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Research Article

The Relationship Between Upper-Limb Lymphedema and Fatigue Among Breast Cancer Survivors

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Background: Breast cancer survivors (BCSs) often face long-term complications, with upper-limb lymphedema and cancer-related fatigue (CRF) being challenging. This study aimed to investigate the relationship between upper-limb lymphedema and fatigue among BCSs.

Method: This cross-sectional study was performed on 102 BCSs, of which 31 (30.4%) had breast cancer–related lymphedema. Duration, stage, and excess volume were considered as indicators of breast cancer–related lymphedema severity. QoL was measured using the EORTC QLQ-C30. The score of the fatigue symptom scale was used based on EORTC QLQ-C30 for CRF assessment. Also, the brief fatigue inventory was used to measure the severity of fatigue among participants.

Results: The mean fatigue symptom scale and brief fatigue inventory scores were 37.90 ± 24.59 and 3.69 ± 1.25, respectively. The mean fatigue symptom scale was significantly different among BCSs with BMI ≤ 25 and BMI > 25 (29.59 ± 24.49 vs. 41.51 ± 23.88, $p = 0.026$). Also, the mean brief fatigue inventory was significantly different among BCSs with the number of dissected lymph nodes (LNs) ≤ 5 and > 5 (3.52 ± 1.18 vs. 4.08 ± 1.34, $p = 0.042$). Additionally, women with breast cancer–related lymphedema had significantly higher scores of fatigue symptom scale and brief fatigue inventory (46.59 ± 27.12 vs. 34.11 ± 22.56, $p = 0.03$, and 4.75 ± 1.21 vs. 3.22 ± 0.96, $p = 0.001$, respectively). Except for a weak correlation between BMI and fatigue symptom scale and brief fatigue inventory (r: 0.279, $p = 0.004$, and r: 0.313, $p = 0.001$, respectively), there was no other significant relationship between CRF and study variables such as breast cancer–related lymphedema duration, stage, and excess volume. Meanwhile, fatigue symptom scale and brief fatigue inventory were significantly correlated with global health and functional scale scores of EORTC QLQ-C30. The ROC curve which models the diagnostic efficacy for fatigue symptom scale showed an AUC of 0.634 ($p = 0.034$, 95% CI: 0.510–0.759), while the ROC curve which models the diagnostic efficacy for brief fatigue inventory showed an AUC of 0.821 ($p < 0.001$, 95% CI: 0.735–0.908).

Conclusion: This study highlighted that while breast cancer–related lymphedema was associated with increased CRF, the severity of lymphedema did not significantly correlate with CRF. Additionally, CRF might be an indicator of breast cancer–related lymphedema among BCSs.

Keywords: breast cancer; breast cancer–related lymphedema; breast cancer survivor; fatigue; quality of life

1. Introduction

Breast cancer remains the most prevalent cancer among women globally, with significant advancements in early detection and treatment options leading to improved survival rates [1]. Consequently, the focus of healthcare has increasingly shifted toward managing the long-term sequelae of breast cancer treatment and enhancing the quality of life (QoL) of survivors [2]. Among these long-term effects, breast cancer–related lymphedema is characterized by the abnormal accumulation of lymphatic fluid in the arm, resulting in swelling, discomfort, and reduced mobility. This condition typically arises as a consequence of breast cancer treatments, such as lymph node (LN) dissection, radiation therapy, and chemotherapy which can damage the lymphatic system [3, 4]. The physical manifestations of breast cancer–related lymphedema are often accompanied by a range of psychosocial impacts, including anxiety, depression, and body image disturbances. Moreover, breast cancer–related lymphedema can significantly interfere with daily activities and occupational functioning, thereby diminishing overall QoL [5, 6].

Fatigue is another debilitating symptom experienced by breast cancer survivors (BCSs). Cancer-related fatigue (CRF) is defined as a persistent, subjective sense of tiredness related to cancer or cancer treatment that is disproportionate to recent activity and not relieved by rest [7]. CRF affects physical, emotional, and cognitive functioning, often leading to profound impairments in QoL. The multifaceted nature of fatigue means that it can be caused by various sources, including the cancer itself, treatments such as chemotherapy and radiation, psychological stress, and other comorbid conditions [7, 8].

Despite the recognized prevalence and impact of both breast cancer–related lymphedema and fatigue among BCSs, the specific relationship between these two conditions remains underexplored. Understanding how breast cancer–related lymphedema and CRF contribute to diminished QoL is crucial for developing targeted interventions that can alleviate these symptoms and improve the overall well-being of survivors. This study aimed to investigate the relationship between breast cancer–related lymphedema and fatigue in BCSs. Specifically, it aimed to determine the extent to which breast cancer–related lymphedema severity influences fatigue levels and how this relationship affects QoL.

2. Methods

This cross-sectional study was conducted and approved by the Motamed Cancer Institute (MCI) (ID: 4021721). Informed consent was obtained from all participants. Prior to data collection, medical records were reviewed to select potentially eligible patients. Participants were interviewed to assess sociodemographic variables, and data on clinical variables were obtained from medical records. Participants also received consent to fill out the questionnaires for QoL and CRF assessment. This study was written based on the STROBE guideline [9].

2.1. Participants. Female BCSs were selected among patients who had undergone routine follow-up. To be eligible for the study, participants had to meet the following criteria: (1) diagnosed with primary breast cancer, (2) completed cancer treatment (including surgery, with or without radiotherapy or chemotherapy) for ≥ 6 months before the study, (3) aged 18 years or older, and (4) possessed cognitive function and communication abilities sufficient to complete study questionnaires and assessments. Participants were excluded if they (1) had evidence of metastatic or recurrent cancer at the time of the study, (2) had a history of other types of cancer, (3) were diagnosed with or currently receiving treatment for clinical depression, and (4) had any comorbid condition that could contribute to fatigue (e.g., uncontrolled thyroid disorder).

2.2. Data Collection. The data collection for this study was conducted over a period from January 2024 to May 2024. Both fatigue and QoL (brief fatigue inventory and EORTC QLQ-C30 questionnaire) levels and variables related to lymphedema status were assessed concurrently during a follow-up visit.

In this study, the brief fatigue inventory was used to measure the severity of fatigue among participants over the past week. The brief fatigue inventory is widely recognized for its simplicity, understandable language, and short completion time, making it an effective tool for measuring fatigue among cancer patients. The brief fatigue inventory includes nine questions, each answered using an 11-point rating scale. The first three questions rate the severity of fatigue. These questions are rated from 0 (no fatigue) to 10 (the most severe level of fatigue). The remaining six questions assess how fatigue interferes with different aspects of a patient's daily life, such as the ability to walk, mood, ability to work, enjoyment of life, and social connections. The Persian version of the brief fatigue inventory questionnaire had adequate reliability and validity [10].

Data regarding breast cancer–related lymphedema duration, stage, and excess volume were considered as indicators of breast cancer–related lymphedema severity. The stage of breast cancer–related lymphedema was assessed based on the guideline reported by the International Society of Lymphology [11]. Also, the volume of both was assessed using a tape measure with estimation based on the formula. The difference between the affected arm and the contralateral arm was computed to determine the excess volume [12]. The presence of excess volume greater than 10% was deemed an indicator for diagnosing breast cancer–related lymphedema [13].

QoL was measured using the EORTC QLQ-C30 (European Organization for Research and Treatment of Cancer Quality of Life Core Questionnaire version 3.0). The EORTC QLQ-C30 consists of different multiitem scales: five functional scales (physical, role, cognitive, emotional, and social), nine symptom scales (fatigue, pain, nausea/vomiting, dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties), and a global health scale. The global health scale describes patients' subjective QoL based on two

questions about physical condition and overall QoL, referred to as QoL. The fatigue symptom scale was determined based on the EORTC QLQ-C30 for CRF assessment. This questionnaire has been translated to Persian with adequate reliability and validity [14].

2.3. Data Analysis. The participants were divided into two groups according to various variables including age (≤ 50 vs. > 50 years), occupation (employed vs. unemployed), education level (primary vs. secondary), body mass index (BMI) (≤ 25 vs. > 25 kg/m^2), survivorship duration (≤ 24 months vs. > 24 months), number of LNs removed (≤ 5 vs. > 5), and presence of breast cancer–related lymphedema (Yes vs. No). Fatigue was assessed using both the fatigue symptom scale and brief fatigue inventory through two groups defined by each variable. The mean and standard deviation (SD) were used to present the descriptive statistics. The Kolmogorov–Smirnov test was used to check the normality of data distribution. Since the data distribution was normal, parametric tests were used. The *t*-test compared the mean difference between the two groups. Pearson's correlation coefficient (*r*) examined the association between study variables. Linear regression analysis was employed to model the correlation between a dependent (such as fatigue symptom scale and brief fatigue inventory) variable and several independent variables (such as the presence of breast cancer–related lymphedema). The univariate and multivariate analyses evaluated the variables. In the multivariate model, adjustments were applied to those variables that had a p value of 0.2 or less in the univariate analysis. In order to assess the diagnostic efficacy of the fatigue symptom scale and brief fatigue inventory for breast cancer–related lymphedema, a receiver operating characteristic (ROC) curve analysis was carried out. Statistical analysis was performed using IBM SPSS version 23.0 (IBM Corp., Armonk, NY, USA), with p values < 0.05 considered statistically significant.

3. Results

A total of 115 women were identified as potential participants. Of these, 6 refused to participate. Thus, 109 participants were recruited for the study. After screening and exclusion of those with incomplete questionnaires or ongoing radiotherapy or chemotherapy, complete data from 102 participants were included in the final analysis, of which 31 (30.4%) participants had breast cancer–related lymphedema.

The mean age and BMI of participants were 53.34 ± 10.37 and 27.44 ± 4.47, respectively. The mean fatigue symptom scale and brief fatigue inventory scores were 37.90 ± 24.59 and 3.69 ± 1.25, respectively. Additionally, the mean global health and functional scale scores of EORTC QLQ-C30 were as follows: global health—65.77 ± 23.19, physical function—68.75 ± 20.63, role function—78.75 ± 23.82, emotional function—65.93 ± 25.12, cognitive function—73.36 ± 24.51, and social function—75.49 ± 25.11. The mean excess volume among women with breast cancer–related lymphedema was 469.68 ± 349.37. Also, the duration of breast cancer–related lymphedema ranged from 1 to 192 months and the majority of them had stage 2 (41.9%) of breast cancer–related lymphedema.

The mean fatigue symptom scale and brief fatigue inventory scores were significantly different among BCSs with BMI ≤ 25 and BMI > 25 (29.59 ± 24.49 vs. 41.51 ± 23.88, $p = 0.026$, and 3.23 ± 1.02 vs. 3.88 ± 1.29, $p = 0.015$, respectively). Also, the mean brief fatigue inventory was significantly different among BCSs with a number of dissected LNs ≤ 5 and > 5 (3.52 ± 1.18 vs. 4.08 ± 1.34, $p = 0.042$). Additionally, women with breast cancer–related lymphedema had significantly higher scores of fatigue symptom scale and brief fatigue inventory (46.59 ± 27.12 vs. 34.11 ± 22.56, $p = 0.03$, and 4.75 ± 1.21 vs. 3.22 ± 0.96, $p < 0.001$, respectively). The results of fatigue symptom scale and brief fatigue inventory scores based on study variables are presented in Table 1.

There was no significant relationship between CRF and variables related to lymphedema such as breast cancer–related lymphedema duration, stage, and excess volume, but there was a weak correlation between BMI and fatigue symptom scale and brief fatigue inventory (r: 0.279, $p = 0.004$, and r: 0.313, $p = 0.001$, respectively). Meanwhile, fatigue symptom scale and brief fatigue inventory were significantly correlated with global health and functional scale scores of EORTC QLQ-C30 as presented in Table 2. Fatigue symptom scale showed moderate correlation with global health (r: −0.397, $p < 0.001$), physical function (r: −0.607, $p < 0.001$), role function (r: −0.564, $p < 0.001$), emotional function (r: −0.523, $p < 0.001$), cognitive function (r: −0.403, $p < 0.001$), and social function (r: −0.446, $p < 0.001$) scores. Also, brief fatigue inventory had a moderate to strong correlation with global health (r: −0.469, $p < 0.001$), physical function (r: −0.721, $p < 0.001$), role function (r: −0.657, $p < 0.001$), emotional function (r: −0.487, $p < 0.001$), cognitive function (r: −0.453, $p < 0.001$), and social function (r: −0.622, $p < 0.001$) scores. There was no other significant correlation between global health and functional scale scores of EORTC QLQ-C30 and study variables as presented in Table 2.

Based on the univariate regression analysis, brief fatigue inventory was significantly related to BMI, number of LNs removed, and presence of breast cancer–related lymphedema ($\beta = 0.65$ [0.12–1.18], $p = 0.015$; $\beta = -0.55$ [−1.08–−0.02], $p = 0.042$; and $\beta = 1.52$ [1.08–1.96], $p < 0.001$, respectively) and fatigue symptom scale was significantly related to BMI and presence of breast cancer–related lymphedema ($\beta = 12.25$ [1.87–22.62], $p = 0.021$; $\beta = 12.47$[2.21–22.74], $p = 0.018$, respectively). Based on the multivariate regression analysis which adjusted for other variables that had a p value of 0.2 or less in the univariate analysis, brief fatigue inventory was significantly related to BMI and presence of breast cancer–related lymphedema ($\beta = 0.52$ [0.07–0.97], $p = 0.022$, and $\beta = 1.57$ [1.06–2.07], $p < 0.001$, respectively) and fatigue symptom scale was significantly related to BMI and presence of breast cancer–related lymphedema ($\beta = 10.76$ [0.56–20.95],

Table 1: Mean fatigue scores (fatigue symptom scale of EORTC QLQ-C30 and brief fatigue inventory) overall and according to participant characteristics.

Variable (*N*, %)	Fatigue symptom scale (mean ± SD)	*p* value*	Brief fatigue inventory (mean ± SD)	*p* value*
Total (102, 100%)	37.90 ± 24.59		3.69 ± 1.25	
Age (year)				
≤ 50 (42, 41.18%)	34.39 ± 24.14	0.22	3.64 ± 1.18	0.72
> 50 (60, 58.82%)	40.37 ± 24.8		3.73 ± 1.31	
Occupation				
Yes (21, 20.59%)	33.88 ± 20.87	0.45	3.60 ± 1.16	0.71
No (81, 79.41%)	38.68 ± 25.52		3.71 ± 1.28	
Education				
Primary (72, 70.59%)	38.11 ± 25.28	0.97	3.74 ± 1.27	0.50
Secondary (30, 29.41%)	37.40 ± 23.24		3.56 ± 1.22	
BMI (kg/m^2)				
≤ 25 (30, 29.41%)	29.59 ± 24.49	**0.026**	3.23 ± 1.02	**0.015**
> 25 (72, 70.59%)	41.51 ± 23.88		3.88 ± 1.29	
Survivorship duration (month)				
≤ 24 (46, 45.10%)	42.75 ± 25.33	0.81	3.90 ± 1.30	0.13
> 24 (56, 54.90%)	33.92 ± 23.44		3.52 ± 1.19	
LNs removed (number)				
≤ 5 (30, 29.41%)	37.40 ± 26.17	0.89	3.52 ± 1.18	**0.042**
> 5 (72, 70.59%)	38.11 ± 24.08		4.08 ± 1.34	
Breast cancer–related lymphedema				
Yes (31, 30.39%)	46.59 ± 27.12	**0.03**	4.75 ± 1.21	**< 0.001**
No (71, 69.61%)	34.11 ± 22.56		3.22 ± 0.96	

Note: %: percent. * *p* values obtained from the *t*-test. Bold: statistically significant.
Abbreviations: BMI, body mass index; *N*, number; SD, standard deviation.

$p = 0.039$, and $\beta = 10.20[-0.02–20.43]$, $p = 0.051$, respectively). The full result of univariate and multivariate analysis is shown in Table 3. The ROC curve for fatigue symptom scale showed an area under the curve (AUC) of 0.634 ($p = 0.034$, 95% CI: 0.510–0.759) which is presented in Figure 1. The fatigue symptom scale score of 61.11 showed a sensitivity and specificity of 38.7% and 88.7%, respectively. Also, the ROC curve for brief fatigue inventory showed an AUC of 0.821 ($p < 0.001$, 95% CI: 0.735–0.908) as shown in Figure 1. The brief fatigue inventory score of 4.77 showed a sensitivity and specificity of 54.8% and 95.8%, respectively.

4. Discussion

BCSs with a BMI of more than 25 had higher fatigue symptom scale and brief fatigue inventory scores. Also, having more than five LNs removed was associated with higher brief fatigue inventory scores. Additionally, women with breast cancer–related lymphedema had significantly higher scores of both fatigue symptom scale and brief fatigue inventory. The findings from the univariate and multivariate regression analyses provide significant insights into the relationship between fatigue and various clinical factors in patients with breast cancer–related lymphedema. The brief fatigue inventory and fatigue symptom scale were both significantly associated with the presence of breast cancer–related lymphedema. In the univariate analysis, brief fatigue inventory scores were positively correlated with the presence of breast cancer–related lymphedema. This indicates that the presence of breast cancer–related lymphedema might be associated with increased fatigue levels. Also, the fatigue symptom scale demonstrated significant positive relationships with breast cancer–related lymphedema. The considerable β coefficient ($\beta = 12.47$) implies that breast cancer–related lymphedema contributes meaningfully to the fatigue symptom scale, reinforcing the idea that managing breast cancer–related lymphedema could be pivotal in reducing fatigue. The multivariate analysis confirmed the findings from the univariate analysis. This consistency across analyses strengthens the validity of these associations. This finding highlights the potential importance of assessing fatigue levels in BCSs to identify those at higher risk of breast cancer–related lymphedema. The ROC curve analysis provides information about the diagnostic accuracy of fatigue symptom scale and brief fatigue inventory associated with breast cancer–related lymphedema. The maximum insight that can be gained from these ROC curves is that they help evaluate how the lymphedema variables assessment can be explained by these two fatigue scales. The AUC values indicate that brief fatigue inventory (AUC = 0.821) has a better discriminatory power compared to fatigue symptom scale (AUC = 0.634) in distinguishing between BCSs with and without breast cancer–related lymphedema. However, both show moderate to high specificity, suggesting they may be useful tools in identifying BCSs at risk of breast cancer–related lymphedema. The results of this study suggest that incorporating fatigue symptom scale and brief fatigue inventory assessments into routine follow-up care for BCSs may help identify individuals at higher risk of

Table 2: The correlation between fatigue symptom scale, brief fatigue inventory, global health and functional scale scores of EORTC QLQ-C30, and study variables.

Variables	Fatigue symptom scale	Brief fatigue inventory	Global health	Physical function	Role function	Emotional function	Cognitive function	Social function
Occupation	*r*: 0.062 *p* = 0.53	*r*: 0.028 *p* = 0.78	*r*: −0.125 *p* = 0.21	*r*: 0.036 *p* = 0.71	*r*: 0.089 *p* = 0.37	*r*: 0.034 *p* = 0.73	*r*: −0.042 *p* = 0.67	*r*: 0.050 *p* = 0.61
Education	*r*: −0.013 *p* = 0.89	*r*: −0.067 *p* = 0.50	*r*: 0.111 *p* = 0.26	*r*: −0.003 *p* = 0.97	*r*: 0.064 *p* = 0.52	*r*: 0.019 *p* = 0.85	*r*: 0.102 *p* = 0.30	*r*: 0.059 *p* = 0.55
Survivorship duration (month)	*r*: −0.096 *p* = 0.60	*r*: 0.013 *p* = 0.90	*r*: −0.010 *p* = 0.95	*r*: 0.090 *p* = 0.367	*r*: 0.013 *p* = 0.90	*r*: 0.083 *p* = 0.65	*r*: −0.035 *p* = 0.85	*r*: 0.136 *p* = 0.17
LNs removed (number)	*r*: 0.044 *p* = 0.66	*r*: 0.174 *p* = 0.08	*r*: 0.123 *p* = 0.21	*r*: 0.075 *p* = 0.45	*r*: −0.075 *p* = 0.45	*r*: 0.140 *p* = 0.155	*r*: −0.016 *p* = 0.87	*r*: −0.072 *p* = 0.47
Breast cancer–related lymphedema duration (month)	*r*: −0.096 *p* = 0.60	*r*: 0.151 *p* = 0.42	*r*: −0.010 *p* = 0.95	*r*: −0.173 *p* = 0.35	*r*: −0.115 *p* = 0.53	*r*: 0.083 *p* = 0.65	*r*: −0.035 *p* = 0.85	*r*: −0.088 *p* = 0.63
Breast cancer–related lymphedema stage	*r*: −0.140 *p* = 0.45	*r*: −0.0221 *p* = 0.91	*r*: 0.005 *p* = 0.97	*r*: −0.110 *p* = 0.55	*r*: −0.120 *p* = 0.51	*r*: 0.258 *p* = 0.16	*r*: −0.087 *p* = 0.64	*r*: 0.013 *p* = 0.94
Excess volume (mL)	*r*: 0.063 *p* = 0.73	*r*: 0.001 *p* = 0.99	*r*: 0.047 *p* = 0.80	*r*: −0.079 *p* = 0.67	*r*: −0.241 *p* = 0.199	*r*: 0.164 *p* = 0.377	*r*: 0.074 *p* = 0.69	*r*: −0.162 *p* = 0.388
Fatigue symptom scale	—	**r: 0.795** **p < 0.001**	**r: −0.397** **p < 0.001**	**r: −0.607** **p < 0.001**	**r: −0.564** **p < 0.001**	**r: −0.523** **p < 0.001**	**r: −0.403** **p < 0.001**	**r: −0.446** **p < 0.001**
Brief fatigue inventory	—	—	**r: −0.469** **p < 0.001**	**r: −0.721** **p < 0.001**	**r: −0.657** **p < 0.001**	**r: −0.487** **p < 0.001**	**r: −0.453** **p < 0.001**	**r: −0.622** **p < 0.001**

Note: p: *p* value; *r*: correlation coefficient. Bold: statistically significant.

Table 3: The result of univariate and multivariate regression analysis.

Variables	Brief fatigue inventory				Fatigue symptom scale			
	Univariate		Multivariate		Univariate		Multivariate	
	β [95% CI]	*p*	*β* [95% CI]	*p*	*β* [95% CI]	*p*	*β* [95% CI]	*p*
Age (> 50 years vs. ≤ 50 years)	0.08 [−0.41–0.58]	0.730	—	-	5.97 [−3.81–15.77]	0.229	—	—
Occupation (employed vs. unemployed)	−0.08 [−0.69–0.52]	0.783	—	—	−3.76 [−15.74–8.22]	0.535	—	—
Education level (primary vs. secondary)	0.18 [−0.35–0.72]	0.505	—	—	0.71 [−9.94–11.36]	0.895	—	—
BMI (> 25 kg/m^2 vs. ≤ 25 kg/m^2)	0.65 [0.12–1.18]	**0.015**	0.52 [0.07–0.97]	**0.022**	12.25 [1.87–22.62]	**0.021**	10.76 [0.56–20.95]	**0.039**
Survivorship duration (> 24 months vs. ≤ 24 months)	−0.37 [−0.86–0.11]	0.131	−0.10 [−0.51–0.31]	0.631	−8.82 [−18.42–0.77]	0.071	−6.54 [−15.97–2.87]	0.171
Number of lymph nodes removed (> 5 vs. ≤ 5)	−0.55 [-1.08–−0.02]	**0.042**	0.25 [−0.24–0.75]	0.319	0.71 [−9.94–11.36]	0.895	—	—
Presence of breast cancer–related lymphedema (yes vs. no)	1.52 [1.08–1.96]	< **0.001**	1.57 [1.06–2.07]	< **0.001**	12.47 [2.21–22.74]	**0.018**	10.20 [−0.02–20.43]	**0.051**

Note: p, *p* value.

Abbreviation: BMI, body mass index.

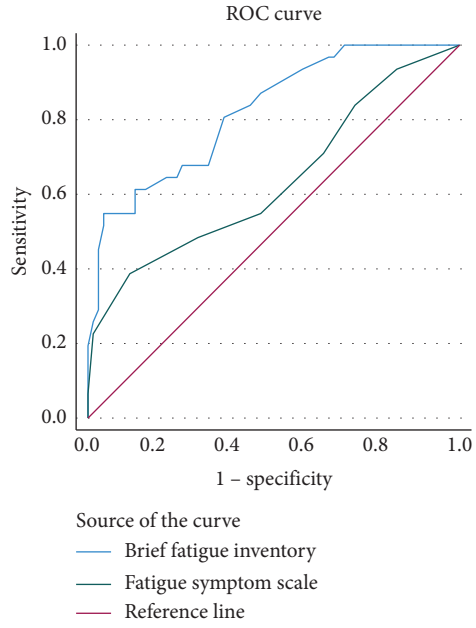

Figure 1: ROC curves showing the sensitivity and specificity of fatigue symptom scale and brief fatigue inventory in breast cancer-related lymphedema.

developing breast cancer–related lymphedema. Early identification of high-risk patients could lead to more targeted interventions and closer monitoring, potentially reducing the incidence and severity of breast cancer–related lymphedema. It is important to note that while these findings are statistically significant, further research is needed to validate the use of fatigue symptom scale and brief fatigue inventory as predictive tools for breast cancer–related lymphedema and to determine their clinical application.

CRF is a debilitating symptom among BCSs, significantly impacting their QoL and daily functioning. CRF is characterized by persistent tiredness and lack of energy, which is not proportional to recent activity and is not relieved by rest. The importance of addressing CRF in BCSs cannot be overstated, as it affects physical, emotional, and cognitive domains, leading to decreased physical performance, mood disturbances, and impaired social interactions [7]. Several risk factors contribute to the development and persistence of CRF in BCSs. These include psychological factors like anxiety, depression, and sleep disturbances which are strongly linked to CRF [15, 16]. In this study, different aspects of QoL such as physical, emotional, cognitive, and social functioning were related to CRF. However, the type of surgery, chemotherapy, radiotherapy, and other variables related to breast cancer were not significantly related to CRF. While some studies have suggested an association between certain treatments like chemotherapy and increased fatigue, results have been inconsistent and conflicting [7]. Some studies have shown higher levels of fatigue in patients treated with chemotherapy or hormonal therapy; however, others have not found a significant correlation [17, 18]. Similarly, the type of surgery or radiation therapy received has not consistently been shown to be predictive of fatigue levels [19, 20]. Longitudinal studies that track patients over time are needed to better understand how factors like treatment type, duration, and time since treatment impact fatigue in BCSs. This information is important for developing effective interventions to manage and alleviate fatigue in this population.

Moreover, lifestyle factors such as physical inactivity, poor nutritional status, and high BMI have been identified as significant contributors to CRF [21]. Obesity can lead to various comorbidities, such as cardiovascular disease, diabetes, and sleep apnea, which can further contribute to fatigue [22]. Additionally, excess body weight can increase the physical burden on the body, leading to reduced mobility and higher energy expenditure for basic activities. Interventions aimed at achieving and maintaining a healthy weight can not only alleviate fatigue but also improve overall health outcomes and reduce the risk of cancer recurrence [23]. Physical inactivity is particularly detrimental as it leads to decreased muscle strength and endurance, exacerbating feelings of fatigue. Regular physical activity has been shown to improve energy levels, reduce fatigue, and enhance overall well-being among BCSs. Engaging in moderate exercise, such as walking, swimming, or yoga, can help mitigate the effects of CRF by improving cardiovascular health, muscle strength, and mental health [24, 25].

The physical burden of breast cancer treatment, including the removal of LNs and subsequent development of lymphedema, also plays a crucial role. Lymphedema can cause discomfort and pain, further exacerbating fatigue levels. Lymphedema can cause significant discomfort and pain, manifesting as swelling, heaviness, and tightness in the affected limb. This physical discomfort can severely limit a survivor's ability to perform daily activities, leading to reduced physical activity and further deconditioning [26]. The persistent nature of lymphedema means that many survivors face ongoing challenges in managing this condition, which can contribute to chronic fatigue. Pain and discomfort associated with lymphedema can disrupt sleep, another key factor exacerbating fatigue levels [27, 28]. Additionally, the psychological impact of lymphedema should not be underestimated. The visible changes and physical limitations imposed by lymphedema can lead to emotional distress, anxiety, and depression, which are known to be closely linked with increased fatigue [29]. The need for constant self-management, including wearing compression garments, performing manual lymphatic drainage, and avoiding activities that could exacerbate swelling, adds to the emotional and physical burden on survivors. Moreover, the development of lymphedema often necessitates ongoing medical care and interventions, which can be time-consuming and costly. Frequent visits to healthcare providers for monitoring and treatment, coupled with the need for specialized therapies, can contribute to the overall fatigue experienced by survivors. The financial burden and the need for constant vigilance can add to the stress and fatigue experienced by BCSs [30].

Effective management of lymphedema may help reduce physical discomfort, potentially alleviating some aspects of fatigue. Conversely, addressing fatigue through behavioral and

psychological interventions might help survivors better manage their lymphedema. Although a variety of interventions for breast cancer–related lymphedema management have been investigated, complete decongestive therapy (CDT) remains the standard management of lymphedema [11, 31]. CDT typically consists of four components: manual lymphatic drainage, compression therapy, exercise, and skincare. Each of these components contributes to reducing lymphedema and its associated symptoms; however, there is limited evidence regarding its impact on CRF among women with breast cancer–related lymphedema. Two recent interventional studies did not show any significant improvement in fatigue following CDT among women with breast cancer–related lymphedema [32, 33]. On the other hand, a recent study has reported a significant reduction of sleep disturbances and CRF among BCSs with lymphedema [34]. Nevertheless, more interventional studies are needed to investigate whether by effectively reducing swelling, pain, and discomfort, CDT helps alleviate CRF. Addressing these risk factors through comprehensive survivorship care plans, which include physical rehabilitation, psychological support, and lifestyle interventions, is essential for improving the QoL in BCSs.

Although this study is among a few reports on the relationship between breast cancer–related lymphedema and CRF, some limitations need to be pointed out. This was a cross-sectional study with a limited number of participants. Future studies with prospective design and a larger population will bring more understanding to this topic. Also, the assessment of CRF was based on two brief questionnaires. Although EORTC QLQ-C30 and brief fatigue inventory have been successfully used in CRF research, we were unable to study specific aspects of CRF such as physical, emotional, and cognitive domains.

5. Conclusion

Higher BMI, number of dissected LNs, and breast cancer–related lymphedema are associated with CRF. Also, while physical function was related to worse fatigue scores, the severity of breast cancer–related lymphedema had no significant correlation with CRF. Moreover, CRF may be associated with the presence of breast cancer–related lymphedema among BCSs. The significant associations found in both univariate and multivariate analyses suggest further research and clinical intervention aimed at improving patient outcomes through targeted management of lymphedema. Future studies need to investigate proper interventions to reduce CRF among women with breast cancer–related lymphedema.

Nomenclature

AUC	Area under the curve
BCSs	Breast cancer survivors
BMI	Body mass index
CDT	Complete decongestive therapy
CRF	Cancer-related fatigue
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer Quality of Life Core Questionnaire version 3.0
LNs	Lymph nodes
p	p value
QoL	Quality of life
r	Correlation coefficient
ROC	Receiver operating characteristic
SD	Standard deviation

Data Availability Statement

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

Ethics Statement

This study was conducted and approved by the Motamed Cancer Institute (ID: 4021721).

Consent

Researchers explained the study's purpose of this study to all participants. Written informed consent was obtained from all participants included in the study.

Conflicts of Interest

The authors declare no conflicts of interest.

Author Contributions

M.S., S.S., and H.Y. contributed to writing the first draft and collecting data. Also, M.S. and H.Y. performed statistical analysis. A.M. and F.A. contributed to the review and validation of the first draft and its editing, while Z.S. administrated the project and supervised the process. All authors reviewed and approved the final manuscript.

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