM SPSS Statistics software (version 25.0; IBM Corp., Armonk, NY, USA). Descriptive statistics were used to assess the distribution of each variable. The distribution of the DSES scores is approximately normal; the skewness (−0.83) is between −1 and +1 [34]. This is not the case for the distribution of the DCS score (skewness = 1.03) [34]. We

Table 2 *Surrogate Background Information and Positive/Negative Affect and Associations with Surrogate Decision Self-Efficacy and Decisional Conflict.*

Variable		Decision Self-efficacy		Decisional Conflict			
	n (%)	Mean ± SD	*t*/*F*	≤37.5 *n* (%)	>37.5 *n* (%)	*B* (*SE*)	*OR*
Gender			0.19				
Woman	109 (62.6)	82.58 ± 16.48		86 (62.3)	23 (63.9)		
Man	65 (37.4)	82.09 ± 16.64		52 (37.3)	13 (36.1)	−0.07 (0.39)	0.94
Marital status			1.52				
Married/Widowed	121 (69.5)	83.66 ± 16.61		99 (71.7)	22 (61.6)		
Single/Divorced	53 (30.5)	79.55 ± 16.02		39 (28.3)	14 (39.8)	0.48 (0.39)	1.62
Religion			0.86				
None	78 (44.8)	83.59 ± 15.27		65 (47.1)	13 (36.1)		
Yes	96 (55.2)	81.43 ± 17.45		73 (52.9)	23 (63.9)	0.45 (0.39)	1.58
Relationship with the patient			0.32				
Spouse	42 (24.2)	84.57 ± 14.72		34 (24.6)	8 (22.2)		
Children	94 (54.0)	81.93 ± 16.95		75 (54.3)	19 (52.8)	0.07 (0.47)	1.08
Siblings	15 (8.6)	80.15 ± 15.85		11 (8.0)	4 (11.1)	0.44 (0.70)	1.55
Parents	15 (8.6)	82.87 ± 20.77		13 (9.4)	2 (5.6)	−0.42 (0.86)	0.65
Other	8 (4.6)	79.82 ± 14.90		5 (3.6)	3 (8.3)	0.94 (0.83)	2.55
Employment status			3.17**				
Unemployed/Retired	73 (42.0)	87.00 ± 14.35		61 (44.2)	12 (33.3)		
Employed	101 (58.0)	79.12 ± 18.13		66 (47.8)	22 (61.6)	0.22 (0.30)	1.25
Highest education			1.97				
High school or below	63 (36.2)	85.64 ± 15.44		54 (39.1)	9 (25.0)		
College or above	111 (63.8)	80.56 ± 16.85		84 (60.9)	27 (75.0)	0.66 (0.42)	1.93
Experience of medical decision-making for families							
Yes	79 (45.40)	82.99 ± 14.65		62 (44.9)	17 (47.2)		
None	95 (54.60)	81.91 ± 17.95		76 (55.1)	19 (52.8)	−0.09 (0.38)	0.91
Source of information			1.16				
Medical staff	128 (73.6)	83.27 ± 15.58		102 (73.9)	26 (72.2)		
Medical staff and others	46 (26.4)	79.99 ± 18.79		36 (26.1)	10 (27.8)	0.09 (0.42)	1.09
Decision-making preference			−0.21				
Reintubation	136 (78.2)	82.26 ± 15.76		111 (80.4)	25 (69.4)		
No reintubation	38 (21.8)	82.89 ± 19.13		27 (19.6)	11 (30.6)	0.59 (0.42)	1.81
Understanding patients' decision-making preferences			2.05*				
Yes	101 (58.1)	84.56 ± 15.29	0.19	85 (61.6)	16 (44.4)		
None	73 (41.9)	79.42 ± 17.70		53 (38.4)	20 (55.6)	0.70 (0.38)	2.00
	Mean ± SD		*r*.			*B* (SE)	*OR*
Age	53.16 ± 13.16		.13			−0.01 (0.01)	0.99
Positive affect	18.53 ± 6.00		.10			−0.02 (0.03)	0.98
Negative affect	18.16 ± 6.05		−.39***			0.13 (0.03)	1.13***
Decision self-efficacy	82.41 ± 16.50					−0.11 (0.02)	0.89***
Number of new confirmed COVID-19 cases in the country on the day the surrogates' filled out the questionnaire	11.63 ± 13.50		−.06			<0.01 (0.01)	1.00

Note. COVID-19 = Coronavirus Disease 2019; *OR* = Odds Ratio; SD = Standard Deviation; SE = Standard Error; *p< .05; **p< .01; ***p< .001

therefore treated the DSES score as a continuous variable, while the DCS score was separated into two groups (cutoff point 37.5) [28,29]. Both scores were analyzed using parametric tests. Univariate statistical methods were initially used to identify factors related to surrogates' decision self-efficacy and decisional conflict, followed by multivariate analysis to determine the most important predictors. The univariate analysis methods used in this study consisted of an independent-sample *t*-test, one-way independent analysis of variance, Pearson product-moment correlation, and binary logistic regression. Hierarchical linear regression was employed for multivariate analysis to determine the predictors of decision self-efficacy, and binary logistic hierarchical regression was used to identify the predictors of decisional conflict. Based on the Ottawa Decision Support Framework [18] and self-efficacy theory [19], the potential predictors included in the models were as follows: For the decision self-efficacy models, patients' and surrogates' background information was included in model 1; surrogates' positive and negative affect were included in model 2. For the decisional conflict models, patients' and surrogates' background information was included in model 1; surrogates' positive and negative affect were included in model 2; and surrogates' decision self-efficacy was included in model 3. Furthermore, the mediating effect was tested after controlling for patients' and surrogates' background information using PROCESS macro version 4.0 for SPSS (Model 4) [35]. A two-tailed test was conducted, and $p < .05$ was considered statistically significant.

Results

Demographic and disease characteristics

A total of 174 surrogates were included in this study. All patients involved in this study were intubated individuals in the internal medicine ICU who suffered from respiratory failure. The patients' ages ranged from 21 to 98 years, with a mean age of 68.69 years ($SD = 15.55$), and 63.8% of them were male. The mean APACHE II

score was 23.18 points, and the mean Charlson comorbidity index was 5.87, suggesting the presence of multiple comorbidities in these patients. The average duration of ventilator use in the ICU among patients was 9.89 days. The patients had an average stay of 14.55 days in the ICU. Table 1 displays additional patient background information. The age of the surrogates ranged from 21 to 83 years, with a mean age of 53.16 years ($SD = 13.16$), and 62.6% of them were female. Table 2 shows further background information of the surrogates. The average number of new confirmed COVID-19 cases during the study period was 11.63 in Taiwan (SD = 13.50; range = 0–92, Q1 = 5, Q2 = 8, Q3 = 11).

Score distributions for the DCS

In this study, 20.7% ($n = 36$) of the participants had DCS scores of >37.5, with a mean score of 54.86 ($SD = 12.35$). The proportions of those exceeding DCS subscale scores of 37.5 for the uninformed, values clarity, support, uncertainty, and effective decision subscales were 22.4%, 21.3%, 17.8%, 25.9%, and 21.8%, respectively.

Factors predicting surrogates' decision self-efficacy

The univariate analysis results are presented in Tables 1 and 2. The results indicate that retired or unemployed participants had higher decision self-efficacy than employed participants ($t = 3.17$; $p = .002$; unemployed or retired > employed). Participants who were aware of the patients' decision-making preferences had better decision self-efficacy than those who were unaware ($t = 2.05$; $p = .042$; clear > unclear). Positive affect was not significantly associated with decision self-efficacy ($r = .10$; $p = .172$). Conversely, there was a negative correlation between negative affect and decision self-efficacy; the higher the negative affect was, the lower the decision self-efficacy ($r = -.39$; $p < .001$) (Table 2).

Significant factors from the univariate analysis of the DSES were used in a linear hierarchical multiple regression to explore predictive factors for surrogates' decision self-efficacy. The first stage of the regression model included background information of the surrogate, such as employment status and whether the surrogate knew the patient's decision-making preferences. The second stage of the regression model included both the positive and negative affect of the surrogate. The combination of background information and positive/negative affect of the surrogate explained 21.0% of the variation in the "decision self-efficacy of the surrogate" ($R^2 = .21$; $p < .001$). Participants who were employed had lower decision self-efficacy than those who were unemployed or retired ($B = -6.60$; $p = .005$). The higher the negative affect of the participants was, the lower their decision self-efficacy ($B = -0.99$; $p < .001$) (Table 3).

Factors predicting surrogates' decisional conflict

This study categorized participants into two groups based on their decisional conflict scores: those who scored ≤37.4 were included in the "no decisional conflict" group, while those who scored ≥37.5 were included in the "decisional conflict" group. Binary logistic regression was employed for univariate testing and revealed that the surrogates of patients who needed assistance with activities of daily living before hospitalization had a 2.64 times higher risk of experiencing decisional conflict than the surrogates of independent patients ($B = 0.97$; $p = .011$; assistance > independent; odds ratio [OR] = 2.64) (Table 4). Furthermore, every one-point increase in surrogates' negative affect scores led to a 1.13-fold increase in the risk of decisional conflict ($B = 0.13$; $p < .001$; $OR = 1.13$). Conversely, each one-point increase in surrogates' decision self-efficacy score decreased the risk of decisional conflict by 0.89-fold ($B = -0.11$; $p < .001$; $OR = 0.89$) (Table 4).

Factors found to be statistically significant in the univariate analysis were included in a binary logistic hierarchical multiple regression model to identify predictors of decisional conflict. The first model included the patients' background information related to activities of daily living before hospitalization; the second model additionally included the surrogates' positive and negative affect; and the third model included the surrogates' decision self-efficacy. Model 3 had an omnibus test ($p < .001$), Hosmer-Lemeshow test ($p = .59$), and *Nagelkerke* ($R^2 = .54$), and a 54% accuracy for predicting "surrogate decisional conflict." Surrogates for patients who needed assistance from others had a 3.78 times higher risk of experiencing decisional conflict than surrogates of patients who could take care of themselves before hospitalization ($B = 1.33$; $p = .011$; needing assistance > taking care of themselves, $OR = 3.78$). For every one-point increase in the surrogate's decision self-efficacy score, the risk of decisional conflict decreased by 0.9-fold ($B = -0.11$; $p < .001$; $OR = 0.90$) (Table 4).

Mediating effect of decision self-efficacy

Univariate analysis revealed a significant negative correlation between surrogates' negative affect and decision self-efficacy ($r = -.39$; $p < .001$). Furthermore, there was a significant relationship between surrogates' decision self-efficacy and decisional conflict ($B = -0.11$; $p < .001$; $OR = 0.89$). The mediating effect of decision self-efficacy on the relationship between surrogates' negative affect and decisional conflict was evaluated using Model 4 with the PROCESS macro in SPSS. Negative affect was treated as the independent variable, decision self-efficacy was treated as the mediating variable, decision-making difficulty was treated as the

Table 3 *Predictors for Decision Self-Efficacy of Surrogates.*

Predictor	Model 1			Model 2		
	B (SE)	β	p	*B* (SE)	β	p
Surrogate background information						
Employment status						
Unemployed/Retired (ref)						
Employed	−7.28 (2.48)	−0.22	.004**	−6.60 (2.31)	−0.20	.005**
Understanding patients' decision-making preferences						
Yes (ref)						
None	−4.18 (2.48)	−0.13	.094	−3.86 (2.30)	−0.12	.096
Surrogates' positive affect				0.07 (0.20)	0.03	.704
Surrogates' negative affect				−0.99 (0.19)	−0.36	<.001***
F	6.50			11.10		
p	.002**			<.001***		
R^2	.07			.21		

Note. ref = reference group; SE = Standard Error; *$p < .05$; **$p < .01$; ***$p < .001$.

Table 4 *Predictors of Decisional Conflict of Surrogates.*

Predictor	Model 1			Model 2			Model 3		
	B (*SE*)	*p*	*OR*	*B* (*SE*)	*p*	*OR*	*B* (*SE*)	*p*	*OR*
Patient background information									
Activities of daily living before hospitalization									
Independent (ref)									
Assistance required	0.97 (0.38)	.011*	2.64	1.16 (0.42)	.005**	3.19	1.33 (0.52)	.011*	3.78
Surrogates' positive affect				0.00 (0.03)	.991	1.00	0.02 (0.04)	.601	1.02
Surrogates' negative affect				0.14 (0.04)	<.001***	1.15	0.05 (0.04)	.228	1.05
Surrogates' decision self-efficacy							−0.11 (0.02)	<.001***	0.90
Omnibus	.011*			<.001***			<.001***		
Hosmer-Lemeshow				0.95			0.59		
Nagelkerke R^2	.06			.20			.54		

Note. *OR* = Odds Ratio; ref = reference group; SE = Standard Error; *$p < .05$; **$p < .01$; ***$p < .001$.

dependent variable, and patient activities of daily living before hospitalization and surrogates' employment were treated as the control variables. Although the direct effect of surrogates' "negative affect" on "decisional conflict" did not reach statistical significance ($\beta = 0.05$; $p = .26$; 95% CI = −0.04, 0.13), "negative affect" was significantly associated with "decision self-efficacy" ($\beta = -1.02$; $p < .001$; 95% CI = −1.39, −0.65). In addition, "decision self-efficacy" was significantly associated with "decisional conflict" ($\beta = -0.11$; $p < .001$; 95% CI = −0.15, −0.07). The indirect effect of "negative affect" on "decisional conflict" through "decision self-efficacy" was statistically significant ($\beta = 0.11$; 95% CI = 0.07, 0.19), as shown in Figure 2. These results suggest that the relationship between negative affect and decisional conflict was fully mediated by decision self-efficacy.

Discussion

The mean decision self-efficacy score of the surrogates in this study was 82.41, which was lower than the pretest score reported in a previous intervention study involving surrogates and patients in the United States of African-American [36]. This difference could be attributed to the varying degrees of disease severity among the patients included in the two studies. Moreover, the surrogates in the present study were responsible for making decisions for their loved ones in the ICU, where they may have been affected by feelings of sadness, sleep deprivation, and cognitive blunting [5]. In addition, the study was conducted during the COVID-19 pandemic, which may have affected the decision self-efficacy of the surrogates. A recent study on ENT surgeries suggested that the pandemic affected patients' confidence in making decisions about surgery [37].

The results indicated that unemployed or retired surrogates had a higher level of decision self-efficacy than employed surrogates. However, a study examining decision self-efficacy in African -American men deciding whether to undergo prostate cancer screening found no significant differences in decision self-efficacy among unemployed, retired, and full-time workers [38]. The differences observed in the present study may be due to the hospital's COVID-19 control measures during the data collection period. The ICU had only one designated morning visitation session, making it more convenient for unemployed or retired surrogates to visit and communicate face-to-face with doctors, which may have enhanced their understanding of the patients' conditions. Increased understanding is associated with improved decision-making and self-efficacy [39,40].

We found that 20.69% of surrogates had decisional conflicts, with a total decisional conflict score of ≥37.5. Chiarchiaro et al. examined decisional conflicts among surrogates caring for critically ill patients with respiratory failure requiring mechanical ventilation to assist in respiration. They discussed the challenges of end-of-life medical plans among family members and reported an average decisional conflict score of 21.5 for the surrogates, with only 11% of the participants scoring >37.5 [41]. The proportion of participants in the present study with a DCS score >37.5 was tendentially greater than that in the study by Chiarchiaro et al [40]. One possible explanation for this is that Chiarchiaro et al. enrolled 251 patients and 446 surrogates, suggesting that many patients had more than one surrogate [41]. In addition, the fact that the present study was conducted during the COVID-19 pandemic may also have been a contributing factor. A study on patients undergoing ENT surgery during the COVID-19 pandemic reported an incidence rate

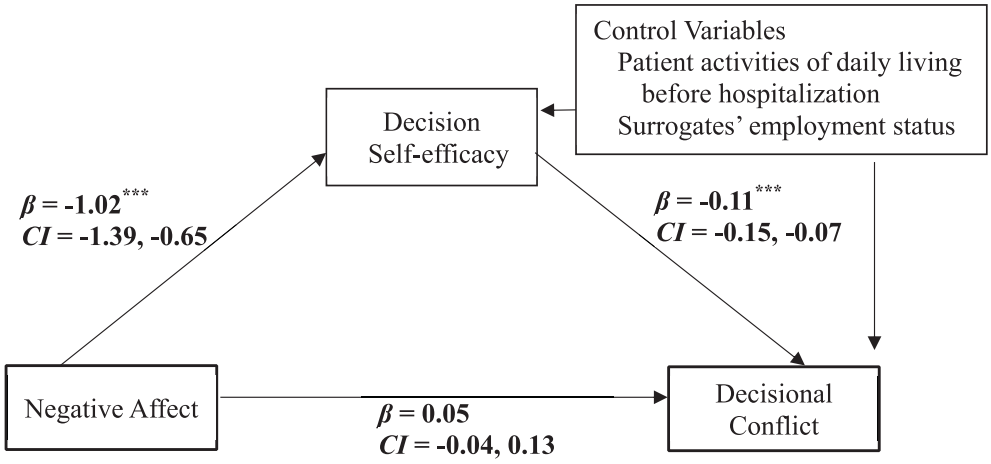

Figure 2. Mediating Role of Decision Self-Efficacy in the Relationship between Negative Affect and Decisional Conflict (Unstandardized β coefficient, 95% Confidence Interval).

of 18.7% for decisional conflict, with higher levels of pandemic-related concerns associated with higher decisional conflict [37].

According to a qualitative study, the surrogates of patients with cancer in ICUs tended to blame themselves and sought to compensate for their loved ones' pain. These surrogates reflected on how the patients had made medical decisions for themselves in the past before making their surrogates had to make their final medical decisions for them. However, the limited number of ICU visitation hours restricted the surrogates' ability to interact with patients, leading to concerns. The study also revealed that sentimental predictions of patients' medical outcomes by surrogates can contribute to decisional conflict and that negative emotions can negatively impact decision-making [42].

In the present study, surrogates' decision self-efficacy was higher in those with lower negative affect, and there was no significant association between positive affect and decision self-efficacy. This finding differs from that of a previous study, which reported that both positive and negative affect had significant impacts on self-efficacy. For example, one study suggested that patients with cancer with higher positive affect and lower negative affect had better cancer-coping self-efficacy [43], whereas another study found that higher positive affect in patients with stroke was associated with better general self-efficacy [44]. The surrogates in the present study cared for critically ill patients in the ICU and experienced high levels of anticipatory grief, anxiety, and depression. Anticipatory grief affects problem-solving abilities [6], which may lead to reduced decision-making abilities and confidence among surrogates under such conditions.

The univariate analysis performed in this study indicated a positive correlation between surrogates' negative affect and decisional conflict. However, this association was not significant in the multivariate analysis. Further examination revealed that the impact of negative affect on decisional conflict was completely mediated by decision self-efficacy, which explains the lack of significance of negative affect in the multivariate analysis. Previous research on parental decision-making for ENT surgery in children found that those with higher negative affect and lower positive affect experienced higher decisional conflict [45].

This study is based on the spirit of the Ottawa Decision Support Framework [18] and self-efficacy theory [19], which aims to understand the decisional needs faced by surrogates. Our research findings were that surrogates with higher decision self-efficacy experienced less decisional conflict and that decision self-efficacy was a significant predictor of decisional conflict. This finding aligns with those of previous studies of the decision-making abilities of patients with different diseases [22,26,46,47]. Consequently, enhancing individuals' decision self-efficacy has the potential to mitigate decisional conflict, regardless of whether they are making medical decisions for themselves or others. In essence, enhancing surrogates' decision self-efficacy contributes to the ameliorating decisional conflict, ultimately leading to improved decisional outcomes.

Furthermore, this study demonstrated that surrogates' negative affect had an indirect effect on decisional conflict that was fully mediated by decision self-efficacy. The more negative emotions surrogates experienced, the lower their decision-making self-efficacy was, which, in turn, increased the likelihood of decisional conflict. Therefore, interventional measures to decrease negative emotions should be introduced to enhance decision self-efficacy and reduce decisional conflict. Previous studies investigating patients with coronary heart disease have revealed the mediating role of meaning-making in the relationship between self-efficacy and psychological well-being. In particular, positive affect has been identified as a significant moderator that strengthens the association between meaning-making and psychological well-being. On the other hand, the moderating role of negative affect was found not to be significant [48]. However, the findings of the present study diverged from these previous observations. The results indicate that the mediating role of negative affect was significant, whereas that of positive affect was not. Several factors could have contributed to this discrepancy, including the duration of the patients' ICU stay and the occurrence of the COVID-19 outbreak. The average ICU stay for patients enrolled in this study was two weeks, which could potentially have influenced their negative affect as a longer disease course has been associated with higher levels of negative affect in previous literature [48]. Furthermore, the negative impact of the COVID-19 pandemic on the mental health of the general population could serve as another influencing factor resulting in the observed discrepancy [49].

We also found that surrogates of patients who required assistance with activities of daily living before hospitalization experienced more decisional conflicts than surrogates of independent patients. This finding is consistent with that of a previous study on surrogates of patients with cancer [50]. This study demonstrated that the functional status of patients with cancer in daily life before hospitalization significantly predicts decisional conflict among surrogates making end-of-life treatment decisions, including intubation, cardiopulmonary resuscitation, ventilator use, vasopressor use, and blood transfusion administration. Therefore, it is recommended that prehospital admission assessments include an evaluation of each patient's activities of daily living. This will aid healthcare providers in understanding patients' prehospitalization status and enable them to provide individualized assessment and intervention for surrogates of patients in need of assistance.

Limitations

This study had several limitations. First, it was a cross-sectional study that used structured questionnaires to collect data and thus was unable to establish a causal relationship. In addition, the findings of the study only reflect the decisional conflicts of surrogates at the time of the study and cannot account for changes, wavering, hesitation, or uncertainty in the decision-making process over time. Therefore, future studies may benefit from incorporating mixed research methods that equally emphasize qualitative and quantitative approaches to better understand the challenges, changes, and mental journeys of surrogates in the decision-making process. Second, the study was conducted in an internal medicine ICU where residents explained the disease condition to the surrogates and obtained consent forms as part of their clinical duties. However, although attending physicians in the ICU still held discussions with family members two to three times a week, because the resident physicians rotate every month, inconsistencies in interpretation may have arisen. Future studies could benefit from including a checklist of reintubation consent statements, and verifying the consistency of residents' explanations of reintubation consent forms. Finally, the study assessed the positive and negative affect of surrogates during the COVID-19 pandemic, and the hospital infection control center reduced ICU visiting hours from three times a day to once a day. The pandemic, coupled with the stress of having a family member in the ICU, may have influenced the positive and negative affect of the surrogates. Thus, more research is needed to clarify the relationships among positive and negative affect, decision self-efficacy, and decisional conflict.

Conclusions

This study investigated the decision self-efficacy and decisional conflict of surrogates who made life-sustaining decisions regarding reintubation after planned extubation for critically ill patients and evaluated associated factors in the decision-making process.

We found that unemployed or retired surrogates and those with lower negative affect had higher decision self-efficacy. Surrogates with lower decision self-efficacy and those making decisions for patients requiring assistance with daily activities before hospitalization experienced greater decisional conflicts. In addition, decision self-efficacy completely mediated the effect of negative affect on decisional conflict. Therefore, future interventions should focus on improving decision self-efficacy and reducing the negative affect of surrogates to limit decisional conflict.

Relevance to practice

Based on the findings of this study, future clinical interventions should aim to reduce decisional conflict by enhancing surrogates' self-efficacy and decreasing their negative affect. In a joint policy statement issued by the American Society of Critical Care Medicine and the American Thoracic Society in 2016, shared decision-making was emphasized as a means of communication and collaboration with critically ill patients and surrogates. This statement also highlights the importance of establishing partnerships with surrogates of patients in ICUs [51]. Various studies have shown that the use of patient decision aids (PDAs) significantly improves decision self-efficacy and reduces decisional conflict in different patient populations. For example, patients with type 2 diabetes who used PDAs were found to have significantly improved knowledge of hypoglycemic drugs, improve decision self-efficacy, and reduced decisional conflict [52]. Similarly, PDAs have also been shown to improve decision self-efficacy and reduce decisional conflict among parents or caregivers of children with peanut allergies [53] and among genetically at-risk couples [54]. Thus, the use of PDAs may be a viable approach to enhancing the decision self-efficacy of surrogates and consequently to reducing their decisional conflict.

Bandura [19,20] proposed various methods to enhance self-efficacy including increasing an individual's experience of success; providing alternative experiences; offering guidance, advice, explanations, and encouragement; and mediating tension and anxiety. These strategies may be effective in improving the negative affect and decision self-efficacy of surrogates, thereby reducing decisional conflict. Empowering measures such as empathic support, psychoeducation, and experiential exercises have also been shown to improve anxiety, peritraumatic distress, and experiential avoidance in surrogates of critically ill patients [55]. When patients require assistance with daily living activities and surrogates appear to have negative emotions, providing additional explanations about reintubation, arranging face-to-face or virtual meetings with attending physicians, or involving relevant experts from a collaborative care team can facilitate increased participation of surrogates in discussions. The above-mentioned literature aligns with the concepts of the Ottawa Decision Support Framework. Interventions involving decision support, such as providing clinical consultations to clarify concepts, implementing assistive tools, and enhancing self-efficacy, are all methods that can reduce decision needs [18]. In combination with our research findings, healthcare providers can intervene with decision support for surrogates who experience higher levels of negative emotions, aiming to alleviate tension and anxiety among these surrogates. This approach is intended to reduce decision needs through decision support, thereby optimizing the process of medical decision-making to achieve better decisional outcomes.

Author contribution

LSJ: Conceptualization, methodology, investigation, resources, formal analysis, interpretation of data, data curation, writing - original draft, and project administration.

CHC: Conceptualization, methodology, formal analysis, interpretation of data, data curation, supervision, writing - review & editing.

KSC: Conceptualization, methodology, resources, writing - review & editing, interpretation of data.

LKF: Conceptualization, methodology, interpretation of data, writing - review & editing.

Ethical Approval

The study of the project was reviewed and approved by National Taiwan University (NTU) Hospital Research Ethics Committee (Approval no. 202106085RINC).

Conflicts of interest

The authors declare that they have no conflicts of interest.

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Data Availability Statement

The data used in this study are managed by the corresponding author, to whom readers can direct any questions. The data are not publicly available due to the consideration of ethics; the researchers shall maintain the participants' privacy. Raw research data should be used only for academics and not to be shared.

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Research Article

Mediation Effects of Coping Styles on Fear of Progression and Reproductive Concerns in Breast Cancer Patients of Reproductive Age

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SUMMARY

Purpose: This study aimed to investigate reproductive concerns among breast cancer patients of reproductive age, analyze the influencing factors, explore the relationship between coping styles, fear of progression (FOP), and reproductive concerns, and identify the multiple effects of coping styles on the relationship between FOP and reproductive concerns among Chinese breast cancer patients.

Methods: A cross-sectional, descriptive study was conducted among breast cancer patients in four tertiary grade A hospitals in Fujian, China, from January 2022 to September 2022. A total of 210 patients were recruited to complete paper-based questionnaires, which included the general data questionnaires, the Reproductive Concerns After Cancer Scale (RCACS), the Fear of Progression Questionnaire-Short Form (FOP-Q-SF), and the Medical Coping Modes Questionnaire (MCMQ). Structural equation models were utilized to evaluate the multiple effects of coping styles on FOP and reproductive concerns.

Results: Reproductive concerns in breast cancer patients had a mean score of 53.02 (*SD*, 10.69), out of a total score of 90, and coping styles for cancer (confrontation, avoidance) were closely associated with FOP and reproductive concerns. FOP showed a significant positive correlation with reproductive concerns ($r = .52$, $p < .01$). At the same time, confrontation was significantly negatively correlated with both FOP ($r = -.28$, $p < .01$) and reproductive concerns ($r = -.39$, $p < .01$). Avoidance was positively correlated to both FOP ($r = .25$, $p < .01$) and reproductive concerns ($r = .34$, $p < .01$). The impact of FOP on reproductive concerns is partially mediated by confrontation and avoidance, with effect sizes of .07 and .04, respectively. These mediating factors account for 22.0% of the total effect.

Conclusions: The FOP directly impacted reproductive concerns, while coping styles could partially mediate the association between FOP and reproductive concerns. This study illustrates the role of confrontation and avoidance in alleviating reproductive concerns, suggesting that it is necessary to focus on the changes in reproductive concerns among reproductive-age breast cancer patients. Healthcare professionals can improve disease awareness and reduce patients' FOP, thereby promoting positive psychological and coping behaviors and ultimately alleviating reproductive concerns.

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Introduction

Breast cancer is the most prevalent malignant neoplasm among women worldwide, constituting 11.7% of all newly diagnosed cancer cases, as reported in the 2020 edition of Global Cancer Statistics released by the Agency for Research on Cancer Center in 2021 [1]. With advancements in early diagnosis and medical technology, the 5-year survival rate of breast cancer patients has reached an impressive range of 68.1% to 93.2% [2]. However, this presents a significant challenge for childbearing-age patients who have yet to start a family [3], as the prolonged duration of tumor treatment and unaddressed fertility issues pose potential obstacles [4,5]. Reproductive issues have become an increasingly integral aspect of post-cancer fertility considerations for pre-menopausal breast cancer patients, owing to advancements in breast cancer care and subsequent improvements in treatment outcomes, as well as the prevailing social trend toward delayed childbearing [3].

Reproductive concerns refer to individuals' anxieties regarding reproduction and the care of offspring [6]. These concerns include apprehensions about female infertility, the impact of infertility on a romantic relationship, the possibility of congenital disabilities or cancer, and the inability to raise children due to one's poor health [6]. Reproductive concerns were initially raised in patients diagnosed with lymphoma and gynecological malignancies [7]. Previous studies have revealed that fertility concerns affect approximately 57.0% of young women with cancer [8]. The high levels of post-cancer reproductive concerns can lead to psychological distress, which may surpass the impact of cancer on patients [9], and is closely associated with a decline in quality of life and persistent depression [10]. Medical technology advancement has significantly enhanced breast cancer patients' long-term survival rates [11]. However, despite these improvements, the pathophysiological characteristics of cancer have hindered the effective prevention and resolution of its progression or recurrence [12]. The recurrence rate of breast cancer patients in China ranges from 5.0% to 30.0% [13]. For young patients, disease recurrence signifies a decline in their overall health status, leading to psychological distress and heightened reproductive concerns [3,14]. Previous studies have demonstrated a moderate positive correlation between FOP and reproductive concerns after cancer diagnosis, with FOP exacerbating these concerns among female patients diagnosed with digestive system cancer [15]. However, the precise mechanism through which fear of disease progression impacts concerns about fertility remains elusive.

FOP refers to the apprehension of illness progression or recurrence in the same or another part of the body system [16]. The available literature indicates that approximately 50% of cancer survivors experience varying degrees of FOP [16]. FOP has emerged as a prevalent psychological issue among breast cancer patients, which can exacerbate both psychological and physiological disorders, dampen patients' motivation for cancer treatment and positive outlook on life, and persist long after the completion of active therapy [17,18]. When faced with stressful events, coping styles are influenced by situational factors, individual differences, and the external environment [19]. Breast cancer patients exhibit diverse coping styles in response to physiological and psychological stress levels following diagnosis, treatment, and disease survival. According to the disease self-regulation model proposed by Lee-Jones et al, individual coping styles may be associated with the level of FOP; patients with a limited understanding of the disease and a high level of FOP may experience challenges in psychological and social adaptation following surgery [20]. Additionally, prior research has demonstrated a significant correlation between negative coping strategies and heightened levels of fertility-related anxiety [21].

Coping is an adaptive mechanism that allows individuals to effectively manage, mitigate, or regulate the impact of stressors they may encounter [22]. According to Feifel et al, coping is a dynamic cognitive and behavioral process that arises in response to traumatic life events [23]. Coping styles possess a dual nature, capable of exerting both positive and negative influences on individuals' lives [24]. Typically, the confrontational coping style is regarded as adaptive and resilient, while the avoidant coping style is deemed maladaptive [22]. Coping style play a crucial role in influencing patients' psychological stress responses and well-being, serving as an intermediate variable between life events and stress responses [25,26]. A confrontational coping style may facilitate patients in developing a more accurate perception of disease-related stress, mitigating maladaptive psychological or behavioral responses and ultimately reducing the level of FOP [27]. Conversely, an avoidant coping style could somewhat exacerbate patients' perceived disease progression, increasing FOP levels. Additionally, it has been observed that FOP may have a negative impact on positive psychology and disease perception, thereby influencing coping strategies among female cancer patients [18]. Previous research has demonstrated that patients may experience a loss of confidence in their treatment and quality of life, leading to adopting avoidance coping strategies and exacerbating reproductive anxiety [21]. However, other studies have suggested that some patients who utilize confrontational coping styles may be concerned about their children's health or lack sufficient informational support, resulting in less noticeable improvements in fertility-related anxiety [28].

According to Folkman's stress and coping theory, patients employ appropriate coping strategies to effectively address the physical discomfort and psychological challenges associated with their disease [29]. This theory categorizes relevant variables into pre-variables, moderators, and outcome variables. Personal traits and environmental factors serve as pre-variables that influence the outcome through the mediating effects of cognitive evaluation and coping styles. The outcome measure represents the ultimate level of adaptation to stress. Numerous studies have investigated factors associated with reproductive concerns in breast cancer patients [30–33]; however, only a limited number have simultaneously examined the role of FOP and coping styles [18,27]. Therefore, further investigation is warranted to examine the interplay among coping styles, FOP, and reproductive concerns in breast cancer patients of reproductive age. Based on the above theory and practical implications, this study adopts FOP as the pre-variable of stress and coping theory, coping styles as the moderating variables, and reproductive concerns level as the outcome variable. We propose two hypotheses.

H1: FOP is positively associated with reproductive concerns.
H2: Coping styles mediate the correlation between FOP and reproductive concerns.

This study aimed to investigate the status and influence factors of reproductive concerns among breast cancer patients of reproductive age and to explore the relationship between coping styles, FOP, and reproductive concerns by adopting Pearson correlation analysis and structural equation modeling to provide a reference for medical staff to carry out fertility care for patients to relieve fertility anxiety and improve life quality.

Methods

Study design

This cross-sectional descriptive study aimed to investigate the status and influential factors of reproductive concerns among breast cancer patients of reproductive age and to explore the effects of FOP on the reproductive concerns among breast cancer patients of reproductive age and the mediating effects of coping styles.

Setting and sample

This study was conducted from January 2022 to September 2022. The participants were the convenience extraction of patients treated at breast surgery departments from 4 tertiary grade A hospitals in Fujian, China. The inclusion criteria in this study were as follows: (1) clinical diagnosis of breast cancer; (2) undergoing surgery or neoadjuvant chemotherapy; (3) age ranging between 18 and 44 years; (4) possession of normal cognitive abilities; (5) awareness of the disease diagnosis and willingness to participate in this research. Patients who had other malignancies, confidential treatment, or met WHO's diagnostic criteria for infertility [34] prior to treatment were excluded from the study.

To ensure adequate statistical power, we calculated the sample size using the formula $N = (U_\alpha \sigma/\delta)^2$ [35], where $U_\alpha = 1.96$, $\delta = 2$, and $\sigma = 9.15$, which was grounded on the standard deviation of the reproductive concerns scores among women breast cancer patients in the primary research [36], the estimated sample size was 80. We considered a 20% invalid questionnaire; the sample size was at least 100. A sample size of at least 200 cases was considered in studies with general structural equation modeling. Finally, the sample size was determined to be at least 200 cases [37, p. 5].

Measurements

Demographic and clinical characteristics

A comprehensive data questionnaire was administered to collect patients' socio-demographic, clinical, and reproductive characteristics, including age, marital status, educational attainment, employment status, place of residence, survival time, cancer stage, and treatment received. Additionally, the questionnaire also gathered information on the number of biological children and fertility intentions.

Reproductive Concerns After Cancer Scale

The Reproductive Concerns After Cancer Scale (RCACS) was compiled by Gorman et al in 2013 and was adopted to assess the extent of an individual's worries about reproduction and caring for offspring. RCACS includes six dimensions and 18 items, namely fertility potential (3 items), partner disclosure (3 items), children's health (3 items), personal health (3 items), infertility acceptance (3 items), and becoming pregnant (3 items). Each item is rated on a 5-point Likert scale ranging from “strongly disagree” to “strongly agree,” with items 5, 10, and 15 being reverse-scored. The total score is 18–90, with a higher score indicating higher reproductive concerns [38]. In the Chinese version translated by Qiao et al in 2016, Cronbach's α coefficient for each dimension ranged from 0.72 to 0.86, while that for the total RCACS was found to be at an acceptable level of reliability (Cronbach's $\alpha = 0.79$) [39].

Fear of Progression Questionnaire Short Form

The Fear of Progression Questionnaire Short Form (FOP-Q-SF) was simplified by Mehnert et al [40] in 2006 to evaluate cancer patients' fear of disease progression. The Chinese version of FOP-Q-SF consists of two dimensions: physical health and social family, with Cronbach's α coefficients of 0.83 and 0.81, respectively. The Cronbach's α coefficient for the total scale was 0.88. FOP-Q-SF is a questionnaire comprising 12 items, each rated on a 5-point Likert scale ranging from “never” (1) to “always” (5). Scores on the questionnaire range from 12 to 60, with higher scores indicating greater levels of fear regarding disease progression [41].

Medical Coping Styles Questionnaire

The Medical Coping Modes Questionnaire (MCMQ) was initially developed by Feifel et al in 1987. It was frequently used to assess patients' ways of dealing with disease [23]. The confrontation and avoidance subscales of the Chinese version of MCMQ were utilized in this study, with all items being evaluated on a 4-point Likert scale. The total scores for the confrontation and avoidance subscales range from 8 to 32 and 7 to 28, respectively. Higher scores indicate a greater tendency toward utilizing these coping styles. The Cronbach's α coefficients for confrontation and avoidance were found to be 0.69 and 0.60, respectively [42].

Data collection

Medical staff and breast surgery managers at the four hospitals recommended patients who met the inclusion criteria to participate. Researchers explained what to look for in completing the questionnaires before they were distributed. Participants completed the questionnaires individually. For illiterate patients, well-trained researchers read the questionnaires and recorded responses. When patients had finished the questionnaire, researchers collated whether the item was entirely written.

Ethical considerations

The procedures of this study were approved by the Medical Ethics Committee of Putian University (Ethics Review Approval Number: 2022-016). Before the investigation, written informed consent was obtained from each participant, who was duly informed about their research rights, including the right to withdraw from the study. Additionally, all participants in the study received a gift card.

Data analysis

The data analytical procedures were performed using IBM SPSS software (version 22.0) and IBM Amos software (version 24.0). Descriptive statistics, including percentages, means, and standard deviations, were used to summarize social demography, clinical characteristics, reproductive features, and questionnaire scores. Pearson correlation analysis examined the bivariate relationships among coping styles, FOP, and reproductive concerns. Structural equation modeling (SEM) was employed to investigate the mediating role of coping styles. The statistical significance of the correlation and effects was evaluated by generating a 95% bias-corrected confidence interval from 5000 resamples using the bias-corrected bootstrapping method. After bias correction, we determined a significant mediation effect when excluding zero in the 95% bootstrap confidence intervals. A χ^2/df value ranging from 1 to 3 indicates a favorable model fit, while an RMSEA value below 0.06 indicates an acceptable model fit. The recommended criterion for IFI, CFI, GFI, and AGFI is all above 0.90 as indicative of acceptable model fit [37, pp. 40–46].

Results

Common method biases

Harman's single-factor test was conducted on all measurement items in this study before data analysis, extracting eight common factors with eigenvalues >1. The first common factor had an extraction variance of 24.0%, which was 40.0% lower than the critical value, indicating the absence of any common method bias within the research data.

Patient characteristics and reproductive concerns

The demographic and clinical characteristics of the participants and group differences in reproductive concerns are presented in Table 1. A total of 225 patients met the inclusion criteria, with 15 withdrawing due to physical reasons, ultimately resulting in 210 patients completing the study, yielding a response rate of 93.3%. The mean age of the respondents was 38.32 years (SD, 4.51; range, 18–44). Among the 210 participants, more than 27.6% possessed a bachelor's degree or higher level of education. Regarding reproductive characteristics, it was found that 20.0% of young women had no biological children and that an intention to have children was expressed by approximately 31.4%. Regarding clinical variables, 74 (35.2%) patients exhibited a survival length exceeding 24 months. Among the five demographic variables, age and education degree significantly correlated with reproductive concerns. Patients below the age of 34 reported significantly higher scores in terms of reproductive concerns ($p < .001$), and those who pursued undergraduate or above degrees displayed elevated levels of reproductive concerns compared to others ($p < .05$). Distinct fertility statuses were associated with varying degrees of reproductive concerns among patients ($p < .001$), and individuals expressing an intention to have children experienced heightened levels of concern ($p < .001$). Furthermore, patients with a survival length surpassing 24 months reported higher reproductive concerns scores than other categories within the clinical variables ($p < .05$).

Table 1 *Univariate Associations of Sociodemographic and Disease-related Characteristics with Reproductive Concerns (N = 210).*

Characteristics	*n* (%) or *M* ± *SD*	Reproductive concerns		
		M ± *SD*	*F* or *t*	*p*
Age, in years	38.32 ± 4.51		4.08	<.001**
18~34	67 (31.9)	57.45 ± 11.14		
35~44	143 (68.1)	50.95 ± 9.85		
Marital status			3.35	.097
Married	165 (78.6)	52.14 ± 11.31		
Unmarried	34 (16.2)	53.29 ± 7.78		
Divorce/other	11 (5.2)	51.09 ± 3.94		
Degree of education			5.74	.004*
Middle school or under	89 (42.4)	50.79 ± 9.02		
Senior high school	63 (30.0)	52.87 ± 8.34		
Undergraduate or above	58 (27.6)	56.71 ± 14.00		
Employment status			−.94	.351
Employed	65 (31.0)	51.94 ± 11.45		
Unemployed	145 (69.0)	53.50 ± 10.35		
Residence			1.70	.092
City	123 (58.6)	53.93 ± 11.05		
Rural	87 (41.4)	51.38 ± 10.19		
Length of survival, in months	33.16 ± 10.85		−2.68	.008*
≤24	136 (64.8)	51.59 ± 9.35		
>24	74 (35.2)	55.66 ± 12.44		
Cancer stage			6.94	.071
I	72 (34.3)	53.65 ± 8.82		
II	89 (42.4)	52.04 ± 12.14		
III/IV	49 (23.3)	51.07 ± 8.96		
State of Fertility			3.71	<.001**
No children	42 (20.0)	57.95 ± 9.34		
One child or more	168 (80.0)	51.79 ± 10.68		
Fertility intentions			3.86	<.001**
Yes	66 (31.4)	57.29 ± 11.27		
No	144 (68.6)	51.07 ± 9.85		

Note. *$p < .05$. **$p < .001$.

Pearson correlation between coping styles, FOP, and reproductive concerns

Table 2 shows that the mean score for reproductive concerns was 53.02 (*SD*, 10.69), whereas the mean score for FOP was 40.53 (*SD*, 9.24). Furthermore, all participants exhibited a mean score of 22.00 (SD, 3.73) and 17.03 (SD, 3.72) for confrontation and avoidance, respectively.

The Pearson correlations between the variables are presented in Table 3. FOP exhibited a significant positive correlation with reproductive concerns ($r = .52$, $p < .01$). Confrontation demonstrated a significant negative association with both FOP ($r = -.28$, $p < .01$) and reproductive concerns ($r = -.39$, $p < .01$). Moreover, avoidance displayed a positive association with both FOP ($r = .25$, $p < .01$) and reproductive concerns ($r = .34$, $p < .01$).

The multiple mediating effects of coping styles on FOP and reproductive concerns

The current study employed FOP as the independent variable, utilizing confrontation and avoidance as mediating variables, and reproductive concerns as the dependent variable to construct a parallel multiple mediating model. The parameters of the structural equation model were estimated using the maximum likelihood method and Bootstrap method while testing for the corresponding mediating effects. The goodness-of-fit indices yielded satisfactory results: $\chi^2/df = 1.76$, RMSEA = 0.06, IFI = 0.98, CFI = 0.98, GFI = 0.96, and AGFI = 0.91, indicating that the model exhibited a good fit.

The bias-corrected percentile bootstrap analysis revealed significant indirect effects of confrontation and avoidance on the relationship between FOP and reproductive concerns (Table 4

Table 2 *The Mean Score of Reproductive Concerns, FOP and Coping Style (N = 210).*

Variables	Dimensions	Mean	SD
Reproductive concerns		53.02	10.69
	Personal health	9.74	1.96
	Children's health	9.49	2.65
	Infertility acceptance	8.66	2.50
	Partner disclosure	8.53	2.52
	Fertility potential	8.35	2.54
	Becoming pregnant	8.26	2.51
FOP		40.53	9.24
	Physical health	20.64	4.77
	Social family	19.89	5.14
Coping style	Confrontation	22.00	3.73
	Avoidance	17.03	3.72

Note. FOP = fear of progression.

Table 3 *Pearson Correlations Between Coping style, FOP and Reproductive Concerns.*

Variables	1	2	3	4
1. Confrontation	1			
2. Avoidance	−.28**	1		
3. FOP	−.28**	.25**	1	
4. Reproductive concerns	−.39**	.34**	.52**	1

Note. FOP = fear of progression.
*$p < .05$.
**$p < .01$.

Table 4 *The Effect Sizes with Confrontation and Avoidance as Mediators.*

Type of effect	Effect size (standardization)	Bootstrap 95% CI	Ratio (%)
Total effect	.50	0.17~0.35	
Direct effect	.39	0.13~0.28	78.0
Total indirect effect	.11	0.02~0.10	22.0
Indirect effect 1	.07	0.01~0.07	14.0
Indirect effect 2	.04	0.00~0.05	8.0
Diff	.03	−0.02~0.06	

Note. $N = 210$; bootstrap sample = 5000.
Indirect effect 1 = FOP→confrontation→reproductive concerns; Indirect effect 2 = FOP→avoidance→reproductive concerns; Total indirect effect = Indirect effect 1 + Indirect effect 2.
Diff = Indirect effect 1 − Indirect effect 2.

and Figure 1). The total indirect effect was .11 (95%; CI [0.02, 0.10]). The indirect effects followed two paths: FOP→confrontation→reproductive concerns (Indirect effect 1, estimated effect = .07, 95%; CI [0.01, 0.07]); FOP→avoidance→reproductive concerns (Indirect effect 2, estimated effect = .04, 95%; CI [0.00, 0.05]). The mediation effects of the two paths accounted for 14.0% and 8.0% of the total effect on the relationship between FOP and reproductive concerns, respectively. The comparison between the indirect effects of confrontation and avoidance did not yield statistically significant results (95%; CI [−0.02, 0.06]).

Discussion

Reproductive concerns

According to our survey, the mean score for reproductive concerns was 53.02, surpassing Bártolo et al's study (49.38) in northern Portugal [10]. Women of childbearing age are at a pivotal stage in their lives as they bear the responsibility of childbirth, child-rearing, and family care. To some extent, children are often viewed as the embodiment of hope and the continuation of life; thus, infertility-induced psychological conflicts can be particularly intense. The personal health dimension scored highest among reproductive concerns, consistent with the relevant studies [43,44]. Existing studies have proved that the incidence of complications associated with fertility in women increases significantly after cancer treatment. However, it was unclear whether pregnancy affected the prognosis of patients [45]. Childbirth led to a high level of concern due to the uncertainty of its impact on the patient's health status. The second highest score was for children's health. Prospective mothers naturally want to bear healthy children. However, measures such as chemotherapy and endocrine therapy can have teratogenic effects on reproductive cells [46] and lead to adverse effects in the fetus, which has been shown to cause high levels of concern in young women with breast cancer. The dimension of becoming pregnant received the lowest score, indicating a low level of concern regarding pregnancy preparation, which is consistent with the findings of Qiao et al [39]. This may be attributed to the fact that 80.0% of participants in this study had already given birth to more than one child and, therefore, possessed some experience preparing for pregnancy.

Related factors

Our findings showed that the age, degree of education, state of fertility, fertility intentions, and length of survival impacted the reproductive concerns of breast cancer patients at childbearing age. Their reproductive needs have not been met for younger patients having strong fertility intentions. However, anti-cancer treatment impaired breast cancer patients' fertility [47], which was contrary to the desire for pregnancy after the end of treatment, so they showed a high level of fertility concerns. The patients with higher education levels reported a higher level of reproductive concerns. On the one hand, this group has been educated for a long time, and some patients were not pregnant at the time of diagnosis. On the other hand, patients with high education levels had a higher demand for knowledge [30]. Currently, China's reproductive counseling services for cancer patients are not perfect [48], which can not meet the information needs of patients, and their reproductive anxiety level has correspondingly improved. The more children cancer patients have, the lower their level of fertility anxiety, which was consistent with the research results of Shah et al [31]. The reasons were that, influenced by traditional culture, women played the role of “carrying on the family line and having children” in the family [49]. Young women with breast cancer who had not given birth expected to have their children and build a sound family. In addition, patients who had not given birth to children worry about their health affecting their ability to prepare for pregnancy and the quality of their children, so they had higher worries about childbearing. The results of this study showed that patients with a length of survival of more than 24 months had higher scores of reproductive concerns. Research [32] showed that sexual dysfunction and fertility problems of breast cancer patients often occurred two years after diagnosis, showing a trend of

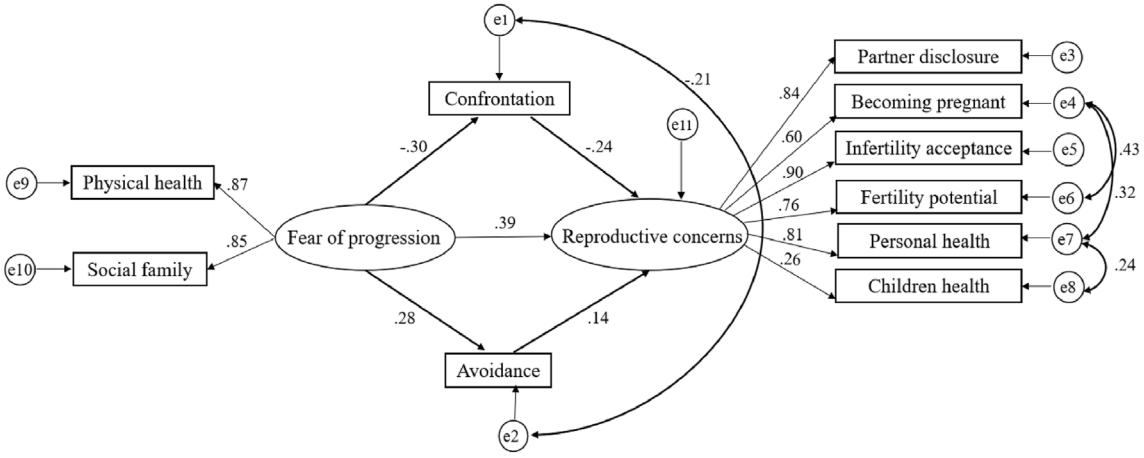

Figure 1. Parallel Multiple Mediating Model. *Note*. The data in the figure are standardized path coefficients, and e1 to e11 are residuals.

"postponement." Patients prioritized survival and ignored long-term reproductive needs in the early stage of disease diagnosis and treatment [50]. However, as the disease progresses, breast cancer survivors' physical functions recover, and their fertility attitudes change, fertility anxiety may increase. Therefore, it is recommended that medical staff understand the fertility needs of patients before treatment and fully communicate the possible fertility impact of the treatment plan. At the same time, it is suggested to set up a reproductive protection consulting room in the cancer ward and make good use of online platforms such as medical websites and mobile phone APP to promote cancer reproductive knowledge to meet the needs of patients of different categories and cultural backgrounds for reproductive knowledge.

FOP exerts a direct positive effect on reproductive concerns

In this study, Pearson correlation analysis showed that there was a moderate positive correlation between FOP and reproductive concerns in breast cancer patients of reproductive age ($p < .01$). The direct effect of FOP on reproductive problems after cancer was 0.39 according to the Amos analysis, indicating that FOP could increase reproductive concerns in breast cancer patients of reproductive age. Koch-Gallenkamp et al [51] demonstrated that women survivors 5–7 years after cancer diagnosis were at higher risk of developing moderate or high FOP. Takeuchi et al [14] noted that the recurrence of the disease often led them to postpone plans to have a family or children. Female patients with breast cancer fear that the condition's progression may affect their physical health, deprive them of life, and reduce their success rate in pregnancy preparation and childbirth [3]. Some patients also fear that pregnancy will lead to the development of cancer or that their health status will limit future childcare and work [14]. All of the above factors have led to high reproductive concerns. The meta-analysis findings indicate that web-based cognitive behavioral therapy can effectively mitigate adverse effects in cancer patients [52]. Therefore, medical professionals should guide patients to enhance their understanding of disease-related knowledge and establish new cognitive-behavioral patterns through cognitive interventions. Additionally, relaxation training techniques such as breathing exercises and muscle relaxation can be employed for behavior intervention. By linking cognition with behavior, a novel approach could be established to alleviate anxiety and depression symptoms among patients, reduce fear of cancer recurrence, and ease fertility concerns.

Coping styles exert direct effects on reproductive concerns

Our results also showed a negative correlation between confrontational coping style and reproductive concerns. In contrast, an avoidant coping style was positively associated with such concerns. Although the impact of cancer on fertility remains unclear, it is likely to be a devastating experience and a significant cause of depression [10]. Different coping styles could have varying effects on health outcomes and quality of life for individuals facing infertility [53]. Wang et al [25] proposed that effective coping styles can mitigate reproductive concerns among breast cancer patients. Those with an upbeat coping style tend to adopt healthy lifestyles, such as focusing on the positive aspects of life, seeking support from relatives, and utilizing specialist counseling services [54]. The family system theory posits that the family functions as an interactive system, with each member assuming distinct responsibilities in response to changes in family dynamics. Moreover, alterations in one member's behavior, cognition, or emotions can impact those of other members [55]. Research indicates that partner support was the most crucial form of social support for married breast cancer patients and that patients with higher perceived partner support had lower reproductive concerns than those with lower perceived partner support [56]. In this study, most of the breast cancer patients of childbearing age were married. The medical staff could guide the spouse's support to meet the emotional and spiritual needs of the patients to alleviate their reproductive concerns.

FOP exerts an indirect positive effect on reproductive concerns

The results of the Bootstrap test revealed that confrontation and avoidance acted as parallel mediators between the FOP and reproductive concerns in breast cancer patients. FOP could indirectly influence reproductive concerns through confrontation and avoidance. The parallel mediators accounted for 22.0% of the total effect, with confrontation contributing 14.0% and avoidance contributing 8.0%. The high level of FOP significantly influences patients' propensity to adopt avoidance coping styles, resulting in elevated levels of reproductive concerns. Confrontation coping styles, on the other hand, had the opposite effects. Butow et al believe that the FOP among cancer survivors is driven by metacognition that cannot adapt to danger [57]. According to the stress and coping theory [29], a higher level of FOP among breast cancer patients indicates increased negative emotions toward the disease, a lack of active adaptation and cognitive processing, and limited access to social resources and support. This predisposes them to adopt avoidance coping styles, ultimately leading to a heightened level of reproductive concerns. A previous study has shown that an avoidant coping style also has advantages and can serve as a temporary protective factor for a period [58]. Most patients were more concerned with treating their disease in the early stages of diagnosis. They paid little attention to or chose to avoid fertility issues [59]. However, with the extension of survival, some patients may regret not taking fertility protection earlier [33]. The pain of being unable to have a child can increase fertility concerns. Patients with lower levels of FOP, on the contrary, develop a rational understanding of their disease experiences, suppress negative emotions, and adopt confrontation coping strategies. The confrontation coping style encouraged patients to be proactive in their evaluation, seek social support, and vent their emotions [60]. Research showed that the adoption of a confrontational coping style by breast cancer patients may facilitate their adjustment to the disease and its treatment [61]. At the same time, patients who actively face the disease will learn about fertility information in the context of anti-cancer plans and thus exhibit lower levels of reproductive concerns. Medical personnel could employ health education lectures, pamphlets, videos, and other strategies to disseminate breast cancer-related knowledge and reproductive information, effectively rectifying patients' misconceptions regarding the disease. Correct disease cognition can alleviate the FOP level of breast cancer patients at childbearing age, encourage patients to face it actively, and thus reduce reproductive concerns.

There are certain limitations to this study. Firstly, recruiting research subjects from only four tertiary grade A hospitals using a convenient sampling method limits the sample's representativeness as these hospitals are located in a single geographical area of China. Secondly, this study is cross-sectional, future longitudinal studies may be necessary to establish causal relationships between variables.

Conclusion

The current study indicates that FOP has a positive direct impact on reproductive concerns, confrontation coping style has a negative direct impact, and avoidance coping style has a positive direct impact. Additionally, confrontation and avoidance act as parallel

mediators in the relationship between FOP and reproductive concerns in breast cancer patients. Comprehending the reproductive needs of patients and evaluating their concerns regarding reproduction at an early stage is crucial for healthcare professionals. Medical professionals could employ cognitive behavioral therapy to mitigate patients' uncertainties regarding the disease, quell the fear of disease progression, foster positivity in psychology and behavior, and allay fertility concerns.

Author contributions

Cuiting Liu: Conceptualization, Methodology, Formal analysis, Writing - first draft, Writing - review & editing.

Cuiping Liu: Investigation, Data curation, Methodology, Writing - review & editing.

Huiting Gao: Investigation, Data curation, Methodology.

Xuefen Yu: Investigation, Data curation, Methodology.

Chunying Chen: Conceptualization, Project administration, Supervision.

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Conflicts of interest

The authors declare no conflicts of interest.

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Research Article

The Mediator Role of Meaning in Life in the Life Quality of Patients With Chronic Heart Failure

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SUMMARY

Purpose: Heart failure (HF) is a highly recurrent disease with a high sudden death rate and a substantial influence on disease-related quality of life (QOL). Social support, symptom distress, care needs, and meaning in life all have significant impacts on QOL. We hypothesized that meaning in life plays a mediating role in the relationship of social support, symptom distress, and care needs with QOL among patients with chronic HF.

Methods: Based on cross-sectional analysis, we recruited 186 HF outpatients who completed structured questionnaires for social support, symptom distress, care needs, meaning in life, and QOL. Structural equation modeling was used to analyze the mediating role of meaning in life in the relationship of social support, symptom distress, and care needs with QOL.

Results: The final model showed good model fit. Meaning in life was associated with global QOL ($\beta = 0.18$, $p = .032$). Although symptom distress ($\beta = -0.26$, $p = .005$) and care needs ($\beta = -0.36$, $p = .021$) were negatively associated with global QOL, meaning in life played a partial mediating role between symptom distress and global QOL ($\beta = -0.02$, $p = .023$) and between care needs and global QOL ($\beta = -0.07$, $p = .030$). However, meaning in life played a complete mediating role between social support and global QOL ($\beta = 0.08$, $p = .047$). The model showed that meaning in life, symptom distress, and care needs explained 50% of global QOL.

Conclusions: In patients with chronic HF, meaning in life played a mediating role in the relationship of social support, symptom distress, and care needs with QOL. Implementing an intervention to enrich meaning in life may help patients manage the issues caused by symptoms and alleviate their unmet needs.

Introduction

Heart failure (HF) is a complex and multifactorial syndrome. Both cardiac and noncardiac comorbidities contribute to poor clinical outcomes, resulting in recurrent hospitalization and impaired quality of life (QOL) among patients with HF [1]. According to a systematic review, nearly 52% of HF outpatients require holistic care to satisfy their spiritual burden [2]. Meaning in life is composed of personal values, experiences, goals, and beliefs [3]. Based on the description by Steger, meaning in life is defined as

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people's subjective judgments emerging from their connections, interpretations, aspirations, and evaluations for life [4]. Meaning in life makes our experiences understandable, guides us to achieve our desired future, and makes us feel that our lives matter and are worthwhile. In patients with incurable chronic diseases, the presence of meaning in life may help them face their situation and positively identify and achieve their life goals [5–7]. A positive sense of the value of existence is associated with better health and social function, as well as a sense of well-being [8]. Furthermore, a recent study advocated that spiritual care, especially helping HF patients develop meaning in life, plays an important role in improving QOL [9]. Although accumulated evidence supports the role of meaning in life in the QOL of patients with chronic HF, the associated mechanisms have not been fully explored. Understanding how meaning in life exerts its effect on QOL improvement is important for nursing staff to provide spiritual care to patients with HF.

Patients with HF are at risk of disability and impaired social function. They may be depressed by the loss of previous abilities, have low self-esteem, and question their self-worth [10]. The capricious nature of HF, the uncertainty of sudden death, and disability also have a negative impact on QOL [11]. Thus, in addition to disease care, we should pay attention to QOL. Previously, symptom distress, care needs, and social support were found to be associated with QOL at acute and chronic stages of HF [12]. To improve QOL, we need to address symptom distress and care needs and provide social support.

Care needs are defined as the needs that should be satisfied based on patients' expectations for their physical, psychological, social, and existential needs [13]. Social support includes disease care information and emotional support from medical professionals and family for patients with loss of role function due to disability [14,15]. Researchers have found that social support, care need satisfaction, and symptom distress are substantially related to meaning in life [16–18]. Continuous social support and efforts to improve care needs may provide additional care elements to promote HF patients' meaning in life and well-being. The presence of meaning in life may influence fatigue and overall symptom experiences [17], alleviate symptoms for patients with incurable diseases [18], and help patients overcome the depression caused by a variety of debilitating diseases and physical disabilities [19]. Under the pressure of the possibility of sudden death, the presence of a life goal that recognizes the value of one's existence helps the patient understand and accept life with the disease and be better satisfied with life [20]. According to these findings and the importance of improving QOL for patients with chronic HF, it is necessary to explore whether meaning in life exerts a mediating effect between all these factors and QOL.

Thus, this study recruited patients who had HF for longer than 6 months and tested the hypothesis that meaning in life plays a mediating role in the relationship of social support, symptom distress, and care needs with QOL in patients with chronic HF. The conceptual framework of this study is shown in Supplementary Figure S1.

Methods

Study design

This cross-sectional study was approved by the institutional review board of Chang Gung Memorial Hospital (Approval No. 201601084B0).

Participants and data collection

Patients were enrolled at a local teaching hospital in northern Taiwan. This study used convenience sampling to recruit patients who had HF for longer than 6 months. After recruitment, structured questionnaires were distributed at the outpatient department. The inclusion criteria were as follows: patients who (1) had a diagnosis of HF (International Classification of Diseases, Tenth Revision code I50.9); (2) were able to communicate in Chinese with clear consciousness; (3) had a history of myocardial infarction, ventricular hypertrophy, abnormal left ventricular end-diastolic diameter (men: >58 mm, women: >52 mm) [21]), abnormal systolic or diastolic pressure (average home blood pressure ≥140/90 mmHg), or abnormal valve structure as shown by cardiac echocardiograms (moderate to severe or severe valvular heart disease); (4) were ≥20 years of age. Patients were excluded if they (1) suffered from an immediately life-threatening or end-stage terminal illness and were awaiting cardiac surgery; (2) lived in a nursing home; (3) had a diagnosis of dementia; (4) were unable to complete the questionnaire due to cognitive dysfunction. For the sample size calculation, with normally distributed variables and no missing data, a reasonable sample size for structural equation modeling (SEM) was approximately 100–150 [22,23]. During the study period from July 2017 to June 2019, 186 patients were enrolled in our study.

Measures

To ensure the same data collection procedure for all participants, all questionnaires were administered by an HF case manager who was a researcher and familiar with the questionnaire. Demographic information, such as age, sex, duration of HF, New York Heart Association functional class, economic status, living conditions, education level, marital status, and comorbidities such as chronic kidney disease (CKD) and diabetes, was collected. Comorbidity was assessed via health care professionals responsible for the patients or medical records.

Symptom distress in patients with HF was evaluated using the Chinese version of the symptom distress scale. The scale is a self-report instrument and includes 17 symptoms with a total score of 17 to 85. Higher scores indicate higher levels of symptom distress [24]. The reliability and validity of this questionnaire in this study were supported by a Cronbach's alpha value of 0.93.

The 30-item Heart Failure Needs Assessment Questionnaire (HFNAQ) was used to measure the level of care needs. This questionnaire assesses the perceptions of the patients' care in four domains, i.e., the physical, social, spiritual, and psychological domains in the past month. The total HFNAQ score ranges from 30 to 150. Higher scores indicate a higher level of care needs [13]. To translate the English version of the HFNAQ into Chinese, forward and back translations were used. In our study, the reliability of this questionnaire was supported by a Cronbach's alpha value of 0.88.

The Chinese version of the Social Support Questionnaire was used to measure the level of social support. The questionnaire has 15 items with a total score of 0 to 45. A higher score indicates a higher level of social support [25]. The reliability of this questionnaire was supported by a Cronbach's alpha value of 0.96 in our study.

The Chinese version of the Meaning in Life Questionnaire (MLQ) was used to assess meaning in life [26]. This questionnaire consists of two subscales: the presence of meaning in life subscale (MLQ-P) and the search for meaning in life subscale (MLQ-S). The total score

ranges from 5 to 35 for each subscale. A higher score indicates a stronger sense of meaning in life or search for meaning in life. The MLQ-P and MLQ-S had Cronbach's alpha coefficients of 0.82 to 0.87 [3]. In this study, we used only the MLQ-P score to represent meaning in life for further statistical analysis, and the Cronbach's alpha value was 0.78.

QOL was measured using the Chinese version of the Short Form-36 Health Survey (SF-36) [27]. The SF-36 measures eight domains of health: physical functioning, role limitations due to physical health problems, bodily pain, general health, vitality, social functioning, role limitations due to emotional problems, and mental health. The 8 scales can be combined into 2 summary measures (subscales), providing overall estimates of physical health (physical component score, PCS) and mental health (mental component score, MCS). The PCS contains four domains: physical functioning, role limitations due to physical health problems, bodily pain, and general health. The MCS contains the other four domains: vitality, social functioning, role limitations due to emotional problems, and mental health. The scores range from 0 to 100 for each subscale. A higher score indicates better QOL. The original reliability of this scale was supported by a Cronbach's alpha value of 0.97 [28]. In our study, the Cronbach's alpha value of the SF-36 was 0.91. The PCS and MCS were used as the observed variables to create a latent variable, “global QOL”, which was described in detail in the statistical analyses section.

Statistical analyses

We used SPSS 26.0 for statistical analyses. SEM was performed using AMOS. Descriptive statistics, independent *t tests*, and Chi-square tests were used to describe subject characteristics and the relationship of characteristics with social support, symptom distress, care needs, meaning in life, and QOL. The multivariate normality of the variables in SEM was estimated by the skewness and kurtosis.

Pearson correlation analysis was performed to examine the relationship of social support, symptom distress, care needs, and meaning in life with QOL. We used SEM to test both observed and latent variables. Social support, symptom distress, care needs, and the presence of meaning in life were used as observed variables. In addition, the PCS and MCS were used to create the “global QOL” variable. The PCS and MCS of QOL were observed variables, and global QOL was a latent variable. The hypothesized model assumed that symptom distress, care needs, and social support variables had direct and indirect associations with global QOL, and these associations were mediated by meaning in life. The estimation method for SEM was the maximum likelihood. The overall model fit was evaluated by the model ratio of X^2 to the degrees of freedom, the comparative fit index (CFI), the goodness-of-fit index (GFI), and the root mean square error of approximation (RMSEA). An acceptable model fit was obtained when the CFI and GFI values were 0.9 or higher and the RMSEA was 0.08 or less [29,30].

Results

Participants' characteristics and their correlations with QOL

The participants' characteristics are presented in Table 1. The average age was 64.4 years. Most of the participants were male (65.6%) and married (65.1%), had a high school education (73.7%), were economically independent (72.0%), and lived with family members (69.9%). Among the participants, 18.3% had CKD and 39.8% had diabetes. The median duration of HF was 6.5 months (interquartile range, 6.2-18.9). The QOL scores of the physical and mental components were 45.7 ± 10.8 and 49.4 ± 11.2, respectively, indicating a low QOL. A higher PCS was associated with younger age ($t = 4.29$, $p < .001$), a shorter duration of HF ($t = -2.87$, $p = .004$), lower New York Heart Association functional class ($t = -5.05$, $p < .001$), higher education level ($t = -2.18$, $p = .038$), economic independence ($t = -3.27$, $p = .001$), and no CKD ($t = 3.61$, $p < .001$); a higher MCS was associated with younger age ($t = 2.32$, $p = .022$), lower New York Heart Association functional class ($t = -2.21$, $p = .028$), and no CKD ($t = 2.49$, $p = .004$) (Table 1).

Table 1 *Demographic Characteristics and Correlations with Quality of Life (N = 186).*

Variables	*n* (%)	PCS		MCS	
		Mean (SD)	*p* value	Mean (SD)	*p* value
Age			<.001		.022
<65 years	92 (49.5)	48.7 (8.9)		51.3 (9.9)	
≥65 years	94 (50.5)	42.2 (11.5)		47.5 (12.1)	
Gender			.280		.433
Man	122 (65.6)	46.1 (10.5)		48.9 (11.5)	
Woman	64 (34.4)	44.3 (11.3)		50.2 (10.6)	
Duration of heart failure			.004		.578
>12 months	50 (26.9)	40.9 (10.5)		48.1 (9.6)	
≤12 months	136 (73.1)	46.1 (10.9)		49.1 (11.8)	
NYHA functional class			<.001		.028
I-II	118 (63.4)	47.6 (9.6)		50.2 (10.3)	
III-IV	68 (36.6)	39.6 (11.6)		46.4 (12.4)	
Education			.038		.073
< 12 years	137 (26.3)	44.4 (10.9)		48.5 (11.1)	
≥ 12 years	49 (73.7)	48.1 (9.9)		51.8 (11.0)	
Married			.919		.685
Single	65 (34.9)	45.3 (11.8)		49.8 (10.6)	
Married	121 (65.1)	45.5 (10.2)		49.1 (11.5)	
Economic status			.001		.088
Independent	134 (72.0)	47.1 (10.2)		50.2 (10.8)	
Dependent	52 (28.0)	41.2 (11.1)		47.1 (11.8)	
Living			.325		.575
With family	130 (69.9)	44.9 (10.5)		49.1 (11.5)	
Alone	56 (30.1)	46.6 (11.2)		20.1 (10.4)	
Chronic kidney disease			<.001		.004
Yes	34 (18.3)	38.4 (12.9)		44.4 (13.2)	
No	152 (81.7)	47.0 (9.6)		50.5 (10.4)	
Diabetes mellitus			.056		.190
Yes	74 (39.8)	43.6 (10.5)		48.0 (11.4)	
No	112 (60.2)	46.6 (10.8)		50.2 (11.0)	

Note: NYHA = New York Heart Association; MCS = Mental Component Summary of Quality of Life; PCS = Physical Component Summary of Quality of Life; SD = Standard Deviation.

Correlations of QOL with meaning in life and other factors

The meaning in life, social support, symptom distress, care needs, and QOL data are shown in Table 2. We analyzed the correlations of QOL with meaning in life and other factors (Table 3). A stronger presence of meaning in life (PCS: $r = .53$, $p < .001$; MCS: $r = .44$, $p < .001$) and more social support (PCS: $r = .22$, $p = .002$; MCS: $r = .22$, $p = .002$) were associated with better physical and

Table 2 *Scores of Meaning in Life, Symptom Distress, Care Needs, Social Support, and Quality of Life (N = 186).*

Variables	Mean (SD)
Meaning in life	26.3 (5.3)
Symptom distress	26.7 (9.0)
Care needs	60.1 (12.6)
Social support	21.6 (7.8)
Quality of life	
PCS	45.7 (10.8)
MCS	49.4 (11.2)

Note: PCS = Physical Component Summary of Quality of Life; MCS = Mental Component Summary of Quality of Life; SD = Standard Deviation.

Table 3 *Relationship of Meaning in Life, Symptom Distress, Care Needs, and Social Support with Quality of Life (N = 186).*

Variables	PCS		MCS	
	r	p value	r	p value
Meaning in life	.53	<.001	.44	<.001
Symptom distress	−.59	<.001	−.45	<.001
Care needs	−.68	<.001	−.51	<.001
Social support	.22	.002	.22	.002

Note: PCS = Physical Component Summary of Quality of Life; MCS = Mental Component Summary of Quality of Life.

mental QOL, respectively. However, more symptom distress (PCS: $r = -.59$, $p < .001$; MCS: $r = -.45$, $p < .001$) and care needs (PCS: $r = -.68$, $p < .001$; MCS: $r = -.51$, $p < .001$) were related to poorer physical and mental QOL, respectively.

SEM analysis of the mediating role of meaning in life

SEM was used to further clarify the mediating role of meaning in life in the relationship of care needs, symptom distress, and social support with global QOL. We conducted SEM analysis by entering all factors into one model (Figure 1). The demographic characteristics which were significantly associated with QOL, including age, New York Heart Association functional class, education, economic status, duration of HF, and CKD, were also controlled for the analysis of SEM. The ranges of the skewness and kurtosis for symptom distress, care needs, social support, meaning in life, PCS, and MCS were from −1.088 to 1.127 and from −0.265 to 1.178, respectively, suggesting acceptable multivariate normality [31]. This model demonstrated a good fit with a relative X^2 (ratio of X^2 to degrees of freedom) of 0.41, a CFI of 0.948, a GFI of 0.936, and an RMSEA of 0.071. We noted that 50% of the global QOL was significantly explained by symptom distress, care needs, and the presence of meaning in life. Figure 1 shows that in the demographic characteristics, CKD was the only characteristic significantly associated with global QOL ($\beta = -0.13$, $p = .021$). The presence of meaning in life ($\beta = 0.18$, $p = .032$), symptom distress ($\beta = -0.26$, $p = .005$), and care needs ($\beta = -0.36$, $p = .021$) were significantly and directly related to global QOL, but social support was not directly associated with global QOL.

Table 4 shows that social support ($\beta = 0.45$, $p = .019$), symptom distress ($\beta = -0.12$, $p = .010$), and care needs ($\beta = -0.39$, $p = .005$) were directly correlated with the presence of meaning in life. In the SEM, as shown in Figure 1 and Table 4, although symptom distress and care needs were significantly associated with global QOL, meaning in life also played a partial mediating role between symptom distress and global QOL ($\beta = -0.02$ $p = .023$) and between care needs and global QOL ($\beta = -0.07$, $p = .030$). In addition, meaning in life played a complete mediating role between social support and global QOL ($\beta = 0.08$, $p = .047$). The presence of meaning in life was not only associated with global QOL but also played a partial or total intermediary role in the relationship of symptom distress, care needs, and social support with global QOL among HF patients.

Discussion

Our study demonstrated that meaning in life was significantly correlated with global QOL among patients with chronic HF. Based on the multiple mediation model using SEM, although social support, satisfaction of care needs, and decreasing symptom distress helped improve global QOL, meaning in life played a complete mediating role between social support and global QOL and played a partial mediating role in the relationship of care needs and symptom distress with global QOL.

QOL represents a multidimensional concept involving physical, psychological, social, and spiritual aspects [9,28]. People living with congestive HF often experience worsening symptoms and declining QOL along with disease progression [32]. We identified the complete mediating role of the presence of meaning in life between social support and global QOL. Even at a chronic stage, patients still need adequate social support. However, social support interventions need to be directional, not aimless. By strengthening meaning in life based on individualized life goals, social support may efficiently optimize the QOL of patients with chronic HF. In the management of disease stress, Almeida et al found that providing meaning of life-centered supportive therapy could help patients achieve disease adaptation and life satisfaction [33]. Thus, for patients entering the chronic stage of HF, medical professionals and

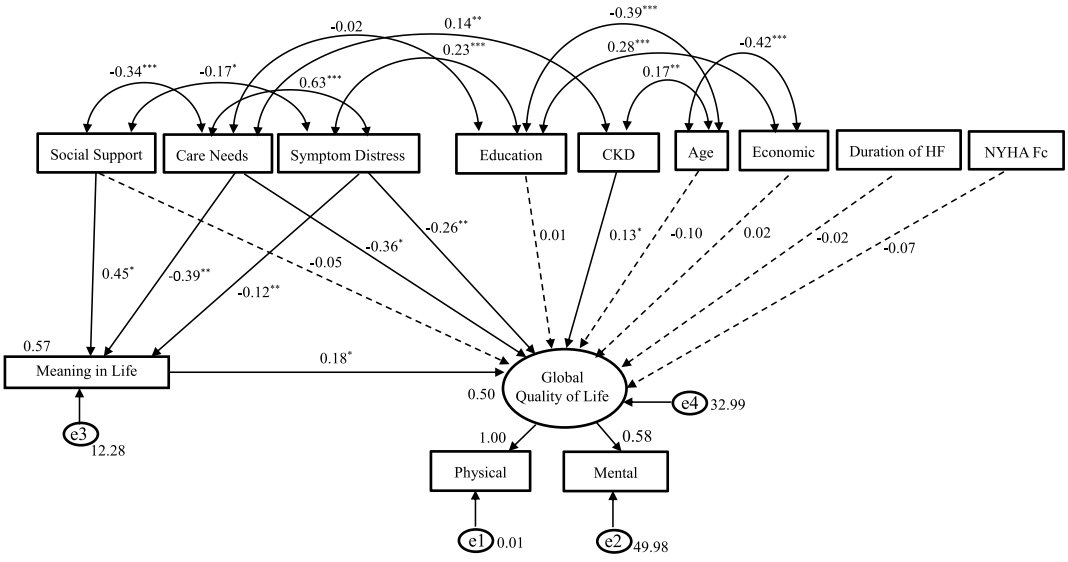

Figure 1. Structural Equation Modeling of the Mediating Role of Meaning in Life in the Relationship of Social Support, Care Needs, and Symptom Distress with Quality of Life. CKD = chronic kidney disease; HF = heart failure; NYHA Fc = New York Heart Association functional class. *$p < .05$, **$p < .01$, ***$p < .001$.

Table 4 *Structural Equation Modeling of The Mediating Role of Meaning in Life in The Relationship of Social Support, Care Needs, Symptom Distress with Quality of Life (N = 186).*

Variables	Meaning in life			Global quality of life		
	β	95% CI	p value	β	95% CI	p value
Meaning in life						
Direct	–	–		0.18	0.03~0.35	.032
Indirect	–	–		–	–	
Total	–	–		0.18	0.03~0.35	.032
Symptom distress						
Direct	−0.12	−0.26~ −0.05	.010	−0.26	−0.42~ −0.14	.005
Indirect	–	–		−0.02	−0.08~ −0.01	.023
Total	−0.12	−0.26~ −0.05	.010	−0.28	−0.44~ −0.16	.007
Care needs						
Direct	−0.39	−0.49~ −0.31	.005	−0.36	−0.49~ −0.20	.021
Indirect	–	–		−0.07	−0.14~ −0.01	.030
Total	−0.39	−0.49~ −0.31	.005	−0.43	−0.56~ −0.29	.013
Social support						
Direct	0.45	0.36~0.53	.019	−0.05	−0.16~0.07	.462
Indirect	–	–		0.08	0.01~0.16	.047
Total	0.45	0.36~0.53	.019	0.03	−0.07~0.12	.570

Note: β = Coefficient; CI = Confidence Interval.

family members should consider providing support focusing on meaning in life development.

To improve the QOL of patients facing HF and multiple comorbidities, meeting their social, spiritual, and psychological needs and decreasing symptom distress are mandatory [13]. Our data show that both care needs and symptom distress were significantly associated with meaning in life. The presence of meaning in life also played a partial mediating role in the relationship of care needs and symptom distress with QOL. Even with advances in therapeutic capability, a substantial number of patients with HF still have symptoms, including exertional dyspnea, fatigue, and weakness. When the symptoms cannot be adequately managed, Li et al [34] noted that meaning in life was commonly reported to be a vital way of coping with HF. Adopting positive beliefs could guide patients with HF toward peace of mind with an optimistic attitude to gain new perspectives. Similarly, Liu et al [16] reported that meaning in life was an important factor in helping HF patients overcome the residual burden of symptoms. With positive beliefs, people can deal with the dilemma of disease with an optimistic attitude and more easily feel satisfied with life [8]. Thus, when we take care of patients with HF, listening and realizing patients' expectations for their life is very important. To improve patients' QOL, efforts to strengthen their meaning of life should be integrated into care for care needs satisfaction and decreasing symptom distress.

In the chronic phase of HF, patients remain at high risk of deterioration. Impacted by functional limitations and a shortened life span, many patients experience a cycle of hopelessness, which may subsequently impair their QOL [35]. In this study, we found that for patients with chronic HF, global QOL was better in those with stronger meaning in life. Consistent with our findings, recent reports support the value of meaning in life in HF patients. Tobin et al [9] noted that in the strategy of improving QOL in patients with HF, spirituality plays a key role. In addition to dealing with the symptoms associated with HF, it is also mandatory to address care in emotional, social, and spiritual aspects. Since HF is a capricious chronic disease, Bekelman et al [36] noted that, in the spiritual aspect, patients with HF are actually more vulnerable than patients with cancer. Therefore, even for patients in the chronic stage of HF, we still need to pay attention to whether they have better self-identity and sense of meaning in life to have better physical and mental health. When patients have a clear goal in life, even in facing the risk of death, they can use positive inner power to transform the sense of distress to improve their QOL.

Although a few demographic characteristics were associated with QOL in our study, CKD was the only characteristic significantly associated with QOL in the SEM. Recent studies showed that in patients with HF and CKD, the interaction between the kidneys and the heart disturbs body's metabolic function, accelerates the progression of atherosclerosis, affects the use of HF medications, and leads to a poor prognosis [37]. Similarly, in our SEM, we found that patients with HF and kidney disease had a poor QOL. Thus, in a clinical setting, the assessment of renal function should be integrated into the care process for this high risk population to reduce the negative impact of kidney problems on QOL.

Limitations

Our study had the following limitations. First, when analyzing the role of meaning in life in QOL, we did not include the assessment of the factors associated with emotional aspects, such as depression and anxiety. Second, our interpretation of the data in this study was limited by its cross-sectional design. Finally, patients from only one teaching hospital were included, potentially leading to significant selection bias. The findings among patients from different levels of hospitals might differ. Multicenter studies using randomized sampling should be conducted in the future to improve the internal validity of this study.

Conclusions

Our study supports that even in patients with chronic HF, meaning in life remains important in QOL improvement. The presence of meaning in life plays a partial or total mediating role in the relationship of symptom distress, care needs, and social support with QOL. Social support should aim to strengthen patients' meaning in life. The spiritual effect associated with enriched meaning in life may help patients manage the issues caused by symptoms and alleviate their unmet needs.

Conflict of interest

No potential conflicts of interest relevant to this article are reported.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.anr.2023.11.003.

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Research Article

Factors Associated with Diabetic Complication Index among Type 2 Diabetes Patients: Focusing on Regular Outpatient Follow-up and HbA1c Variability

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SUMMARY

Purpose: Preventing diabetic complications involves regular outpatient follow-up and maintaining low variability in hemoglobin A1c (HbA1c) levels. This study investigated the factors associated with diabetic complications, with a specific focus on the impact of regular outpatient follow-up and HbA1c variability, among patients with type 2 diabetes.
Methods: The study design was secondary data analysis of electronic medical records from a university hospital in Korea. It included patients aged 40–79 with type 2 diabetes who were prescribed diabetes medication within three months of their first HbA1c test by an endocrinologist and were followed up for at least five years. Follow-up regularity, adjusted standard deviation of HbA1c levels, and diabetic complication indices were collected. Data were analyzed using the Chi-square test, independent *t*-test, repeated measures analysis of variance, and multiple regression analysis.
Results: The study included 1566 patients. Lower follow-up regularity was observed in patients of older age, with comorbidities, diabetic complications, insulin treatment, a history of hospitalization, lower baseline estimated glomerular filtration rate (eGFR) and total cholesterol (TC), and higher HbA1c variability. Higher HbA1c variability was observed in younger patients without comorbidity but with insulin treatment, a history of hospitalization, higher baseline blood glucose (BG), HbA1c, TC, and triglyceride levels. HbA1c variability had the strongest influence on BG and HbA1c levels at the five-year follow-up. Baseline eGFR and TC were the most influential factors for their respective levels at the five-year follow-up. Follow-up regularity significantly affected BG, HbA1c, eGFR, and TC at five-year follow-up.
Conclusions: It has been shown that several variables besides regular follow-up and HbA1c variability have an influence. However, these are the two that can be corrected through nursing intervention and are important, so intervention on these is important.

Introduction

The estimated global prevalence of diabetes among individuals aged 20–79 years was 10.5% in 2021, projected to reach 12.2% by 2045 [1]. In Korea, the prevalence of type 2 diabetes mellitus (T2DM) in individuals aged 30 years or older increased from 13.8% in 2018 to 16.3% in 2021 [2], leading to an escalation in diabetes-related health expenditures [1]. Poor blood glucose (BG) control in patients with diabetes increases glycemic variability and causes microvascular and macrovascular complications [3]. The prevalence of diabetic complications was 84.7% in a 10-year retrospective cohort study in Korea [4], and the medical cost and mortality rates of diabetes patients with complications were higher than those of patients without complications [5]. Therefore, managing diabetic complications is important for patients with T2DM.

Diabetes is an ambulatory care-sensitive condition, and continuous outpatient care plays a key role in preventing diabetic

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complications and hospitalization of patients with diabetes mellitus [6]. Diabetes patients with fewer than three visits and two hemoglobin A1c (HbA1c) tests per year had a 1.54–2.38 times higher risk of developing nephropathy, retinopathy, or cardiovascular diseases [7–9]. These patients exhibited a tendency to develop these complications earlier and with greater severity [7–9]. Higher regularity of primary care was associated with 6.0–11.0% lower odds of hospitalization [10], and the cost of diabetes care was reduced by engaging in regular check-ups with a doctor [11]. Additionally, patients with regular follow-up had better health behaviors, such as diet, physical activity, and medication adherence [7,12]. Patients who received regular outpatient follow-up seemed to receive greater attention through education programs, personal instructions, and screening [13].

HbA1c is recommended to be followed up every three to six months, but the follow-up adherence rate was low (approximately 50.0%) [8,14]. In studies included in the prior systematic review [15,16], the mean ages of irregular and regular follow-up patients were 47.0–55.7 and 47.7–59.8, respectively. Additionally, factors related to irregular follow-up included lower education levels and smoking habits [15,16]. Patients with diabetes who did not undergo regular follow-up had higher levels of baseline BG, HbA1c, total cholesterol (TC), LDL-C, and triglycerides (TGs) [7–9]. Since these indices are associated with the occurrence of diabetes complications, they must be carefully controlled through diabetes management. Clinical guidelines recommend target ranges for BG, HbA1c, estimated glomerular filtration rate (eGFR), and lipid profile [17,18]. Regular follow-up, combined with educational inputs from healthcare providers and effective communication, can be one way to manage these diabetic complication indices. However, since diabetes mellitus is a lifelong condition, patients with T2DM are expected to have a burden of regular follow-up.

Difference in the occurrence of diabetic complications have been reported, even among diabetes patients with similar mean BG levels. Glycemic variability, which refers to the degree of change in BG, has been recognized as an important factor in diabetes management [3]. HbA1c variability, one of the glycemic variabilities, is calculated as the standard deviation (SD) of HbA1c measured over several months to years [3]. In the low HbA1c variability group, the mean levels of diabetic complication indices, such as BG, LDL-C, HDL-C, and TG, during the 11-year period were better than those in the high HbA1c variability group [19]. HbA1c variability was associated with an increased risk of diabetic complications and mortality [20–22], and it was more effective at predicting several diabetes complications, functional limitation, and increased mortality than mean HbA1c [23,24]. Therefore, early minimization of HbA1c variability can mitigate the deterioration of diabetes patients' prognosis [25].

While previous research has provided insights into certain factors associated with regular follow-ups and HbA1c variability [7–9,15,16,19,26], there remains limited evidence regarding their impact on changes in various diabetic complication indices [8,13]. Diabetes patients who had three or more follow-up visits per year showed better improvements in BG and HbA1c during the study period than those with fewer visits [27], and the greater the HbA1c variability, the greater the decline in eGFR in previous studies [25]. However, these studies had a relatively short mean follow-up duration of 20.1 months [27] or focused solely on the changes in eGFR based on HbA1c variability among various diabetes complication indices [25]. Therefore, further investigation and extended follow-up periods were necessary to comprehensively evaluate the impact of regular follow-up and HbA1c variability on diabetic complication indices.

We conducted a retrospective analysis of electronic medical records (EMRs) from Pusan National University Yangsan Hospital to explore factors associated with diabetic complication indices, with a particular focus on regular follow-up and HbA1c variability among patients with T2DM. In this study, the diabetic complication indices included BG, HbA1c, eGFR, TC, TG, HDL-C, and LDL-C [17,18]. Given the established association between future and baseline diabetic complication indices [28,29], our study included baseline diabetic complication indices when exploring the factors related to future diabetic complication indices. The specific purposes of the study were (1) to identify differences in patients characteristics based on regular follow-up, (2) to analyze changes in diabetic complication indices based on regular follow-up, (3) to identify differences in patients characteristics based on HbA1c variability, (4) to analyze changes in diabetic complication indices based on HbA1c variability, and finally, (5) to determine the impact of regular follow-up and HbA1c variability on diabetic complication indices while controlling for other variables.

Methods

Study design and patients

We performed a retrospective cohort study using EMRs collected from November 24, 2008, when Pusan National University Yangsan Hospital opened, until September 15, 2022. Eligible patients were patients with an International Classification of Diseases (ICD)-10 code of E11–14, representing T2DM (E11), malnutrition-related diabetes mellitus (E12), other specified diabetes mellitus (E13), and unspecified diabetes mellitus (E14). Additionally, eligible patients were those who visited an endocrinologist within three months from the baseline HbA1c test, were aged between 40 and 79 years, and had a record of prescription for diabetes medication within three months of the baseline HbA1c test. To ensure a minimum observation period of five years, patients without a record of HbA1c five years after the baseline HbA1c test were excluded.

We identified 31,394 patients with ICD-10 codes E11–14 (Figure S1). Among these, patients without records of the HbA1c test (n = 3526), patients without endocrinologist medical records (n = 5161) or records of diabetes medication prescription (n = 8187) within three months of the baseline HbA1c test, patients who were <40 or ≥80 years of age at baseline (n = 2954), and patients who were followed up less than five years (n = 10,000) were excluded, leaving a total of 3458 patients. For more than five years, 326 patients (group A) were tested for HbA1c at 6-month intervals, 1100 patients (group B) at 12-month intervals, and 140 patients (group C) were followed up less than five times. The follow-up regularity for the remaining 1892 patients was difficult to specify. Finally, 1566 patients from groups A, B, and C were included in the analysis.

Measures

Characteristics of patients and diabetic complication indices

Patient characteristics included gender, age, comorbidity (such as hypertension, dyslipidemia, heart disease, osteoarthritis, cancer, etc.), duration of diabetes, presence of chronic diabetic complications (including nephropathy, neuropathy, retinopathy, foot ulcers), method of diabetes treatment, BMI, and blood pressure (BP) at the baseline. Diabetic complication indices included BG, HbA1c, eGFR, TC, TG, HDL-C, and LDL-C. The timing of the baseline HbA1c was the first measured HbA1c at Pusan National University Yangsan Hospital, and the timing of measuring diabetic complication indices, excluding HbA1c, was within four months from the date of HbA1c measurement. eGFR was calculated using the chronic kidney disease-epidemiology collaboration method based on serum creatinine values. Additionally, hospitalization history during the

five-year observation period in the hospital included in this study was collected.

Follow-up regularity

Follow-up regularity was measured based on the frequency of HbA1c follow-up tests over a five-year period following the patient's baseline HbA1c test. Among the diabetic complication indices, HbA1c is the most critical for patients with T2DM, with recommended follow-up every three to six months [8,18]. Accordingly, patients who had HbA1c follow-ups at intervals of six-month (or less) were categorized as group A. Considering that the diabetes quality assessment criteria set by the Korea Health Insurance Review and Assessment Service included HbA1c testing once a year until 2020 [30], patients who had HbA1c follow-ups at 12-month intervals were categorized as group B. Patients who did not undergo HbA1c testing at least once a year during the five-year period were classified as group C.

HbA1c variability

HbA1c variability was measured as the adjusted SD of serial HbA1c tests to adjust for the differences in the number of measurements between patients [31,32]. The indices of HbA1c variability were calculated as follows:

$$\textbf{adjusted SD}_{\boldsymbol{HbA1c}} = \frac{\mathrm{SD}_{HbA1c}}{\sqrt{\frac{n}{n-1}}}$$

n = number of HbA1c measurements of each individual.

Given the absence of a standardized cutoff for HbA1c variability, many studies have employed relative criteria, such as quartiles or the median of HbA1c variability [31,33–35], to classify HbA1c variability groups. Consistent with this approach, we categorized patients into low and high HbA1c variability groups based on the median value of their HbA1c variability in this study.

Statistical analysis

Statistical analyses were performed using R version 4.2.0 software (The R Foundation, Vienna, Austria) and SPSS version 27 (IBM Corp., Armonk, NY, USA). A p-value of less than .05 was considered statistically significant. We identified outliers using a box plot and histogram. Extreme outliers, which exceeded three times the interquartile range from the upper or lower edge of the box, were replaced with values that were either one unit larger or one unit smaller than the second most extreme value within the variable's original distribution [36]. Continuous and categorical variables were summarized as mean ± SD and percentages. Differences in variables according to follow-up regularity or HbA1c variability were analyzed using the Chi-square test, independent t-test, and analysis of variance (ANOVA). *Post hoc* tests using Scheffe test were conducted on the three follow-up regularity groups to determine which specific group differences were significant.

Changes in diabetic complication indices in five years according to follow-up regularity or HbA1c variability were analyzed by repeated measures ANOVA (RMANOVA). RMANOVA was performed when diabetic complication indices were available at both the baseline (T_1) and five-year follow-up (T_2) time points. For cases with missing data at T_2, the corresponding patients were excluded from the analysis. Mauchly's sphericity test was used to test the homogeneity of variance, and the Greenhouse-Geisser correction was used when the assumption of sphericity was violated. When interaction effects were significant, we conducted simple main effect tests using pairwise comparisons, univariate, and multivariate tests within the RMANOVA analysis process in SPSS version 27. When conducting pairwise comparisons, Bonferroni method was used to adjust for multiple comparisons.

Stepwise multiple regression analysis was performed to identify the factors influencing diabetic complication indices. Model variables were selected using the Akaike Information Criteria algorithm in R to determine the combination of variables with the lowest Akaike Information Criteria.

Ethical considerations

This retrospective study was exempted from the Institutional Review Board of the Pusan National University Yangsan Hospital (IRB No. 05-2022-257). Patients' data acquired from the Pusan National University Yangsan Hospital were kept anonymized, and informed consent was waived.

Results

Differences in characteristics, baseline diabetic complication indices, and HbA1c variability of patients according to follow-up regularity

Among the 1566 patients in this study, 901 (57.5%) were men, with a mean age of 57.04 years at baseline (Table 1). The majority of patients (85.4%) had comorbidities, and the average duration of T2DM was 5.84 years. Additionally, most patients (90.4%) did not have a diagnosis of chronic diabetic complications, and 1360 patients (86.8%) were treated with oral hypoglycemic agents only. Hospitalization during the five-year observation occurred in 46.6% of patients. Significant differences were observed in age, comorbidity, chronic diabetic complications, method of diabetes treatment, follow-up period, and hospitalization history among the groups based on follow-up regularity. *Post hoc* analysis showed that patients in the group with less than five follow-ups over five years (group C) were significantly older than those in the groups that received regular follow-up every six months (group A) or every 12 months (group B) over five years. Additionally, the follow-up period for group B was significantly longer than that for groups A and C.

Regarding diabetic complication indices, eGFR was the lowest in group C at 95.54 mL/min/1.73 m^2 and TC was the highest in group A at 193.47 mg/dL, showing significant differences among the groups. The HbA1c variability over five years was higher in group C (0.97%) than group A (0.80%) and group B (0.85%). The median HbA1c variability was 0.75%.

Changes in diabetic complication indices over five years according to follow-up regularity

Changes in the diabetic complication indices over five years according to follow-up regularity were presented in Figure 1 and Table 2. There were significant interaction effects of group and time on HbA1c, eGFR, and TC levels. The effect of time on HbA1c was significant, with HbA1c at T_2 being lower than HbA1c at T_1 in all groups. Additionally, the effect of group on HbA1c was significant at T_2, with both groups A and B exhibiting significantly lower HbA1c levels than group C. In terms of eGFR, the effect of time was significant, with eGFR at T_1 being higher than eGFR at T_2 in all groups. The effect of group on eGFR was significant at T_2, with group B showing significantly higher eGFR levels than both group A and C. Regarding TC, the effect of time was significant, with TC at T_2 being lower than TC at T_1 in all groups. Additionally, the effect of group on TC was significant at T_2, with both group A and B having significantly lower TC levels than group C. There were no significant differences in BG, TG, HDL-C, and LDL-C levels according to follow-up regularity for five years.

Table 1 *General Characteristics, Baseline Diabetic Complication Indices, and HbA1c Variability according to Follow-up Regularity (N = 1566).*

		Total (n = 1566)	Group A[a] (n = 326)	Group B[b] (n = 1100)	Group C[c] (n = 140)	x^2/F	p
		n (%) or M ± SD					
General characteristics							
Gender	Men	901 (57.5)	205 (62.9)	613 (55.7)	83 (59.3)	5.46	.065
	Women	665 (42.5)	121 (37.1)	487 (44.3)	57 (40.7)		
Age (year)		57.04 ± 8.82	55.65 ± 8.39	56.93 ± 8.62	61.11 ± 10.18	19.48 a, b < c[†]	<.001
Comorbidity	No	228 (14.6)	47 (14.4)	173 (15.7)	3 (5.7)	10.02	.007
	Yes	1338 (85.4)	279 (85.6)	927 (84.3)	132 (94.3)		
DM duration (year) (n = 1225)		5.84 ± 6.94	5.85 ± 7.11	5.72 ± 6.83	6.98 ± 7.47	1.44	.237
Chronic DM Cx	No	1416 (90.4)	314 (96.3)	981 (89.2)	121 (86.4)	17.62	<.001
	Yes	150 (9.6)	12 (3.7)	119 (10.8)	19 (13.6)		
DM treatment	OHA only	1360 (86.8)	282 (86.5)	966 (87.8)	112 (80.0)	13.90	.008
	IN only	79 (5.0)	17 (5.2)	46 (4.2)	16 (11.4)		
	OHA + IN	127 (8.1)	27 (8.3)	88 (8.0)	12 (8.6)		
BMI (kg/m^2) (n = 1349)		24.84 ± 3.55	24.99 ± 3.52	24.84 ± 3.48	24.45 ± 4.11	0.94	.389
SBP (mmHg) (n = 1555)		129.82 ± 18.68	128.27 ± 18.09	130.40 ± 18.83	128.93 ± 18.78	1.80	.165
DBP (mmHg) (n = 1555)		80.57 ± 12.74	80.25 ± 12.19	80.94 ± 12.58	78.37 ± 12.11	2.78	.062
Follow-up period (year)	5–6	614 (39.2)	182 (55.8)	371 (33.7)	61 (43.6)	61.24	<.001
	7–8	396 (25.3)	74 (22.7)	283 (25.7)	39 (27.9)		
	≥9	556 (35.5)	70 (21.5)	446 (40.5)	40 (28.6)		
	M ± SD	8.21 ± 2.38	7.38 ± 2.11	8.51 ± 2.39	7.83 ± 2.40	31.39 a, c < b[†]	<.001
Hospitalization history	No	836 (83.4)	173 (53.1)	621 (56.5)	42 (30.0)	34.94	<.001
	Yes	730 (46.6)	153 (46.9)	479 (43.5)	98 (70.0)		
Baseline diabetic complication indices							
BG (mg/dL) (n = 1328)		205.59 ± 122.04	208.11 ± 120.35	202.92 ± 122.29	220.95 ± 123.50	1.24	.289
HbA1c (%)		8.22 ± 1.96	8.42 ± 1.93	8.17 ± 1.94	8.15 ± 2.09	2.13	.119
eGFR (mL/min/1.73 m^2) (n = 1538)		99.90 ± 19.53	99.02 ± 23.13	100.71 ± 18.24	95.54 ± 19.66	4.66 c < a, b[†]	.010
TC (mg/dL) (n = 1427)		186.47 ± 49.05	193.47 ± 52.21	184.29 ± 48.23	188.06 ± 46.77	4.04 b, c < a[†]	.018
TG (mg/dL) (n = 1363)		189.56 ± 138.72	201.87 ± 136.14	187.59 ± 140.75	175.42 ± 124.97	1.76	.173
HDL-C (mg/dL) (n = 1361)		45.99 ± 12.17	45.61 ± 12.21	45.89 ± 11.91	47.93 ± 14.25	1.54	.215
LDL-C (mg/dL) (n = 1102)		109.66 ± 41.40	113.82 ± 46.95	108.49 ± 39.69	107.53 ± 38.08	1.71	.181
HbA1c variability (%)							
	M ± SD	0.85 ± 0.48	0.80 ± 0.39	0.85 ± 0.47	0.97 ± 0.71	6.12 a, b < c[†]	.002

Note. BG = blood glucose; BMI = body mass index; Cx = complications; DBP = diastolic blood pressure; DM = diabetes mellitus; eGFR = estimated glomerular filtration rate; HbA1c = hemoglobin A1c; HDL-C = high-density lipoprotein cholesterol; IN = insulin; LDL-C = low-density lipoprotein cholesterol; M = mean; n = number; OHA = oral hypoglycemic agent; SBP = systolic blood pressure; SD = standard deviation; TC = total cholesterol; TG = triglyceride.

[a] Group regularly followed up every six months over five years.

[b] Group regularly followed up every 12 months over five years.

[c] Group with less than five follow-ups for five years.

[†] Scheffe test.

Differences in characteristics and baseline diabetic complication indices according to HbA1c variability

Differences in patient characteristics and baseline diabetic complication indices according to HbA1c variability were presented in Table 3. Patients were classified into low and high HbA1c variability groups, with a median HbA1c variability of 0.75%. Patients in the high HbA1c variability group were younger, had a lower prevalence of comorbidities, and received insulin treatment more frequently than those in the low HbA1c variability group. Patients with high HbA1c variability had significantly higher baseline BG, HbA1c, TC, and TG levels than those with low HbA1c variability. Additionally, a higher proportion of patients in the high HbA1c variability group had a history of hospitalization during the five-year observation period.

Changes in diabetic complication indices over five years according to HbA1c variability

Changes in the diabetic complication indices over five years according to HbA1c variability were presented in Figure 2 and Table 4. There were significant interaction effects of group and time on BG, HbA1c, eGFR, and TC levels. During the five-year follow-up, BG decreased from 158.35 mg/dL to 158.07 mg/dL in the low HbA1c variability group, while it decreased from 233.09 mg/dL to 212.70 mg/dL in the high HbA1c variability group. HbA1c level decreased from 7.3% to 6.9% in the low variability group, while it decreased from 9.2% to 8.0% in high variability group. In terms of eGFR, low variability group showed a decreased from 98.77 mL/min/1.73 m^2 to 95.02 mL/min/1.73 m^2, while high variability group exhibited a decrease from 99.03 mL/min/1.73 m^2 to 91.80 mL/min/1.73 m^2. TC decreased from 181.35 mg/dL to 149.64 mg/dL in low variability group, whereas it decreased from 191.21 mg/dL to 152.38 mg/dL in high variability group. There was no significant difference in the TG, HDL-C, and LDL-C levels according to HbA1c variability over five years.

Factors affecting diabetic complication indices at five-year follow-up

The dependent variables were the diabetic complication indices that showed significant changes over the five-year period according to the follow-up regularity and HbA1c variability. The independent variables were chosen from all patients' characteristics using a stepwise algorithm in R (Table 5). Due to missing data in HDL-C, LDL-C, and TG levels, only TC was included as a representative value of cholesterol levels in the multiple regression analysis. The Durbin-Watson value was close to 2.00 (1.91–2.03), indicating no issue of autocorrelation. The variation inflation factor showed

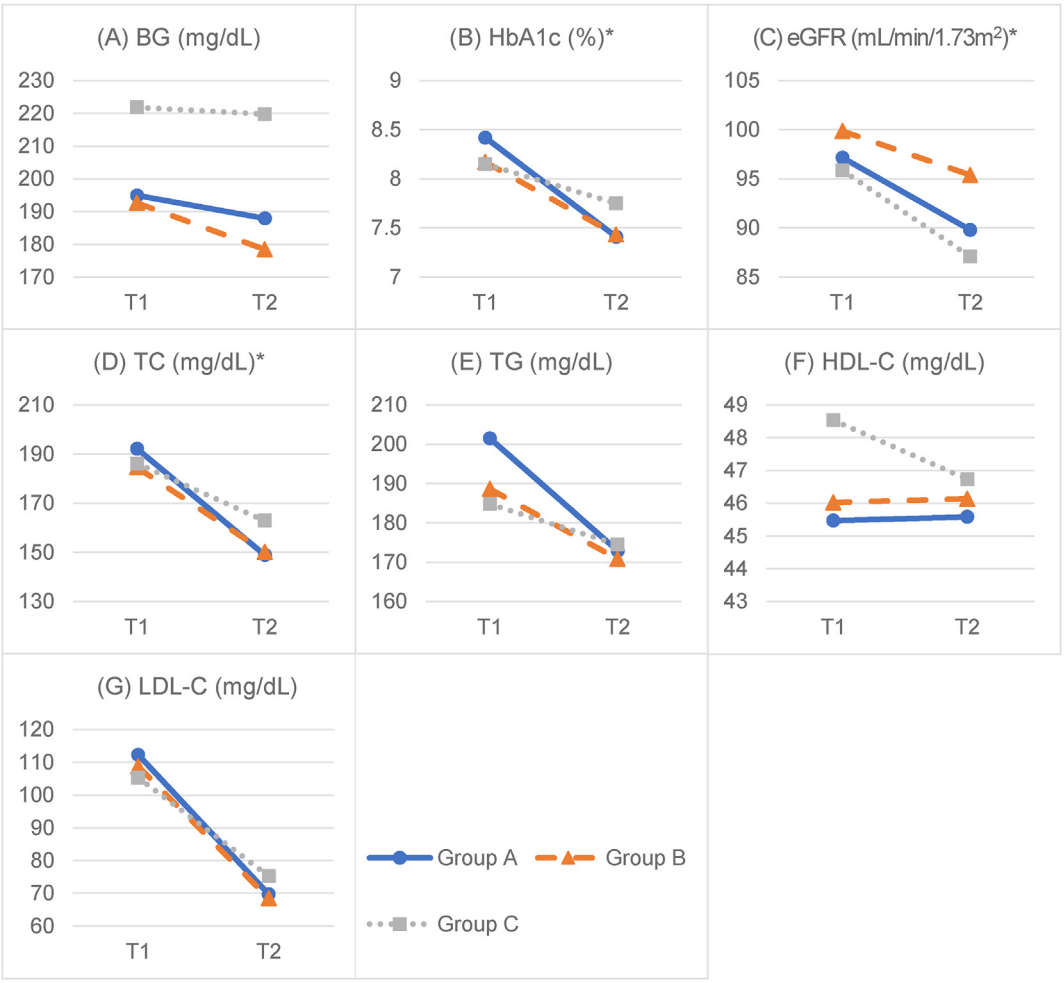

Figure 1. Changes in Diabetic Complication Indices over Five Years according to Follow-Up Regularity. *Note.* BG = blood glucose; eGFR = estimated glomerular filtration rate; Group A = regularly followed up every six months; Group B = regularly followed up every 12 months; Group C = followed up less than five times for five years; HbA1c = hemoglobin A1c; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; *n* = number; T_1 = baseline; T_2 = five-year follow-up; TC = total cholesterol; TG = triglyceride. *Significant interaction effects of time and group at $p < .05$.

that values of all variables were not greater than 10 (1.03–2.34), indicating no issue of multicollinearity.

BG at the five-year follow-up was affected by HbA1c variability, duration of DM, and baseline BG, followed by baseline BP, explaining 16.0% of the variance. HbA1c at the five-year follow-up was significantly influenced by HbA1c variability, duration of DM, baseline HbA1c, eGFR, and follow-up regularity, followed by baseline BMI, explaining 23.0% of the variance. eGFR at the five-year follow-up was influenced by baseline eGFR, gender, age, follow-up regularity, history of hospitalization, baseline SBP, HbA1c variability, and duration of DM, followed by baseline DBP and chronic diabetes complications, explaining 55.0% of the variance. TC at the five-year follow-up was significantly affected by baseline TC, age, follow-up regularity, baseline HbA1c, and BMI, followed by gender and duration of DM, explaining 14.0% of the variance.

Discussion

The present study examined the factors influencing diabetic complication indices, with a focus on regular follow-up and HbA1c variability. Among 3458 patients who met the selection criteria for this study, HbA1c of only 326 patients was continuously followed up at six-month intervals. In a previous study, the rate of adherence to HbA1c testing within the recommended interval of three to six months was only 50.0%, with 2085 (32.5%) patients in the top third (>66.0%) adherence rate [8]. Among patients with uncontrolled diabetes with HbA1c >10.0%, the prevalence of delayed follow-up HbA1c testing was 45.0% [14], suggesting that poor follow-up was an urgent issue in patients with DM.

This study measured follow-up regularity based on HbA1c tests rather than outpatient visits. When considering outpatient visits as the basis for follow-up regularity, it presented challenges in distinguishing within EMRs between records of visits for medical consultations and those for non-medical purposes, such as visit solely for obtaining medical documents or visit by caregivers to refill medication. Patients in group A, who had the highest regular follow-up adherence and conducted HbA1c testing every six months, were younger and rarely had chronic diabetic complications at baseline. Similarly, diabetes patients who were followed up three or more times a year were younger than those who were followed up less than three times a year [27], and the presence of complications was associated with inconsistent follow-up [16]. In contrast, younger age was a factor related to low follow-up frequency in other studies [15,16,27]. Mixed conclusions were drawn regarding insulin treatment, as evidenced by several studies showing positive, negative, and no association with follow-up non-attendance, which warrants further research

Table 2 *Changes in Diabetic Complication Indices over Five Years according to Follow-up Regularity (N = 1566).*

Diabetic Cx index	G[a]	*n*	T_1	T_2	S	F	*p*	Simple time effect	
			Mean ± Standard deviation					F	*p*[†]
BG (mg/dL) (*n* = 842)	A	148	194.91 ± 100.86	187.90 ± 82.65	G	8.95	<.001		
	B	598	192.61 ± 105.18	178.40 ± 81.64	T	1.89	.170		
	C	96	221.78 ± 123.14	219.77 ± 125.35	G × T	0.53	.590		
HbA1c (%) (*n* = 1566)	A	326	8.42 ± 1.93	7.41 ± 1.25	G	1.44	.238	80.84	<.001
	B	1100	8.17 ± 1.94	7.43 ± 1.35	T	101.76	<.001	149.04	<.001
	C	140	8.15 ± 2.09	7.75 ± 1.98	G × T	4.67	.009	5.47	.019
Simple group effect F (*p*)[†]			2.13 (.119)	3.51 (.030) A, B < C					
eGFR (mL/min/1.73 m^2) (*n* = 1305)	A	260	97.15 ± 24.78	89.79 ± 27.03	G	8.35	<.001	51.73	<.001
	B	912	99.85 ± 18.85	95.38 ± 21.74	T	125.10	<.001	66.86	<.001
	C	133	95.85 ± 19.57	87.07 ± 24.11	G × T	6.06	.002	37.61	<.001
Simple group effect F (*p*)[†]			3.48 (.031)	11.49 (<.001) A, C < B					
TC (mg/dL) (*n* = 1145)	A	214	192.14 ± 52.81	148.88 ± 33.25	G	2.26	.105	140.48	<.001
	B	836	184.54 ± 48.80	150.15 ± 34.52	T	218.18	<.001	346.77	<.001
	C	95	186.14 ± 49.41	162.80 ± 56.56	G × T	4.88	.008	18.15	<.001
Simple group effect F (*p*)[†]			2.00 (.136)	5.52 (.004) A, B < C					
TG (mg/dL) (*n* = 1096)	A	206	201.51 ± 135.08	172.91 ± 107.17	G	0.44	.643		
	B	805	188.61 ± 139.87	170.83 ± 111.89	T	8.62	.003		
	C	85	184.74 ± 133.34	174.47 ± 124.32	G × T	0.64	.528		
HDL-C (mg/dL) (*n* = 1089)	A	201	45.47 ± 11.59	45.58 ± 11.15	G	1.23	.294		
	B	803	46.02 ± 11.95	46.13 ± 11.18	T	1.25	.264		
	C	85	48.53 ± 14.95	46.73 ± 11.36	G × T	1.28	.278		
LDL-C (mg/dL) (*n* = 881)	A	194	112.26 ± 46.79	69.65 ± 27.26	G	0.59	.553		
	B	624	108.74 ± 40.06	68.37 ± 29.09	T	264.32	<.001		
	C	63	105.27 ± 40.41	75.19 ± 44.29	G × T	1.78	.170		

Note. BG = blood glucose; Cx = complication; eGFR = estimated glomerular filtration rate; G = group; HbA1c = hemoglobin A1c; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; *n* = number; S = source; T = time; T_1 = baseline; T_2 = five-year follow-up; TC = total cholesterol; TG = triglyceride.
[a] Group A and B were regularly followed up every six and 12 months, respectively, and Group C was followed up less than five times for five years.
[†] Bonferroni adjustment for multiple comparisons.

[16]. It is interesting to note that the regular follow-up period was 7.38 years in group A and 8.51 years in group B, indicating a longer maintenance period in group B, who conducted HbA1c testing every 12 months. Frequent follow-up without considering the patient's characteristics might be undesirable and increase the medical costs [37].

Significant effects of group within RMANOVA were demonstrated, with both groups A and B exhibiting lower HbA1c and TC

Table 3 *General Characteristics and Baseline Diabetic Complication Indices of Study Subjects according to HbA1c Variability (N = 1566).*

Characteristics		HbA1c variability[a]		x^2/t	*p*
		Low (*n* = 783)	High (*n* = 783)		
		n (%) or M ± SD			
General characteristics					
Gender	Men	447 (57.1)	454 (58.0)	0.09	.759
	Women	336 (42.9)	329 (42.0)		
Age (year)		57.64 ± 8.42	56.43 ± 9.18	2.73	.006
Comorbidity	No	89 (11.4)	139 (17.8)	12.33	<.001
	Yes	694 (88.6)	644 (82.2)		
DM duration (*n* = 1225)		5.51 ± 6.39	6.16 ± 7.42	2.72	.099
Chronic DM Cx	No	712 (90.9)	704 (89.9)	0.36	.548
	Yes	71 (9.1)	79 (10.1)		
Diabetes treatment	OHA only	711 (90.8)	649 (82.9)	21.96	<.001
	Insulin only	30 (3.8)	49 (6.3)		
	OHA + Insulin	42 (5.4)	85 (10.9)		
BMI (kg/m^2) (*n* = 1349)		27.80 ± 3.31	24.88 ± 3.77	0.20	.658
SBP (mmHg) (*n* = 1555)		129.30 ± 18.08	130.35 ± 19.25	1.24	.265
DBP (mmHg) (*n* = 1555)		80.17 ± 11.99	80.96 ± 12.93	1.56	.212
Hospitalization history	No	457 (58.4)	379 (48.4)	15.21	<.001
	Yes	326 (41.6)	404 (51.6)		
Baseline diabetic complication indices					
BG (mg/dL) (*n* = 1328)		163.48 ± 68.74	246.38 ± 148.27	−13.16	<.001
HbA1c (%) (*n* = 1566)		7.29 ± 1.07	9.15 ± 2.18	−21.51	<.001
eGFR (mL/min/1.73 m^2) (*n* = 1538)		99.84 ± 18.89	99.96 ± 20.17	−0.13	.900
TC (mg/dL) (*n* = 1427)		181.86 ± 45.23	191.16 ± 52.27	−3.59	<.001
TG (mg/dL) (*n* = 1363)		179.80 ± 130.17	199.56 ± 146.40	−2.63	.009
HDL-C (mg/dL) (*n* = 1361)		46.28 ± 11.57	45.69 ± 12.77	0.89	.375
LDL-C (mg/dL) (*n* = 1102)		107.40 ± 39.55	111.92 ± 43.10	−1.81	.070

Note. BG = blood glucose; BMI = body mass index; Cx = complications; DBP = diastolic blood pressure; DM = diabetes mellitus; eGFR = estimated glomerular filtration rate; HbA1c = hemoglobin A1c; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; M = mean; *n* = number; OHA = oral hypoglycemic agent; SBP = systolic blood pressure; SD = standard deviation; TC = total cholesterol; TG = triglyceride.
[a] HbA1c variability of low group <0.75%, HbA1c variability of high group ≥0.75%.

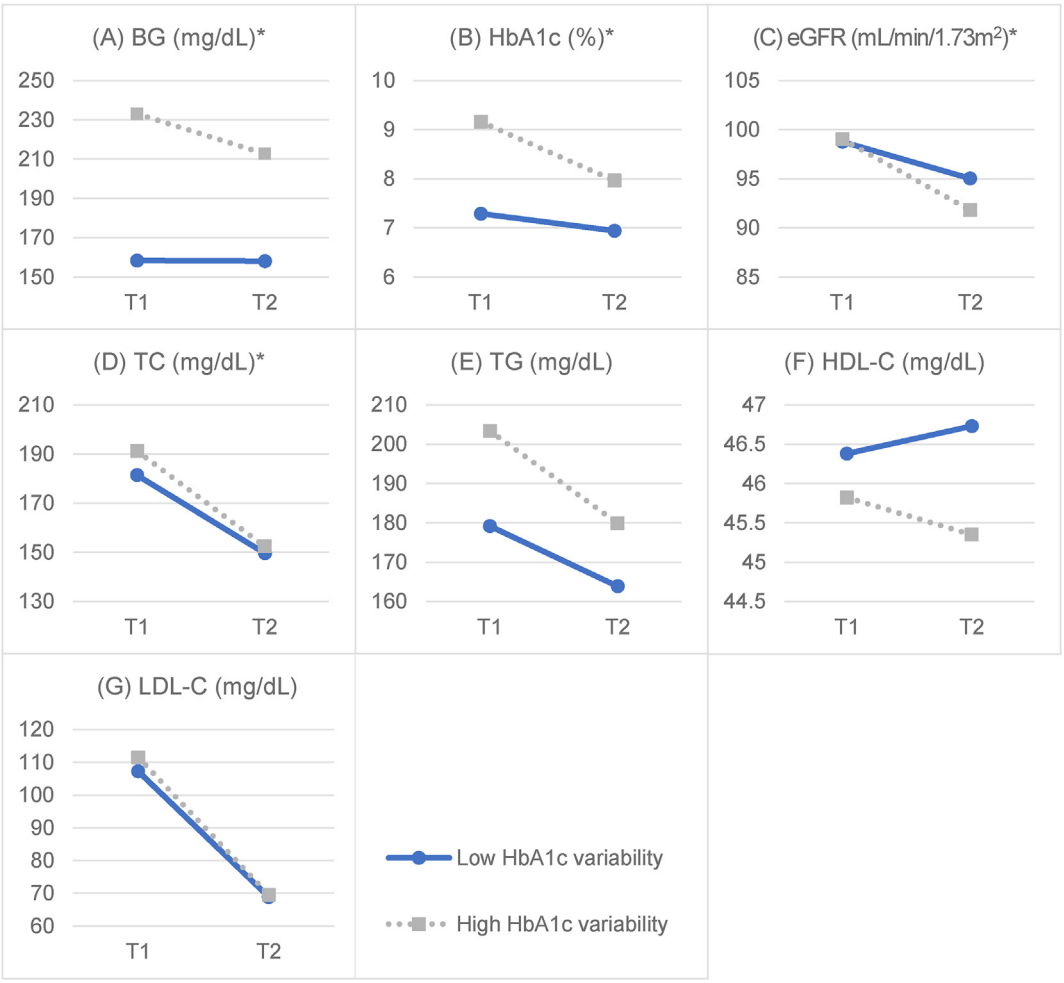

Figure 2. Changes in Diabetic Complication Indices over Five Years according to HbA1c Variability. *Note.* BG = blood glucose; eGFR = estimated glomerular filtration rate; Group A = regularly followed up every six months; Group B = regularly followed up every 12 months; Group C = followed up less than five times for five years; HbA1c = hemoglobin A1c; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; *n* = number; T_1 = baseline; T_2 = five-year follow-up; TC = total cholesterol; TG = triglyceride. *Significant interaction effects of time and group at $p < .05$.

Table 4 *Changes in Diabetic Complication Indices over Five Years according to HbA1c Variability (N = 1566).*

Diabetic Cx index	HbA1c var.[a]	*n*	T_1	T_2	S	F	*p*
			Mean ± Standard deviation				
BG (mg/dL) (*n* = 842)	Low	409	158.35 ± 66.15	158.07 ± 59.53	G	157.52	<.001
	High	433	233.09 ± 128.57	212.70 ± 120.32	T	5.21	.023
					G × T	4.93	.027
HbA1c (%) (*n* = 1566)	Low	783	7.29 ± 1.07	6.94 ± 0.90	G	609.24	<.001
	High	783	9.16 ± 2.18	7.96 ± 1.61	T	235.13	<.001
					G × T	71.87	<.001
eGFR (mL/min/1.73 m^2)	Low	655	98.77 ± 19.68	95.02 ± 21.02	G	1.75	.186
(*n* = 1305)	High	650	99.03 ± 20.88	91.80 ± 25.33	T	144.80	<.001
					G × T	14.48	<.001
TC (mg/dL) (*n* = 1145)	Low	594	181.35 ± 45.57	149.64 ± 32.16	G	9.59	.002
	High	551	191.21 ± 53.30	152.38 ± 41.13	T	497.13	<.001
					G × T	5.08	.024
TG (mg/dL) (*n* = 1096)	Low	573	179.19 ± 129.54	163.85 ± 95.67	G	10.49	.001
	High	523	203.38 ± 146.70	179.89 ± 126.96	T	19.78	<.001
					G × T	0.87	.351
HDL-C (mg/dL) (*n* = 1089)	Low	568	46.38 ± 11.35	46.73 ± 10.58	G	2.38	.124
	High	521	45.82 ± 12.98	45.35 ± 11.77	T	0.03	.854
					G × T	1.64	.201
LDL-C (mg/dL) (*n* = 881)	Low	454	107.20 ± 39.47	68.83 ± 26.92	G	1.70	.193
	High	427	111.46 ± 43.79	69.47 ± 32.90	T	664.12	<.001
					G × T	1.34	.247

Note. BG = blood glucose; Cx = complications; eGFR = estimated glomerular filtration rate; G = group; HbA1c = hemoglobin A1c; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; *n* = number; S = source; T = time; T_1 = baseline; T_2 = five-year follow-up; TC = total cholesterol; TG = triglyceride; var = variability.

[a] HbA1c variability in the low and high groups was <0.75% and ≥0.75%, respectively.

Table 5 *Factors Affecting Diabetic Complication Indices at Five-year Follow-up.*

Variables	BG (n = 566)					HbA1c (n = 870)					eGFR (n = 747)					TC (n = 732)				
	B	SE	β	t	p	B	SE	β	t	p	B	SE	β	t	p	B	SE	β	t	p
Gender (men)						−0.05	0.09	−0.02	−0.58	.562	−6.70	1.26	−0.14	−5.33	<.001	−7.17	2.45	−0.10	−2.93	.003
Age						−0.01	0.01	−0.05	−1.53	.127	−0.31	0.08	−0.12	−4.07	<.001	−0.70	0.15	−0.17	−4.77	<.001
Comorbidity (yes)						−0.18	0.10	−0.05	−1.74	.082										
DM duration	2.43	0.46	0.20	5.28	<.001	0.05	0.01	0.25	8.75	<.001	−0.25	0.08	−0.08	−3.13	.002	−0.43	0.18	−0.08	−2.36	.019
Chronic DM Cx (yes)						0.16	0.13	0.03	1.24	.214	3.29	1.61	0.05	2.05	.041	1.44	3.76	0.01	0.38	.701
BMI	0.48	0.92	0.02	0.53	.599	0.02	0.01	0.06	2.26	.024						1.17	0.35	0.11	3.36	.001
SBP	−0.55	0.24	−0.12	−2.32	.021						−0.11	0.04	−0.09	−2.64	.009					
DBP	0.93	0.39	0.12	2.35	.019						0.13	0.07	0.07	2.00	.046					
Baseline BG	0.11	0.03	0.14	3.50	<.001						−0.01	0.01	−0.04	−1.25	.213					
Baseline HbA1c						0.14	0.02	0.20	6.26	<.001	0.42	0.36	0.04	1.16	.245	−2.58	0.74	−0.13	−3.50	<.001
Baseline eGFR						0.01	0.003	0.10	3.00	.003	0.67	0.03	0.57	19.58	<.001					
Baseline TC											−0.02	0.01	−0.05	−1.90	.058	0.18	0.03	0.23	6.96	<.001
Hospitalization history (yes)											−4.14	1.12	−0.09	−3.71	<.001					
Follow-up regularity (group B)	−11.74	8.75	−0.06	−1.34	.180	0.08	0.10	0.02	0.80	.426	4.72	1.46	0.09	3.23	.001	0.62	3.21	0.01	0.19	.846
Follow-up regularity (group C)	44.21	13.16	0.15	3.36	.001	0.48	0.16	0.09	2.91	.004	1.70	2.28	0.02	0.75	.456	19.47	5.50	0.13	3.54	<.001
HbA1c variability (high)	38.15	6.86	0.22	5.56	<.001	0.70	0.09	0.25	8.12	<.001	−3.91	1.23	−0.08	−3.18	.002	3.35	2.71	0.05	1.24	.217
R^2	.17					.24					.55					.15				
Adjusted R^2	.16					.23					.55					.14				
F (p)	15.35 (<.001)					30.13 (<.001)					73.86 (<.001)					14.78 (<.001)				

Note. BG = blood glucose; BMI = body mass index; Cx = complications; DBP = diastolic blood pressure; DM = diabetes mellitus; eGFR = estimated glomerular filtration rate; HbA1c = hemoglobin A1c; SBP = systolic blood pressure; TC = total cholesterol.

levels than group C at T_2. Similarly, in a prior study, having more than two follow-ups per year was associated with greater improvements in HbA1c and TC levels [27]. Furthermore, in a study investigating the relationships between follow-up regularity, statin initiation, and medication adherence among individuals at risk of cardiovascular disease, the most regular quintile had 1.22 times the odds of initiating statin medication and a hazard ratio of 0.82 for medication non-adherence compared to the least regular quintile [12]. These findings collectively suggest that maintaining regular follow-up visits is important for managing of HbA1c and TC levels and reducing the risk of future diabetes complications.

Compared to group A and C, group B exhibited a higher eGFR at T_2, which contrasted with a previous study that reported better adherence to HbA1c testing frequency being associated with a reduced risk of chronic kidney disease [8]. This result could potentially be explained by the fact that the baseline and five-year follow-up eGFR values in this study were 87.07–99.85 mL/min/1.73 m^2, which fell within the normal range, exceeding 60 mL/min/1.73 m^2 [18]. To verify the relationship between long-term regular follow-up and changes in renal function among patients with T2DM, it is imperative to conduct future research encompassing a substantial number of patients with poor renal function.

In this study, HbA1c variability was calculated as the SD of HbA1c adjusted by the number of measurements. The HbA1c variability was the lowest in group A and highest in group C. Additionally, patients with higher HbA1c variability were younger with a higher prevalence of insulin use and exhibited higher levels of baseline TC and TG. These findings aligned with previous studies [19,34,38]. There were differences in the changes in diabetic complication indices, including BG, HbA1c, eGFR, and TC, between patients with high and low HbA1c variability in this study. Similarly, the hazard ratios for the risk of nephropathy in the fourth quartile group with the highest HbA1c variability were 1.77–2.40 [32,39], using the first quartile group as a reference. It seems reasonable to include HbA1c variability as a target in the routine management of T2DM. However, there is no standardized method to assess HbA1c variability [3,23,34]. Many studies used a relative measure (e.g. quartiles of HbA1c variability), so comparing the results across studies was difficult. It is necessary to establish a standard approach to summarize HbA1c variability and agree on the clinically significant value so that healthcare providers can easily calculate and interpret it in clinical practice.

In the multiple regression analysis of this study, HbA1c variability and follow-up regularity were identified as significant factors related to diabetic complication indices at the five-year follow-up. HbA1c variability was the strongest predictor for BG and HbA1c levels, and high HbA1c variability significantly reduced eGFR at the five-year follow-up. Follow-up less than five times for five years significantly increased BG, HbA1c, and TC levels at the five-year follow-up. Consistent with these findings, previous studies have shown that higher HbA1c variability was associated with incidence of microalbuminuria [32], and more frequent follow-up visits (>two times per year) resulted in greater reductions in BG, HbA1c, and TC levels [27]. These findings underscore the importance of minimizing HbA1c variability and ensuring regular follow-up in the management of diabetes and prevention of complications.

The medical doctor (ARK) from the hospital, included as an author in this study, reported no notable increase in follow-up visit delays for patients with T2DM during the coronavirus disease (COVID)-19 period. Similarly, a previous study [40] found that before COVID-19, 41.3% of patients had HbA1c test intervals longer than 180 days, with an average interval of 172.5 days. After COVID-19, there was a 20.6 percentage point increase in the proportion of

patients with intervals over 180 days, with an average interval increase of 47.9 days. However, these returned to pre-pandemic levels within three months. Regular assessment, including HbA1c testing, is crucial for diabetes management and cannot be replaced by telemedicine. Thus, it was considered that outpatient follow-up management for T2DM patients in this study was minimally affected by COVID-19.

This study had some limitations. First, being conducted at a single-center restricted the sample size and limited generalizability of the findings. Second, out of the 3458 patients who met the inclusion criteria, 1892 with uncertain follow-up regularity were excluded to differentiate between regular and irregular patterns. Additionally, among the 1566 patients included, there were missing data for diabetic complication indices other than HbA1c. As a result, selection bias in the study population cannot be ignored. Another limitation was the number of HbA1c measurements per subject during follow-up. Although we used the HbA1c variability adjusted by the number of HbA1c measurements, it was possible that the HbA1c variability of patients with fewer tests was overestimated.

Despite these limitations, our study had substantial strengths compared with existing research. We increased the reliability of the results by employing the EMRs of 1566 patients encompassing a comprehensive five-year observation period. Furthermore, we demonstrated the longitudinal significant impact of follow-up regularity and HbA1c variability on diabetic complication indices. These results suggest the importance of nurse-led close monitoring and management of follow-up regularity and HbA1c variability in patients with T2DM. Based on the determining factors identified in our study, targeted interventions should be designed and implemented for better therapeutic outcomes.

Conclusions

Regular follow-up at 6- to 12-month intervals was associated with low HbA1c variability. In addition to regular follow-up and low HbA1c variability, several general characteristics and baseline complication indices contributed to improved diabetic complication indices at the five-year follow up in patients with T2DM. It is noteworthy that regular follow-up and HbA1c variability can be addressed through nursing intervention. Based on the results of this study, outpatient nurses should carefully monitor and manage the follow-up intervals. Furthermore, the advantages of regular follow-up in reducing complications should be integrated into all diabetes patients' education programs. HbA1c variability is increasingly recognized as an important indicator of disease severity and complexity, warranting inclusion in the evaluation of patients with T2DM. Establishing a consensus on a standardized method for measuring HbA1c variability is required.

Author statement

Conceptualization, Methodology, Validation, Writing: HL, GP, ARK; Formal analysis: HL, GP; Investigation: GP, ARK; Supervision: HL, ARK; Funding aquisition: HL.

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Conflicts of interest

None.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.anr.2023.11.004.

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Research Article

Predictive Factors for Infusion Site Induration After Outpatient Chemotherapy in Japan: A Secondary Analysis

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SUMMARY

Purpose: Even in the absence of extravasation, some patients develop induration at the peripheral intravenous catheterization site prior to the next day's treatment. Infusion site induration commonly affects patients who undergo repeated chemotherapy administrations. Vessel health is crucial for the continuation of chemotherapy. However, there is no effective method to prevent induration. Hence, this study aimed to investigate the factors that could cause induration for preventing its occurrence.
Methods: This study was a secondary analysis of a prospective observational study. All participants were undergoing outpatient chemotherapy. Participant characteristics and related catheterization data were collected on the treatment day as baseline, and induration incidence was recorded on the subsequent treatment day. Receiver operating characteristic (ROC) analysis was performed to determine the sensitivity and specificity of cutoff points of the vein and catheter diameter ratios for distinguishing between developed induration and not developed induration. Additionally, cox regression analysis with multiple imputation was used to investigate the factors that predicted induration.
Results: Seventy-one patients participated in the study. The cutoff point of the vein/catheter diameter ratio calculated using ROC analysis was ≥3.7. The ratio of larger-diameter veins to catheter diameter of ≥3.7 times was negatively associated with induration in both complete case analysis (HR: 0.11; $p = 0.034$) and multiple imputation analysis (HR: 0.12; $p = .049$).
Conclusions: Selecting the vein with 3.7 times higher diameter than the catheter diameter for the catheterization site may help prevent induration on the next treatment day.

Introduction

Chemotherapy is generally repeated on a weekly or monthly basis for months to years. Vascular access for chemotherapy can be via a central venous catheter, including peripherally inserted central catheters; a totally implantable central venous access port; or a peripheral intravenous catheter. Administration of irritant and vesicant drugs via a peripheral intravenous catheter is not recommended as per the current guideline [1]; however, a central venous line cannot be used for chemotherapy in some patients owing to underlying medical issues, such as immunocompromised condition, coagulopathy, or superior vena cava syndrome [2–5].

Patients in whom a peripheral intravenous catheter is used require periodic catheter replacement. To prevent extravasation, other insertion sites should be considered if the subcutaneous tissue is damaged [1,6]. Induration refers to pathological hardening of the soft tissue. It is advisable to avoid placing catheters in sites with induration [7].

Healthcare providers avoid indurated sites when performing peripheral intravenous catheterization as it results in fewer veins for catheterization. When the patient has deep or thin veins, multiple catheterization attempts may be needed. Consequently, some patients endure multiple venipunctures for a single catheter

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placement. These repeated attempts increase the patient's pain and risk of adverse events, such as arterial puncture, nerve injury, or infection. For healthcare providers, the need for multiple venipunctures can result in increased workload and infection risk secondary to blood exposure. Furthermore, multiple venipunctures increase the risk of extravasation [6,8]. Preventing induration and preserving intravenous access are high-priority considerations for patients undergoing chemotherapy. Hence, healthcare providers should adopt all possible measures to prevent induration.

Although vessel health preservation is crucial for patients receiving chemotherapy via a peripheral intravenous catheter, strategies to prevent induration are unclear; moreover, there are few reports about induration at the catheterization site [9,10]. Determining which factors prevent induration is the first step in establishing a comprehensive prevention protocol. This study investigated the factors that predicted catheterization site induration after chemotherapy for patients who must repeatedly receive anticancer drugs via a peripheral intravenous catheter using data obtained at an outpatient chemotherapy room in a previous study [11].

Methods

Study design and setting

This prospective observational study was a secondary analysis of subcutaneous damage at catheterization sites resulting from anticancer drug administration [11]. The study setting was an outpatient chemotherapy department at a university hospital in Japan. The data collection period was January–March, 2018. The participants were receiving multiple sessions of outpatient chemotherapy.

Patients were included if their chemotherapy (1) was administered using a short peripheral intravenous catheter and (2) comprised regimens containing taxane, doxorubicin–cyclophosphamide, cisplatin, gemcitabine, or fosaprepitant, all of which are considered to highly stimulate the vessel walls. Patients were excluded if they were (1) < 20 years of age or (2) if ≥ 4 weeks had elapsed between their chemotherapy sessions because the target site could be affected by other treatments and examinations (infusions or blood tests) or external stimuli (e.g., bruising).

As personal vessel wall vulnerability and stimulation caused by the anticancer drug may influence the subcutaneous tissue status, each participant was only able to enroll once to minimalize the influence of personal characteristics on the results.

Data collection procedure

This study used data from a survey conducted in an outpatient chemotherapy room [11].

Medical record data

Age, sex, body mass index, and type of cancer were used to assess patient characteristics. Blood albumin results were used to assess the nutritional status. Treatment cycle and days to the next planned treatment were used to identify the treatment status. The record of drugs administered was used to assess the risk of treatment-induced neutropenia, which determines whether treatment is delivered as planned, i.e., if data for the present study could be collected at the next treatment session. Records of the total drug administration time and the specific drugs administered were used to identify vascular stimulation.

Data collection methods at the site of catheter placement and measurement of vessel diameter in the original study

A researcher used ultrasound to examine the subcutaneous tissue status and to measure the vein diameter at the target catheterization site before peripheral intravenous catheterization was performed by clinical nurses and physicians. During anticancer drug administration, a researcher collected catheter-related data, i.e., catheterization site and vein, catheter size (outer diameter: 24 G, 0.7 mm; 22 G, 0.9 mm), and inserter. On the patient's next treatment day, the previous catheterization site was examined by a clinical nurse and a researcher (who was also a registered nurse) via inspection and palpation. Induration occurrence was assessed qualitatively. If hardened tissue was detected on palpation, the site was considered indurated.

Vein diameter was measured from the ultrasound image using an image analysis software (ImageJ, National Institutes of Health. Bethesda, Maryland, USA). The calculation method was as follows: the minor axis and major axis were measured thrice each and then averaged; subsequently, the mean of the minor axis was added to the mean of the major axis, and the number was divided by two.

Ultrasonographic subcutaneous tissue images were obtained from an ultrasound device (Noblus) with a linear array (5–18 MHz) and a 2D probe (Hitachi Medical, Ltd., Tokyo, Japan). Ultrasound images were assessed by a researcher who was blinded to participant characteristics and treatment details. The status of the subcutaneous tissue, including the vein, was assessed based on previous reports [12,13]. An anechoic vessel lumen and clearly depicted superficial fascia were considered normal.

Statistical analysis

Descriptive statistics were used to present participants' characteristics. Univariate analysis was used to compare patients with and without induration. Examination types were selected based on the variable characteristics; *t*-test, Mann–Whitney, chi-square, and Fisher's exact test were used. Receiver operating characteristics curve (ROC) analysis was performed to determine the sensitivity and specificity of cutoff points of the vein and catheter diameter ratios for distinguishing between developed induration and not developed induration. The area under the curve (AUC) was calculated to quantify the accuracy of the classification.

The cumulative incidence of induration was calculated by dividing the incidence of induration on the next treatment day by the number of participants observed and multiplying it by 100. The cumulative incidence of induration, including missing cases owing to the next treatment day, was calculated using a multiple imputation method as some values for the occurrence of induration were missing.

Twenty imputed data sets were applied using the Markov Chain Monte Carlo method for missing data. The variables used to complement the missing values were age, sex, treatment cycle, planned days for the next treatment day, the risk of neutropenia, fosaprepitant administration, vein/catheter diameter ratio of ≥ 3.7 times, days to the next treatment day, total administration time, and induration development. Combined imputation estimates of cumulative incidence were obtained using Rubin's rule [14].

Cox regression analysis was used to investigate the factors that could predict induration. Complete case analysis and multiple imputations were also used for the analysis. The methods and variables for the multiple imputation were the same as the cumulative incidence of induration mentioned above. Survival duration referred to the days between the specified treatment day (the baseline) and the next treatment day. Explanatory variables were selected from a clinical viewpoint and included treatment cycle, total drug administration time, and vein/catheter ratio of ≥ 3.7 times. Prolonged drug administration time is a risk factor for extravasation [15]. Also, repeated chemotherapy (i.e., the number of treatment cycles) can lead to vessel vulnerability. Therefore, treatment cycles and drug administration time were selected,

together with a vein/catheter diameter ratio of ≥ 3.7, as the explanatory variables. Before introducing the model, the absence of a strong relationship ($p < .05$) among the three variables was confirmed.

Blood albumin levels were significantly different between the groups with and without induration. However, the differences in the mean values were negligible and unlikely to be clinically significant. Thus, albumin level was not selected as an independent variable. Furthermore, the vein and catheter diameter ratio was significantly different between the groups. However, a vein-to-catheter diameter ratio of at least 3.7 times the ratio derived from the survival analysis was used as an independent variable. Additionally, the vein diameter was strongly associated with a vein-to-catheter diameter ratio of ≥ 3.7 ($p < .001$). Thus, it was not selected.

All statistical analyses were performed using JMP®16.0 (SAS Institute Inc.) and IBM SPSS Statistics version 28 (IBM, Armonk, NY, USA). The significance level was 5.0%.

Ethical approval

The patients were provided with adequate information about the study, and all of them provided written informed consent for their participation. For determining the induration, palpation was carefully performed to avoid causing pain to the patients. This study was conducted in accordance with the Declaration of Helsinki, and the study protocol was approved by the Research Ethics Committee of the University of Tokyo (No.11650-(1)).

Results

Participants

A total of 71 patients participated in the study. Their mean age was 62 years. There were 41 female participants (57.7%). Breast cancer was the most common type of cancer ($n = 18$; 25.4%), followed by ovarian cancer ($n = 11$; 15.5%). Prior to baseline catheterization, no patients had abnormal subcutaneous tissue status at the target site. The median interval between the treatment day (baseline) and the next treatment day was 14 days (IQR: 7–21). Fifty-two patients were followed up on the next treatment day within 4 weeks from the baseline treatment day. Nineteen patients were not included in the multivariate complete case analysis because they were not followed up within 4 weeks of their next treatment date owing to patient conditions such as chemotherapy-induced neutropenia or hospitalization (Table 1).

Induration incidence

No patients developed manifestations of extravasation such as swelling, redness, or pain during anticancer drug administration. Of the 52 patients who presented for a second treatment within 4 weeks, 23.1% (12/52) demonstrated induration. Induration incidence, calculated using the multiple imputation method, was 21.0%.

Catheters and placement sites

Most of the placed catheters were 24 G (93.0%; 66/71). Most inserters were nurses (87.3%; 62/71) or physicians (12.7%; 9/71). The most used vein for catheterization was the forearm cephalic vein ($n = 61$; 85.9%), and the second one was the forearm basilic vein 6 (8.5%). The mean vein diameter (standard deviation) was 2.4 (±1.0) mm. Before treatment, all 71 participants had normal subcutaneous tissue (Table 1).

Difference between participants with and without induration

When participants with ($n = 12$) and without induration ($n = 40$) were compared, induration was significantly associated with albumin level ($p = .043$), vein diameter ($p = .032$), and vein/catheter diameter ratio ($p = .043$). There was no significant difference among variables related to drugs (Table 1).

Predicting induration

ROC analysis was performed (Figure 1) (AUC, 0.68; 95% CI, 0.5–0.9). The cutoff point of the ratio over 90% specificity was 3.7 (sensitivity: 0.31; specificity: 0.92). Using the data of all 71 participants, complete case analysis and multiple imputation analysis were performed to investigate the factors predictive of induration on the next treatment day. Induration occurrence on the next treatment day was the dependent variable. Treatment cycle, total drug administration time, and vein/catheter diameter ratio of ≥ 3.7 times were considered as the explanatory variables. In both analyses, a vein/catheter diameter ratio of ≥ 3.7 times was significantly inversely correlated with induration occurrence (HR: 0.11; $p = .034$, HR: 0.12; $p = .049$, respectively) (Table 2).

Discussion

This study showed that a vein/catheter diameter ratio of ≥ 3.7 times was significantly (and inversely) associated with induration on the next treatment day among patients who received anticancer drugs via a peripheral venous catheter.

In this study, vein diameter data were obtained using ultrasound before the vein wall was affected because of the treatment (mechanical stress due to catheter tips and chemical stress due to anticancer agents). Additionally, two professionals assessed the induration (a clinical nurse and a researcher). These controls increased the study's internal validity.

Induration incidence rates at the next treatment were 23.1% (12/52) and 21.0% (the rate which was calculated using the multiple imputation method). These incidence rates were higher than those in a previous report (17.4%; 12/69) that examined outpatients [6]. However, the characteristics of the participants in our study, including the type of anticancer drug administered, differed from those reported in the previous study. In the other study, the participants were administered not only highly irritant but also less irritant anticancer drugs, whereas in this study, all the participants were administered highly irritant drugs, including vesicants, which might have contributed to the higher incidence of induration.

In this study, the cutoff point of vein/catheter diameter ratio was calculated using ROC analysis. Although low sensitivity was observed, the ratio of 3.7 was considered to be a good cutoff point as it showed > 90% specificity of induration occurrence. It is clinically useful to use a cutoff point that prioritizes specificity over sensitivity.

A significant negative association was observed between the vein/catheter diameter ratio of ≥ 3.7 and induration occurrence in both analyses, i.e., unadjusted and adjusted models using multiple imputations ($p = .034$, $p = .049$). Post-chemotherapy induration is thought to reflect fibrosis during the wound healing process [5–7], which occurs because of mechanical and chemical stimulation of the vessel wall (vascular endothelial cell loss and inflammation) from the administration of anticancer drugs. A larger vessel/catheter diameter ratio results in a lower mechanical stimulation of the vessel wall and thus potentially less damage to the endothelial cells of the vessel wall. This reduces the development of induration without causing inflammation of the surrounding tissue.

Table 1 *Participants' Characteristics.*

Research items		All participants ($N = 71$)	Participants who were followed up on the next treatment day			
			Total $N = 52$	Without induration $N = 40$	With induration $N = 12$	*p-value*
Patient's characteristics	Age	62 (48-71)[a]	58.2 (11.6)	57.8 (1.8)	59.4 (3.4)	.676
	Sex					
	Women	41 (57.7)	33 (63.5)	27 (81.8)	6 (18.2)	.270
	Body mass index (kg/m^2)	21.5 (5.0)[b]	21.3 (4.4)[b]	21.2 (0.7)[b]	21.4 (1.3)[b]	
	Type of cancer					
	Breast cancer	18 (25.4)	15 (28.8)	14 (35.0)	1 (8.3)	-
	Ovarian cancer	11 (15.5)	10 (19.2)	6 (15.0)	4 (33.3)	
	Stomach cancer	9 (12.7)	7 (13.5)	5 (12.5)	2 (16.7)	
	Pancreas cancer	8 (11.3)	5 (9.6)	3 (7.5)	2 (16.7)	
	Uterus cancer	7 (9.6)	4 (7.7)	3 (7.5)	1 (8.3)	
	Esophagus cancer	7 (9.6)	6 (11.5)	4 (10.0)	2 (16.7)	
	Prostate cancer	5 (7.0)	1 (1.9)	1 (2.5)	0 (0.0)	
	Others[c]	6 (8.5)	5 (9.6)	4 (2.5)	1 (0.0)	
	Blood albumin (g/dL)[d]	3.9 (0.3)	3.9 (0.3)	3.9 (0.1)	4.1 (0.1)	.043*
	Treatment cycle (treatment times including this time)	3 (2–4)[a]	3 (2–3)[a]	3 (2.0–3.8)[a]	2.5 (1.3–3.0)[a]	.759
	Days to planned next treatment[e]	14 (7–21)[a]	14 (7–21)[a]	14 (7–21)[a]	14 (7–21)[a]	.774
Drug information	Neutropenia risk by treatment (occurrence frequency)					
	Low (less than 10%)	42 (59.2)	32 (61.5)	24 (60.0)	8 (66.7)	.747
	Moderate (10%–20%)	1 (1.5)	0 (0.0)	0 (0.0)	0 (0.0)	
	High (over 20%)	28 (39.4)	20 (38.5)	16 (40.0)	4 (33.3)	
	Total administration time (min.)	396 (371–441)	396 (372–474)[a]	396 (371–436)[a]	441 (381–556)[a]	.081
	Type of anticancer drugs[f]					
	Vesicants	67 (94.4)	49 (94.2)	37 (92.5)	12 (100.0)	> .999
	Irritants	4 (5.6)	3 (5.8)	3 (7.5)	0 (0.0)	
	Fosaprepitant use	17 (23.9)	14 (26.9)	9 (22.5)	5 (41.7)	.189
Catheter characteristics	Inserter					
	Nurse	62 (87.3)	45 (86.5)	34 (85.0)	11 (91.7)	> .999
	Physician	9 (12.7)	7 (13.5)	6 (15.0)	1 (8.3)	
	Catheter size					
	24G	66 (93.0)	49 (94.2)	37 (92.5)	12 (100.0)	> .999
	22G	5 (7.0)	3 (5.8)	3 (7.5)	0 (0.0)	
	Type of vein					
	Cephalic vein	61 (85.9)	44 (86.3)	36 (92.3)	8 (66.7)	.075
	Basilic vein	6 (8.5)	5 (9.8)	2 (5.1)	3 (25.0)	
	Median vein	3 (4.2)	2 (3.9)	1 (2.6)	1 (8.3)	
	Missing data	1	1	1	0	
	Vein diameter (mm)	2.4 (1.0)[b]	2.3 (0.9)[b]	2.4 (0.1)[b]	1.8 (0.2)[b]	.032*
	Vein and catheter diameter ratio[g]	3.3 (0.2)[b]	3.2 (1.2)[b]	3.4 (0.2)[b]	2.5 (0.3)[b]	.043*

Number (%).

* $p < .05$.

[a] Median (interquartile range).

[b] Mean (standard deviation).

[c] The number of other type of cancer: shows the number of the followed participants: Lung cancer 2 (2); B cell non-Hodgkin's lymphoma 1 (0); bile duct cancer 1 (1); colon cancer 1 (1) bladder cancer 1 (0).

[d] $n = 67$; in all participants, $n = 49$; in the followed participants.

[e] In the followed participants, the number shows real days from treatment day to the next treatment day.

[f] Degree of the tissue damage risk when it occur extravasation.

[g] Vein diameter divided of outer diameter of catheter.

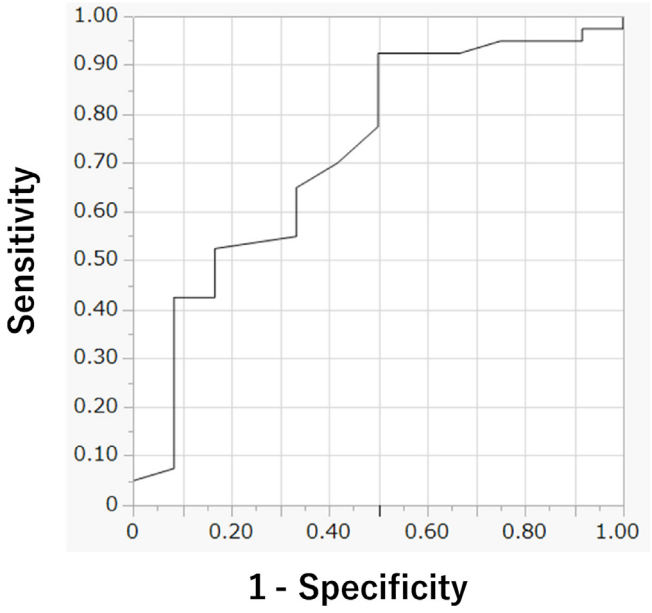

Figure 1. ROC Curve of the Vein/Catheter Diameter Ratios. Note. ROC = receiver operating characteristics.

Larger-diameter veins have been reported to be negatively associated with induration; however, in the previous study, the vein diameter was obtained on the next treatment day [10] and it not known whether it was affected by induration.

Additionally, this result is the first concrete evidence that catheterization site selection could prevent induration. Ideal vein diameters for catheterization in each catheter gauge based on this result are as follows: 2.6 mm in 24 G (outer diameter; 0.7 mm), 3.3 mm in 22 G (outer diameter: 0.9 mm), and 4.1 mm in 20 G (outer diameter: 1.1 mm). Our research team reported that the ideal vessel diameter for catheterization to prevent infiltration during drug administration (it was defined as swelling at least 10 mm in a previous study) was 3.3 times that of the catheter [16]. This study determined the ideal vein size to prevent induration on the next treatment day in patients with no adverse events, such as infiltration, extravasation, or pain during anticancer drug administration. This finding is important to prevent induration occurrence in patients who must be repeatedly administered anticancer drugs via a peripheral intravenous catheter owing to their medical conditions.

Using a softer catheter and attempting catheterization only once help prevent phlebitis, thrombosis with edema, and catheter failure [17,18]. Together with these measures, the results obtained in this study to select the vein may ensure vessel health. Visualization techniques other than ultrasonography have been developed to select the vessel to be punctured [19]. Vessel visualization techniques that use near-infrared light are excellent for confirming the vessel run; however, the exact vessel diameter cannot be obtained. Of course, vessel diameter cannot be accurately determined via visual examination or palpation either. Ultrasonography is a powerful technique for accurately determining a vessel's diameter.

Ultrasound is excellent in terms of portability, and artificial intelligence can automatically detect vessels and display their diameter instantly [20,21] (Figure 2). Healthcare providers should select the most ideal puncture point using such a technology for preventing long-term adverse events and not merely those on the treatment day. Previous studies have reported that using ultrasound to assess veins at the catheterization site helps prevent catheter failure in patients using a peripheral intravenous catheter for a few days [22–24]. Ultrasound-assisted vein assessment may help prevent induration in patients who only use a catheter for a few hours. Selecting the smallest catheter that can be used for an individual patient and ultrasonographically locating a vessel of least 3.7 times the diameter of the catheter to be inserted can potentially prevent induration.

This study has three main limitations. First, the interval between the treatment day and the next observation varied based on the regimen. As subcutaneous tissue alterations, including induration, are believed to occur over time, these changes may not be captured by observing the participant only one time after the baseline treatment. A previous case report detected no post-treatment induration despite subcutaneous edema and thrombus being observed at the catheterization site immediately after anticancer drug administration and 1 week later. However, induration was detected 3 weeks later [9]. As certain data on the day of the next treatment were within 7 days until the observation period, there is a possibility that induration would have developed after observation in such short follow-up cases (< 7 days). However, as some chemotherapy treatments were repeated on a weekly basis, this study is representative of the clinical setting and provided clinically meaningful results.

The second limitation is related to participants' age. Those receiving drugs with a strong chemical stimulation were closely examined for detection of subcutaneous tissue changes. Age was not related to induration occurrence; however, the median age of 62 years, was less than the peak onset age for common cancers [25], and it is possible that the impact of age was insufficiently considered. Future research should examine participants with a wider age range. However, the results of this study may be extrapolated to patients receiving similar drugs.

The third limitation is the small sample size. Despite the limitations of the sample size, the results of the complete-case analysis and the analysis using a multiple imputation method

Table 2 *Predictive Factors of the Infusion Site Induration.*

	$N = 52$				MI			
		95% CI				95% CI		
	HR	LL	UL	*p-value*	HR	LL	UL	*p-value*
Treatment cycle	1.04	0.90	1.21	.562	1.03	0.88	1.21	.698
Total drug administration time (min.)	1.00	1.00	1.01	.273	1.00	1.00	1.01	.240
Vein/catheter diameter ratio ≥ 3.7[a]	0.11	0.01	0.85	.034*	0.12	0.01	0.99	.049*

Cox regression.
Abbreviations: CI = confidence interval; HR = hazard ratio; LL = lower limit; MI = multiple imputation; UL = upper limit.
* $p < .05$.
[a] Reference; vein/catheter diameter ratio < 3.7.

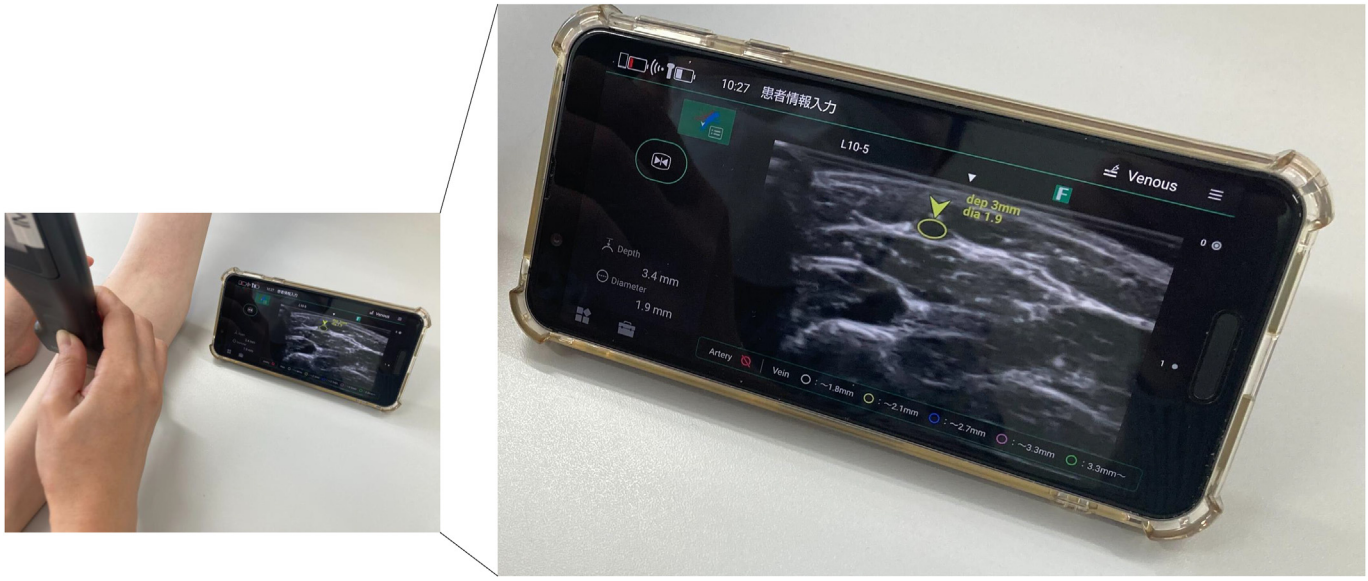

Figure 2. An Ultrasound System with An Automated Vessel Detection System Using Artificial Intelligence. The system detects areas that have characteristics of a vessel (circular or ellipsoidal anechoic area) and displays the vein size and depth in real time.

were consistent, in which a vein-to-catheter diameter ratio of 3.7 or more being significantly inversely associated with induration. Based on these results, we conclude that vascular catheter ratios are significantly associated with the development of induration. Future studies with larger sample sizes may provide more robust results.

Conclusion

This study showed a significant negative association between the vein/catheter diameter ratio and induration. Selecting larger-diameter veins with $\geq$ 3.7 times the catheter diameter as the catheterization site may help prevent induration occurrence on the next treatment day.

Author contribution

Mari Abe-Doi: Conceptualization, Methodology, Data collection, Data curation, Formal analysis, Visualization, Writing - original draft, Funding acquisition. Rryoko Murayama: Writing - review & editing, Funding acquisition. Morita Kojiro and Gojiro Nakagami: Supervision of data analysis and writing. Hiromi Sanada: Project administration, Writing - review & editing, Supervision. All authors read and approved the final manuscript.

Ethical approval

The Research Ethics Committee of the University of Tokyo, which was in accordance with the Declaration of Helsinki approved this study protocol (No.11650-(1))

Conflict of interest

The authors have no conflicts of interest to disclosure.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.anr.2023.11.005.

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Review Article

Effects of Physical Activity on Quality of Life, Anxiety and Depression in Breast Cancer Survivors: A Systematic Review and Meta-analysis

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SUMMARY

Purpose: Anxiety, depression, and poor quality of life (QOL) were considered important concerns that hindered the rehabilitation of breast cancer survivors. A number of studies have investigated the effects of physical activity, but they have not reached the same conclusions. This review aimed to identify the effects of physical activity on QOL, anxiety, and depression in breast cancer survivors.

Methods: PubMed, Embase, Web of Science, Cumulative Index to Nursing and Allied Health Literature (CINAHL), PsycINFO, SinoMed, CNKI, Vip, and WanFang databases were searched for the time period between January 1, 2012, and April 30, 2022. Studies were included if they were randomized controlled trials of the effects of physical activity on QOL, anxiety, or depression in breast cancer survivors. The tools of the Joanna Briggs Institute were used to assess the quality of the included studies. R software version 4.3.1 was used for meta-analysis.

Results: A total of 26 studies, involving 2105 participants, were included in the systematic review. Among these, 20 studies involving 1228 participants were included in the meta-analysis. Compared with the control group, the results indicated that physical activity can significantly improve QOL(Hedges' g = 0.67; 95% CI 0.41−0.92) and reduce anxiety (Hedges' g = −0.28; 95% CI −0.46 to −0.10) in breast cancer survivors. However, the effect of physical activity on depression (Hedges' g = −0.46; 95% CI −0.99 to 0.06) was not statistically significant.

Conclusions: Physical activity was an effective intervention to improve QOL and reduce anxiety in breast cancer survivors, as well as showed positive trends in depression, although without statistical significance. More well-designed studies are required to clarify the effects of different types of physical activities on the QOL, anxiety, and depression among breast cancer survivors.

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https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=363094.

Introduction

Breast cancer is the most prevalent type of cancer worldwide [1] and in China [2]. The number of new breast cancer cases worldwide is estimated to reach 2,833,941 by 2040 [3]. With progress in early screening and treatment technologies for breast cancer, survival rates are gradually increasing [4]. The current 5-year survival rate for early-stage breast cancer is 90% [5], which has resulted in a large number of breast cancer survivors. Breast cancer survivors are patients who have completed primary treatments such as surgery, radiotherapy, and chemotherapy and have entered the hormone treatment or follow-up stages [6]. These patients face a series of physical symptoms, including sleep disorders [7], fatigue [8], sexual

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dysfunction [9], and pain [10], caused by breast cancer itself and its treatment, and suffer from psychological problems such as fear of disease recurrence [11]. Physical symptoms aggravate psychological problems, leading to anxiety and depression, and reduce the quality of life (QOL) of breast cancer survivors during rehabilitation [12]. The prevalence of long-term anxiety symptoms after breast cancer treatment has been reported to be 27.2% [13], and that of depression has been reported to be 1.5–46% [14], which often left breast cancer survivors with more severe symptoms, higher treatment costs, and poorer QOL [15]. It may persist for a long time after treatment and hinder women's return to normal life [16].

Growing evidence suggests that nonpharmacological interventions can help breast cancer survivors return to their state of health as it was before treatment [17]. Physical activity as a nonpharmacological intervention has been applied in cancer rehabilitation programs, which have received increasing attention for improving QOL and reducing anxiety and depression [18,19]. Multiple studies have demonstrated the safety and benefits of physical activity. Based on these beneficial effects, an increasing number of original studies on the influence of physical activity on QOL, anxiety, and depression have been conducted; however, they have not reached the same conclusions. Previous systematic reviews revealed that exercise can improve QOL and reduce anxiety and depression [20,21], whereas other systematic reviews showed that physical activity had no effect on QOL and did not appear to reduce anxiety or depression [22–24]. In addition, some studies only included participants either during treatment or both during and after treatment without quantitatively clarifying the efficacy of physical activity in breast cancer survivors [25,26]. Another study included randomized controlled trials (RCTs) up to December 2011 [27]. Since then, several new RCTs investigating the effectiveness of physical activity on QOL, anxiety, and depression in breast cancer survivors have been published [28–30]. Given these results, reevaluating recent RCTs and reemphasizing the effects of physical activity is imperative. Therefore, a systematic review incorporating the most recent RCTs is necessary.

In contrast to previous systematic reviews, this review focuses exclusively on breast cancer survivors and includes more comprehensive interventions, such as aerobic exercises and resistance training. The review aimed to identify the impact of physical activity on QOL, anxiety, and depression in breast cancer survivors, based on research published over the past 10 years.

Methods

This review of RCTs followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [31].

Search strategy

PubMed, Embase, Web of Science, CINAHL, PsycINFO, SinoMed, CNKI, Vip, and WanFang databases were searched for the time period between January 1, 2012, and April 30, 2022, using title/abstract or Medical Subject Headings (MeSH terms) such as “breast cancer,” “breast neoplasm,” “breast cancer survivors,” “exercise,” “physical activity,” “resistance training,” “aerobic exercise,” “quality of life,” “depression,” and “anxiety.” We also searched for clinical trials on the International Clinical Trials Registry Platform and the Chinese Clinical Trial Registry. Additionally, we manually scanned the reference lists of the selected studies. The search was restricted to Chinese and English. The specific search strategy is presented in the supplementary material (Appendix 1).

Inclusion and exclusion criteria

Study design

RCTs were included; conference abstracts and guidelines were excluded.

Participants

This review included breast cancer survivors aged >18 years who were diagnosed with breast cancer and had completed primary treatment. Breast cancer survivors with ongoing treatment, recurrence, metastasis, or any other type of cancer were excluded from the study.

Interventions

This review included interventions for physical activity, which mainly included aerobic training (e.g., walking, Tai Chi Chuan) and/or resistance training (e.g., sit-ups). Physical activities that focused only on the upper limbs or arms, in combination with other interventions (e.g., diet regulation) or merely health education, were excluded.

Comparison

Usual care (e.g., standard nursing and/or health education) or no intervention.

Outcomes

The primary outcome was QOL. Tools for measuring QOL included the Functional Assessment of Cancer Therapy-Breast (FACT-B), Short Form-36 Health Survey (SF-36), European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30), Functional Assessment of Cancer Therapy – General (FACT-G), Breast Cancer-Specific Quality of Life Questionnaire (EORTC QLQ-BR23), Functional Assessment of Cancer Therapy – Endocrine Symptoms version 4 (FACT-ES), and EuroQol Five Dimensions questionnaire (EQ-5D).

The secondary outcomes were anxiety and depression. Anxiety was measured using the Self-Rating Anxiety Scale (SAS) and Hospital Anxiety and Depression Subscale (HADS). The tools for measuring depression included the Self-Rating Depression Scale (SDS), HADS, the 20-item Center for Epidemiologic Studies Depression Scale (CES-D), and the Beck Depression Inventory (BDI).

Study selection

The retrieved studies were merged into NoteExpress software, and duplicate records were removed. Two independent reviewers (M. Y. S. and Y. J. L.) screened the articles. Disagreements between the two independent reviewers were resolved by discussion or by a third reviewer (C. L. L.).

Quality appraisal

The quality of the included RCTs was critically appraised by two reviewers (M. Y. S. and Y. J. L.) using the tool of the Joanna Briggs Institute for RCTs [32], which included 13 items. Items evaluated as “Yes” were scored as “1” and “Unclear” or “No” as “0”. Therefore, the total available score for quality assessment ranged from 0 to 13. Higher scores indicate better quality. In case of disagreement, the two reviewers reached an agreement through discussion or consultation with a third reviewer (C. L. L.).

Data extraction

Two independent reviewers (M. Y. S. and Y. J. L.) extracted the data using a standardized Excel table that included the author, year

of publication, country, study design, participants, setting, performer of intervention, mean age of participants, type of physical activity, duration and frequency of intervention, data collection points, and outcome measurement tools. The outcome data of the postintervention time point would have a stronger intervention effect; therefore, we extracted the baseline and postintervention data (mean, standard deviation, and sample size for both groups). If the articles did not report standard deviations, we converted the data according to the Cochrane Handbook for Systematic Reviews of Interventions [33]. Five studies were randomly selected for pilot testing. The two reviewers discussed all disagreements and consulted a third reviewer (C. L. L.) until an agreement was reached.

Data synthesis

The meta-analysis was performed using the meta and metafor packages in R software version 4.3.1 [34]. Bias-corrected standardized mean difference effect measures (Hedges' g) and 95% confidence intervals (CIs) were used in the meta-analyses. Random-effects models were used in all meta-analyses because of the differences in study participants and interventions. I^2 statistics and Cochran's Q based on chi-square statistics were used to assess heterogeneity in the effects. We considered the effects to be substantially heterogeneous if the I^2 value was greater than 50% and the p-value of the chi-square test was less than 0.1. Subgroup analyses were performed to compare the effect sizes and significance of the seven QOL scales. Sensitivity analysis was performed by removing RCTs that resulted in high heterogeneity from the meta-analysis to reduce heterogeneity and ensure study stability. Publication bias was tested using Egger's test in Stata version 16.0.

Results

Study selection

A total of 4210 studies were identified using databases and other sources. After removing 1869 duplicate studies, 2282 records were eliminated after reading the titles and abstracts, and 28 records were excluded after screening their full texts. Finally, 26 studies [28–30,35–57] were included in the systematic review, and 20 studies were included in the meta-analysis. The process of searching for and selecting the included studies is shown in Figure 1.

Study characteristics

A total of 26 studies, involving 2105 participants, were included in the systematic review. Among these, 20 studies [28,29,35,36,38–40,42–47,49–51,53–56] involving 1228 participants were included in the meta-analysis. Data from four studies [37,48,52,57] could not be converted; one study [30] reported incomplete outcome data; and one study [41] was a serial publication of the original study that was included in this study. Sample sizes ranged from 19 [51] to 500 [52]. One study [36] was in Chinese, and the other 25 were in English. Most studies were conducted in the USA ($n = 9$, 35.0%) [30,37,39–42,50,51], China ($n = 3$, 12.0%) [28,36,38], Germany ($n = 2$, 8.0%) [53,54], Australia ($n = 2$, 8.0%) [44,57], and Turkey ($n = 2$, 8.0%) [35,49]. The remaining studies were conducted in Japan [29], Iran [43], Italy [55], Spain [45], Korea [46], Kosovo [47], Finland [52], and Columbus [48]. All the participants were women, and their mean age ranged from 33.10 to 69.00 years. Specific forms of intervention varied across studies including aerobic exercises (e.g., walking, Tai Chi Chuan), resistance training (e.g., sit-ups), and aerobic exercise combined with resistance training. The intervention time lasted from 1 to 12 months. The follow-up duration varied from 3 months to 1 year. A detailed characterization is presented in Table 1.

Quality appraisal

The quality scores of the included studies ranged from 8/13 to 11/13, with a mean score of 9.5/13. All included studies provided detailed information on random sequence generation and compared baseline data between the physical activity and control groups. Follow-ups of all the studies were complete, which resulted in a low risk of attrition bias. However, among the 26 studies, seven studies [36,46,47,49,52,55,57] did not report the specific allocation concealment methods, and 12 studies [30,36,37,39·43,44,46,49,53–55,57] did not report blinding, which may have contributed to bias. Overall, the included RCTs were at risk of bias. The detailed results are presented in the supplementary material (Appendix 2).

Effects on QOL

Twenty studies [29,30,35,37–41,43–47,49,51,52,54–57] reported the effect of physical activity on QOL. Five studies [37,39,40,47,57] investigated QOL using FACT-B, five studies [37–39,41,51] using SF-36, seven studies [35,43,45,46,49,52,54] using EORTC QLQ-C30, four studies [37,44,55,56] using FACT-G, four studies [43,46,52,54] using EORTC QLQ-BR23, two studies [30,37] using FACT-ES, and one study [29] using EQ-5D. Data from three studies [37,52,57] could not be converted; one study [30] reported incomplete data on QOL; and one study [41] was a serial publication of the original study that was included in this study. Therefore, 15 studies [29,35,38–40,43–47,49,51,54–56] with 16 results were included in the meta-analysis of QOL; the remaining five studies [30,37,41,52,57] are described in Table 1.

The results of 15 studies showed a significant effect of physical activity on improving QOL (Hedges' g = 0.67; 95% CI 0.41–0.92; Figure 2A). Substantial heterogeneity was observed ($I^2 = 68.9\%$, $p < .001$). After removing Do et al. (2015) (Hedges' g = 0.58; 95% CI 0.44–0.72; $p < .010$; $I^2 = 65.0\%$) and Shobeiri et al. (2016) (Hedges' g = 0.58; 95% CI 0.44–0.72; $p < .010$; $I^2 = 65.0\%$), the heterogeneity was reduced in the sensitivity analysis.

Subgroup analyses were conducted according to the type of QOL scales. The results of the subgroup analysis are shown in Figure 2B. The subgroup analysis showed that the effect (Hedges' g) was 0.91 (95% CI 0.25–1.58) in studies using FACT-B, 0.95 (95% CI 0.64–1.26) in studies using EORTC QLQ-C30, 0.10 (95% CI −0.37 to 0.57) in studies using SF-36, 0.29 (95% CI −0.08 to 0.66) in studies using FACT-G, and 0.04 (95% CI −0.55 to 0.63) in studies using EQ-5D. The FACT-B subgroup revealed substantial heterogeneity, and the FACT-B and EORTC QLQ-C30 subgroups were statistically significant. The test for subgroup differences using the random effects model showed that the different mean effects between subgroups were statistically significant (Q = 15.76, df = 4, $p < .010$).

Effects on anxiety

The effectiveness of physical activity on anxiety was measured using the SAS and HADS in three studies [28,36,42]. The results from three studies showed that physical activity reduced anxiety (Hedges' g = −0.28; 95% CI −0.46 to −0.10; Figure 2C). No substantial heterogeneity was observed ($I^2 = 0.0\%$, $p = .740$). After removing Rogers et al. (2017) (Hedges' g = −0.23; 95% CI −0.48 to 0.02; $p = .070$; $I^2 = 0.0\%$), Zhang et al. (2022) (Hedges' g = −0.28; 95% CI −0.47 to −0.08; $p < .010$; $I^2 = 0.0\%$), and Li et al. (2019) (Hedges' g = −0.34; 95% CI −0.58 to −0.10; $p < .010$; $I^2 = 0.0\%$), respectively, from the sensitivity analysis, the heterogeneity was all 0.0%, indicating that the results were stable.

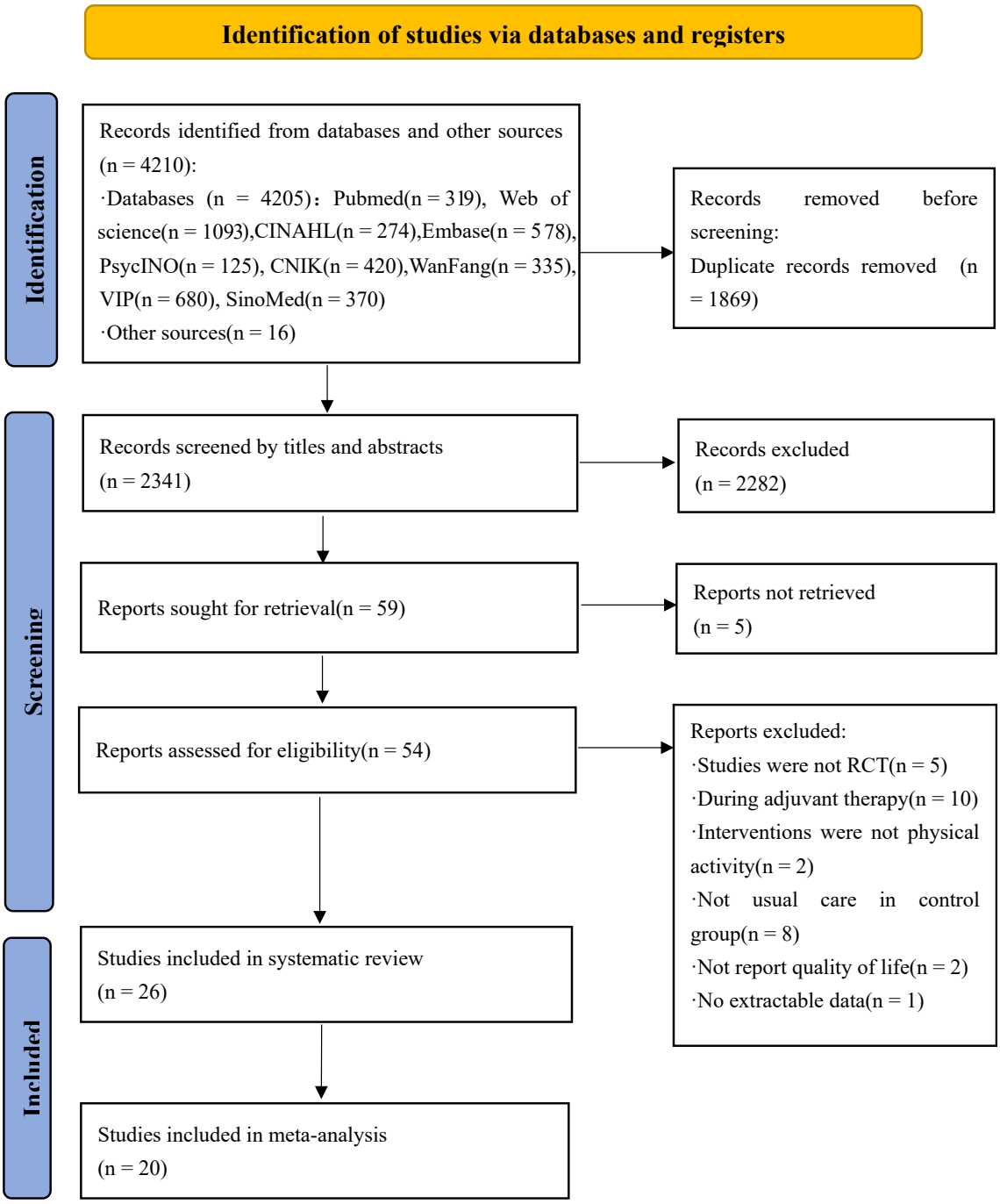

Figure 1. Flow Diagram for the Search and Selection of the Included Studies. *Note.* CNKI = China national knowledge infrastructure; RCT = randomized controlled trial; SinoMed = Chinese biomedical literature database; VIP = Chinese scientific journal database.

Effects on depression

Nine studies [36,39,42,48–50,52,53,57] reported the effectiveness of physical activity on depression as measured by the SDS, HADS, CES-D, and BDI. The data from these three studies [48,52,57] could not be converted. Therefore, six studies with seven results were included in the meta-analysis. The results from six studies showed that physical activity had a favorable but not statistically noticeable influence on depression (Hedges' g = −0.46; 95% CI −0.99 to 0.06; Figure 2D). Substantial heterogeneity was observed (I^2 = 88.1%, p < .001). After removing Dieli-Conwright et al. (2018) (Hedges' g = −0.28; 95% CI −0.46 to −0.11; p < .010; I^2 = 9.0%), the heterogeneity was significantly reduced in sensitivity analysis.

Publication bias

Egger's test showed that the p-value of all studies was >.050, suggesting no publication bias in the included studies. The results of the publication bias analysis are provided in the supplementary material (Appendix 3).

Table 1 *Detailed Characterization of the Studies Included in this Systematic Review (N = 26).*

Author (year)	Country	Study design	Participants (n) (IG/CG)	Setting	Performer of intervention	Age, Mean (SD) (IG/CG)	Intervention	Intervention time	Data collection points	Description of intervention methods	Outcomes
Baglia et al. (2019)	America	RCT	61/60	gym	exercise trainer	62.0 ± 7.0/ 60.5 ± 7.0	strength-training, aerobic exercise	12 months	6 months, 12 months	strength-training: twice a week aerobic exercise: three 50 min or five 30 min	FACT-B SF-36 FACT-G FACT-ES
Bower et al. (2012)	America	RCT	16/15	university	yoga instructor	54.4 ± 5.7/ 53.3 ± 4.9	Yoga	12 weeks	12 weeks, 3 months	twice a week, 90 min a time	BDI-II
Dieli-Conwright et al. (2018)	America	RCT	46/45	hospital	exercise trainer	Total: 53.5 ± 10.4	aerobic exercise, resistance exercise	16 weeks	16 weeks, 28 weeks (exercise group only)	three times a week, 60 min a time	FACT-B SF-36 CES-D
Do et al. (2015)	Korea	RCT	32/30	hospital	physical therapist	47.1 ± 8.5/ 48.3 ± 8.2	aerobic exercise, strengthening exercise, core stability exercise	4 weeks	2 weeks, 4 weeks, 6 weeks, 8 weeks	five times a week, 80 min a time	EORTC QLQ-C30, EORTC QLQ-BR23
Dong et al. (2019)	China	RCT	26/24	NR	physiotherapists	48.00 ± 5.54/ 51.63 ± 7.49	muscle and cardiorespiratory capacity training	12 weeks	12 weeks	three or four times a week, 30 min a time	SF-36
Ergun et al. (2013) (aerobic and resistance)	Turkey	RCT	20/20	NR	specialist doctor	49.05 ± 8.25/ 50.3 ± 10.37	aerobic exercise, resistance exercise	12 weeks	12 weeks	three times a week, 45 min a time	EORTC QLQ-C30, BDI
Ergun et al. (2013) (brisk walking)	Turkey	RCT	20/20	NR	specialist doctor	55.05 ± 6.85/ 50.3 ± 10.37	brisk walking	12 weeks	12 weeks	three times a week, 30 min a time	EORTC QLQ-C30, BDI
Eyigör et al. (2021)	Turkey	RCT	15/16	university	yoga trainer	51.40 ± 10.6/ 50.7 ± 7.6	yoga exercise	10 weeks	10 weeks	twice a week, 60 min a time	EORTC QLQ-C30
Galiano-Castillo et al. (2016)	Spain	RCT	39/37	university	NR	47.4 ± 9.6/ 49.2 ± 7.9	aerobic exercise, resistance exercise	8 weeks	8 weeks, 6 months	three times a week, 90 min a time	EORTC QLQ-C30
Hagstrom et al. (2016)	Australia	RCT	20/19	university	trainer	51.2 ± 8.5/ 52.7 ± 9.4	resistance training	16 weeks	17 weeks	three times a week, 60 min a time	FACT-G
Kiecolt-Glaser et al. (2014)	Columbus	RCT	96/90	home	yoga teacher	51.6 ± 9.2/ 51.8 ± 9.8	Yoga	12 weeks	12 weeks, 3 months	two 90 min sessions per week	CES-D
Li et al. (2019)	China	RCT	98/100	home	rehabilitation therapist, nurse	47.4 ± 8.5/ 49.2 ± 8.6	aerobic exercise	3 months	3 months, 6 months, 9 months	three or four times a week, 30–40 min a time	SAS SDS
Murtezani et al. (2014)	Kosovo	RCT	30/32	hospital	NR	53 ± 11/51 ± 11	aerobic exercise	10 weeks	10 weeks	three times a week, 25–45 min a time	FACT-B
Ochi et al. (2022)	Japan	RCT	21/23	NR	NR	48 ± 6/49 ± 5	high-intensity interval training	12 weeks	12 weeks	three times a week, 10 min a time	EQ-5D
Rogers et al. (2015)	America	RCT	105/108	home	exercise specialist	54.9 ± 9.3/ 53.9 ± 7.7	aerobic exercise	3 months	3 months, 6 months	once a week, 150 min a time	FACT-B
Rogers et al. (2016)	America	RCT	105/108	home	exercise specialist	Total: 54 ± 9	aerobic exercise	3 months	3 months, 6 months	once a week, 150 min a time	SF-36
Rogers et al. (2017)	America	RCT	105/108	home	exercise specialist	Total: 54.4 ± 8.5	aerobic exercise	3 months	3 months, 6 months	once a week, 150 min a time	HADS
Saarto et al. (2012)	Finland	RCT	263/237	home	physical therapist	52.3/52.4	supervised and home training	12 months	12 months	Supervised training: once a week, 60 min a time home training: three times a week	EORTC QLQ-C30, EORTC QLQ-BR23, RBDI
Shobeiri et al. (2016)	Iran	RCT	30/30	gym	NR	42.70 ± 9.60/ 43.50 ± 8.60	aerobic exercise	10 weeks	10 weeks	twice a week, 40–60 min a time	EORTC QLQ-C30, EORTC QLQ-BR23

Sprod et al. (2012)	America	RCT	9/10	university	health and fitness instructor	54.33 ± 3.55/ 52.7 ± 2.11	Tai Chi Chuan	12 weeks	6 weeks, 12 weeks	three times a week, 60 min a time	SF-36
Wang et al. (2021)	America	RCT	23/26	community	personal trainer	55.6 ± 8.2/ 56 ± 11.5	personal fitness training	30 weeks	30 weeks	150 min per week	FACT-ES
Salchow et al. (2021)	Germany	RCT	16/14	university	sport scientists and instructors	54 ± 7/51 ± 8	martial arts	24 weeks	3 months, 6 months	twice a week, 90 min a time	HADS
Strunk et al. (2018)	Germany	RCT	16/14	university	sport scientists and instructors	54.2 ± 7.8/ 51.5 ± 8.4	martial arts	24 weeks	3 months, 6 months	twice a week, 90 min a time	EORTC QLQ-C30, EORTC QLQ-BR23
Luca et al. (2016)	Italy	RCT	10/10	gymnasium	fitness professional and physician	50.2 ± 9.7/ 46.0 ± 2.8	aerobic exercise, resistance exercise	24 weeks	24 weeks	twice a week, 90 min a time	FACT-G
Littman et al. (2012)	America	RCT	27/27	in class and home	yoga instructors	60.6 ± 7.1/ 58.2 ± 8.8	Yoga	6 months	6 months	five times a week, 75 min a time	FACT-G
Naumann et al. (2012)	Australia	RCT	11/10	NR	exercise physiologist	49.0 ± 10.0/ 51.8 ± 11.5	exercise training	8 weeks	8 weeks	three times a week, 45–60 min a time	FACT-B BDI
Zhang et al. (2022)	China	RCT	29/29	hospital	nurse	47.79 ± 5.14/ 47.20 ± 7.65	mindfulness-based Tai Chi Chuan	8 weeks	8 weeks, 1 year	twice a week, one hour a time	SAS

Note. BDI = Beck Depression Inventory; CES-D = 20-item Center for Epidemiologic Studies-Depression Scale; CG = control group; EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; EORTC QLQ-BR23 = Breast Cancer-Specific Quality of Life Questionnaire; EQ-5D = EuroQol five dimensions; FACT-B = Functional Assessment of Cancer Therapy-Breast; FACT-ES = Functional Assessment of Cancer Therapy – Endocrine Symptoms; FACT-G = Functional Assessment of Cancer Therapy – General; HADS = Hospital Anxiety and Depression subscale; IG = intervention group; NR = not reported; RCT = randomized controlled trial; SAS = Self-rating Anxiety Scale; SD = Standard Deviation; SDS = Self-rating Depression Scale; SF-36 = Short Form-36 Health Survey.

Discussion

This review summarizes the available evidence regarding the effectiveness of physical activity on QOL, anxiety, and depression in breast cancer survivors over the past decade. The current analysis demonstrated that physical activity significantly improved QOL and reduced anxiety compared with usual care. In contrast to the previous meta-analysis, the present review failed to support the effects of physical activity on depression. Additionally, intervention forms for physical activity were more abundant, and the tools used to measure QOL were more specific. Although these results should be acknowledged cautiously because of the heterogeneity among studies, the results of this review provide a reference for practice and future research.

The current review found that physical activity has a significant statistical effect on improving the QOL (Hedges' g = 0.67; 95% CI 0.41–0.92) and alleviated anxiety (Hedges' g = −0.28; 95% CI −0.46 to −0.10) of breast cancer survivors, which was consistent with the previous meta-analysis [27]. The beneficial effects of physical activity may be attributed to the following mechanisms: First, it exerts anti-inflammatory effects [58]. Exercise can reduce inflammatory markers such as tumor necrosis factor-alpha [59]. Second, exercise can increase endogenous opioid levels and reduce pain and fatigue [60]. Third, 5-hydroxytryptamine and dopamine secreted during physical activity can effectively regulate pleasure factors, thus reducing anxiety and improving QOL [61]. In short, physical activity had an effect on QOL and anxiety, but the included studies involved seven QOL assessment tools, and the evidence was limited because there were only three studies in the meta-analysis of anxiety. Future studies should reach a consensus on the assessment tools and confirm these findings.

The results of subgroup analyses showed that physical activity improved breast cancer-specific QOL as measured by the FACT-B scale (Hedges' g = 0.91; 95% CI 0.25–1.58) and the EORTC QLQ-C30 scale (Hedges' g = 0.95; 95% CI 0.64–1.26). EORTC QLQ-C30 has its breast cancer-specific module, EORTC QLQ-BR23 [62], and the two were used in combination in most studies. EORTC QLQ-BR23 and FACT-B are applicable to patients with breast cancer at all clinical stages, and they assess breast cancer-specific and sensitive issues such as sexual dysfunction and body perception [62,63], which are difficult for breast cancer survivors to discuss directly with healthcare providers. Self-assessment of survivors through questionnaires allows healthcare professionals to obtain comprehensive information early to tailor physical activity interventions and optimize their QOL. However, current studies have mostly focused on the QOL of breast cancer survivors in the short–term after breast cancer treatment, with follow-up times ranging from 1 month to 1 year. The pressure of tumor recurrence and metastasis continues to affect survivors' bodies and minds, imposing a heavy physical and mental burden on them [64]. Breast cancer survivors have longer survival times than patients with other malignant tumors [65]. With the extended survival time of breast cancer survivors, their QOL is constantly changing. At present, a number of tools for evaluating the long-term QOL of breast cancer survivors, such as Long-Time Quality of Life in Breast Cancer (LTQOL-BC) [66], are available. Therefore, future studies should use breast-cancer-specific and long-term QOL scales to elucidate the impact of physical activity on breast-cancer-specific QOL.

However, this meta-analysis found no statistically significant effects of physical activity on depression. A possible explanation for this insignificant result is that physical activity was not designed for depressive symptoms in some studies [67]. Many breast cancer survivors lack the energy and motivation to complete physical activity [68], which contributes to the relatively small effect. Furthermore, breast cancer survivors may experience a low sense of

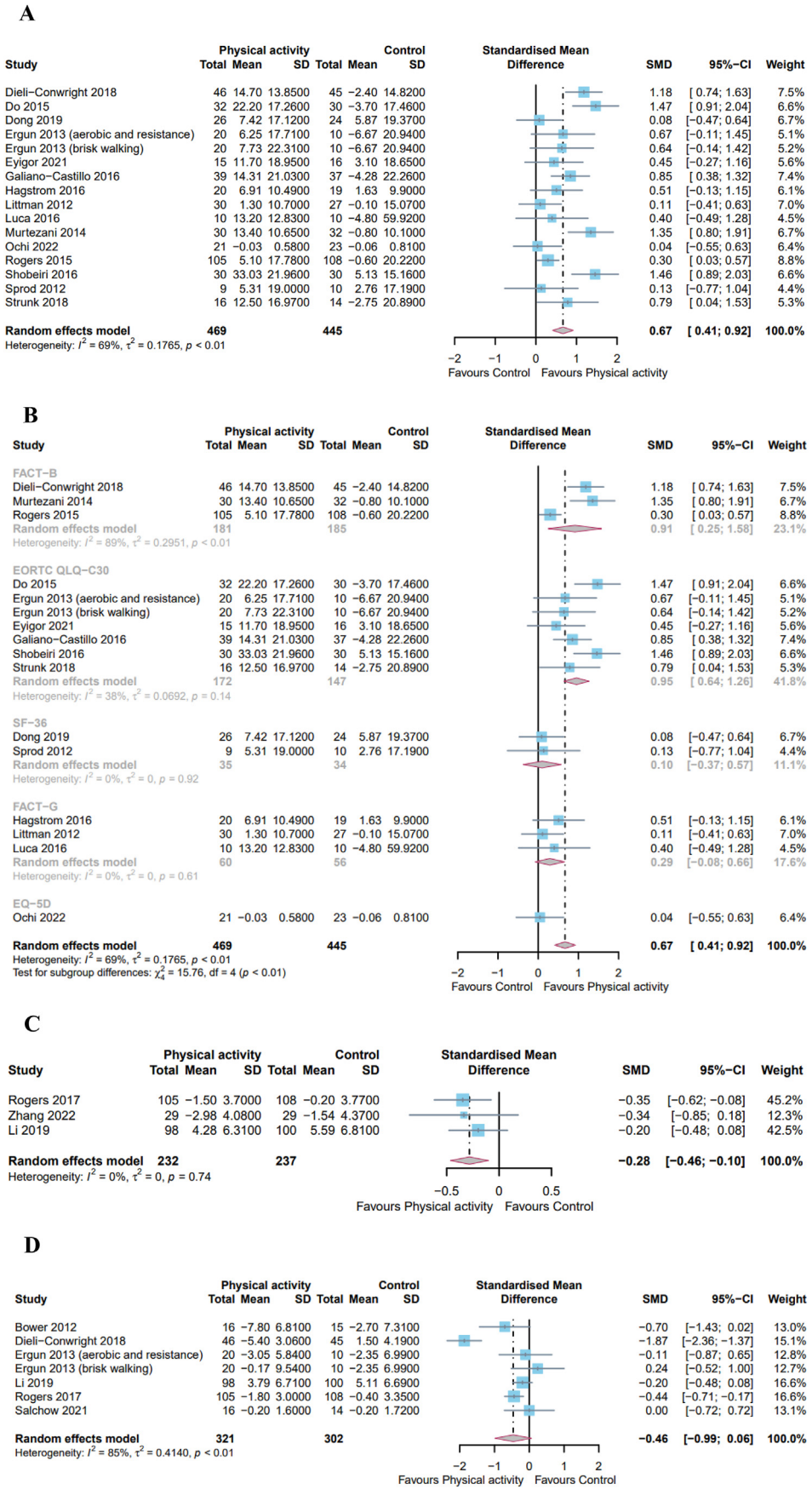

Figure 2. A. Forest Plot for the Effect of Physical Activity on QOL. B. Subgroup Analysis for the Effect of Physical Activity on QOL by different QOL scales. C. Forest Plot for the Effect of Physical Activity on Anxiety. D. Forest Plot for the Effect of Physical Activity on Depression. *Note.* CI = confidence interval; SMD = standardized mean difference (Hedges' g).

self-worth [69], poor body image after surgery [70], and a lack of reliable emotional or social support [71] during the rehabilitation period, suggesting that depressive symptoms are influenced by factors beyond actual physical activity [72]. Although the effect of physical activity on depression was not statistically significant (Hedges' g = − 0.46; 95% CI −0.99 to 0.06), it appeared to reduce depression. Previous studies have shown that maintaining a certain level of physical activity among breast cancer survivors positively affects their psychological health. Sylvester et al. [73] found that increased physical activity in breast cancer survivors leads to decreased depressive symptoms. Therefore, attention should be paid to the effects of physical activity on depression. More high-quality RCTs that eliminate confounding factors are required to determine the effectiveness of physical activity on depression.

The results showing that physical activity improved QOL but had no impact on depression compared with the control group may be puzzling. The small sample size may have influenced the final intervention effect. QOL is a broad concept affected by physical health, mental state, social relationships, and other factors [74]. Depression is characterized by feelings of hopelessness, sadness, changes in sleep and appetite, and so on [67]. Depression was observed to be one of the factors affecting QOL. Therefore, QOL and depression did not necessarily increase or decrease in the same direction. In summary, the influence of physical activity on QOL and depression must be carefully interpreted, as breast cancer is a complex disease, depression and poor QOL in breast cancer survivors are influenced by multiple factors. Future studies with larger sample sizes and more rigorous designs are warranted.

In addition, this review has a meaningful finding: In addition to aerobic and resistance exercises, more studies have focused on the influence of yoga and Tai Chi Chuan on QOL, anxiety, and depression in breast cancer survivors over the past decade. Owing to the limited number of included studies, this study combined various types of physical activities for analysis, which may have underestimated the specific efficacy of yoga and Tai Chi Chuan. Recent studies have confirmed the positive effects of yoga and Tai Chi Chuan on improving QOL and alleviating negative emotions [75,76]. Moreover, yoga and Tai Chi Chuan are typically characterized by low intensity, slow, deep breathing, and a focus on positive thinking and relaxation [77]. Future studies should further investigate and quantitatively elucidate the effects of yoga and Tai Chi Chuan on rehabilitation outcomes in breast cancer survivors to support the development of targeted medical interventions.

Limitations

The present review has some limitations. First, not all the studies were included in the meta-analysis, which may not have reflected the evidence as a whole. Second, the heterogeneity in the types of physical activity and frequency of interventions may limit the strength of our evidence. Third, only studies published in English or Chinese were included.

Conclusions

In conclusion, physical activity can improve QOL, reduce anxiety in breast cancer survivors, and lead to positive trends in depression, although the results were not statistically significant. Based on the benefits of physical activity interventions, healthcare providers can develop personalized exercise programs and recommend that breast cancer survivors become more physically active in their lives for further rehabilitation after treatment. Further well-designed studies are required to investigate the impact of different types of physical activities on QOL, anxiety, and depression among breast cancer survivors.

Registration

This systematic review and meta-analysis was registered in PROSPERO (registration number CRD42022363094). https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=363094.

Author contributions

Mengying Sun: searching, screening, bias assessment, data extraction and analysis, manuscript writing and editing; Chunlei Liu: design, screening, bias assessment, data extraction, manuscript writing and editing; Yanjuan Lu: screening, bias assessment and data extraction; Fei Zhu: manuscript editing; Huanxi Li: searching; Qian Lu: design, manuscript writing and editing.

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Conflict of interest

The authors have no conflicts of interest to disclose.

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Not applicable.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.anr.2023.11.001.

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Reviewer acknowledgment

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