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Cancer-related fatigue in breast cancer patients after surgery: a multicomponent model using partial least squares—path modeling

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Abstract

***Objective*: The aim of this study is to examine factors contributing to cancer-related fatigue (CRF) in breast cancer patients who have undergone surgery.**

***Methods*: Sixty women (mean age: 50.0) completed self-rated questionnaires assessing components of CRF, muscular and cognitive functions. Also, physiological and subjective data were gathered. Data were analyzed using partial least squares variance-based structural equation modeling in order to examine factors contributing to CRF after breast surgery.**

***Results*: The tested model was robust in terms of its measurement quality (reliability and validity). According to the structural model results, emotional distress ($\beta = 0.59$; $p < 0.001$), pain ($\beta = 0.23$; $p < 0.05$), and altered vigilance ($\beta = 0.30$; $p < 0.05$) were associated with CRF, accounting for 61% of the explained variance. Also, emotional distress ($\beta = 0.41$; $p < 0.05$) and pain ($\beta = 0.40$; $p < 0.05$) were related to low physical function and accounted for 41% of the explained variance. However, the relationship between low physical function and CRF was weak and nonsignificant ($\beta = 0.01$; $p > 0.05$).**

***Conclusion*: Emotional distress, altered vigilance capacity, and pain are associated with CRF in postsurgical breast cancer. In addition, emotional distress and pain are related to diminished physical function, which, in turn, has no significant impact on CRF. The current model should be examined in subsequent phases of the treatment (chemotherapy and/or radiotherapy) when side effects are more pronounced and may lead to increased intensity of CRF and low physical function.**

Introduction

Cancer prevalence has increased in recent years. Particularly, breast cancer is the most prevalent type of cancer in Europe with 53,000 new cases per year [1]. A frequent symptom experienced by patients during breast cancer treatment is fatigue. Cancer-related fatigue (CRF) is usually associated with chemotherapy and radiotherapy but may affect patients even after surgery only [2,3]. Nevertheless, only few studies have focused on the effect of surgery on CRF in breast cancer patients and the factors associated [3,4], which constitutes a gap in research.

Factors associated with cancer-related fatigue

Cancer-related fatigue is defined as a distressing, persistent, and subjective sense of physical, emotional, and/or cognitive tiredness or exhaustion [2]. The perception of fatigue results from the dysregulation of physiological, biological, and psychological systems. Thus, CRF is a multidimensional outcome including physical, behavioral, cognitive, sensory, and affective components [5].

Under this perspective, fatigue may be caused by cancer, its treatments, and other individual or context-related factors. The National Comprehensive Cancer Network (NCCN) pointed out associated factors such as diminished physical performance, emotional distress, pain, anemia, sleep disturbances, nutritional disorders, and comorbidities [2]. Thus, understanding CRF's complexity and pathophysiology requires including factors beyond the subjective perception [6].

Although CRF is more prevalent during chemotherapy and radiotherapy [7,8], it can occur after surgery alone [3]. Some studies have reported that mastectomy may cause more CRF and more disruption in activity levels than other less invasive surgery procedures [9].

Besides the type of treatment, depression and anxiety have been consistently associated with CRF [9] as well as pain and sleep disturbances [3]. In fact, some authors argue that depression, pain, and insomnia should be considered as part of a symptom cluster including CRF, given that they may occur simultaneously and influence each other [10].

Anemia is also associated to CRF [11]. Cancer and its treatment can directly cause and exacerbate anemia [12]. Although more frequent during chemotherapy [13], anemia may appear after surgery alone [14]. However, results are inconsistent regarding the relationship between anemia and CRF.

Another factor associated with fatigue is reduced physical activity. Physical inactivity has shown to increase CRF by inducing detraining and muscle atrophy [15], whereas keeping physically active during treatment has shown to diminish CRF [16,17]. CRF due to treatment may be aggravated by diminished physical activity and lead to reduced physical function, diminished ability to work and to engage in social and leisure activities [18]. Evidence shows that higher levels of fatigue are associated with low physical function (LPF) [19]. Finally, appetite loss was shown to be higher in women after breast cancer surgery than in healthy women [20]. Appetite loss after surgery, especially for proteins intake, is also associated with fatigue at 1-year follow-up [21].

Beyond NCCN's model, there is also evidence that cognitive functioning is related to CRF, especially direct attention capacity [22]. Direct attention is constantly required to account for the several demands (informational, affective, and behavioral) and tasks (treatment activities or self-care) that patients face when dealing with life stressors related to cancer. Because this capacity is limited, it can be overused when stress increases, leading to cognitive fatigue [23]. Cognitive fatigue may occur after surgery or even before any treatment [22].

Postoperative cancer-related fatigue

As mentioned, several studies have assessed the impact of contributing factors on CRF in breast cancer [9,17,24]. However, most have focused on the effects of chemotherapy and radiotherapy [7,8]. Only one study [16] showed that diminished physical activity, depressive mood, impaired sleep, rest, and fatigue 1 year before diagnosis are important contributors to severe CRF, even before treatment. Surprisingly, few studies have assessed factors associated with postoperative fatigue such as psychological distress [4] and sleep problems [3].

Cancer-related fatigue may increase over time, beginning with diagnosis and escalating with each new treatment, negatively affecting several aspects of life [25]. Patients experiencing high levels of postoperative CRF reported more severe CRF after adjuvant treatments [26], especially after mastectomy [8]. Thus, efforts should be directed at understanding CRF contributors in the post-surgical period in order to propose prevention and early treatment strategies.

In view of the abovementioned contributing factors to fatigue, a comprehensive model was derived (Figure 1) and tested. This exploratory study aimed to identify how these factors related to CRF in breast cancer patients who had undergone surgery only and to examine how they related to each other.

Method

Participants

Sixty-two patients attending the Montpellier Cancer Institute in France were invited to participate. All were diagnosed with breast cancer and had undergone surgery. Exclusion criteria were metastatic disease, second primary tumors, contraindication to practice moderate physical activity, contraindication to adjuvant chemotherapy or radiotherapy, pregnancy or breast feeding, inability to attend or to comply with treatments or follow-up, and inability to understand trial instructions.

Two patients did not complete the physical evaluation because of their physical condition. Finally, cross-sectional data from 60 patients were analyzed. Clinical and

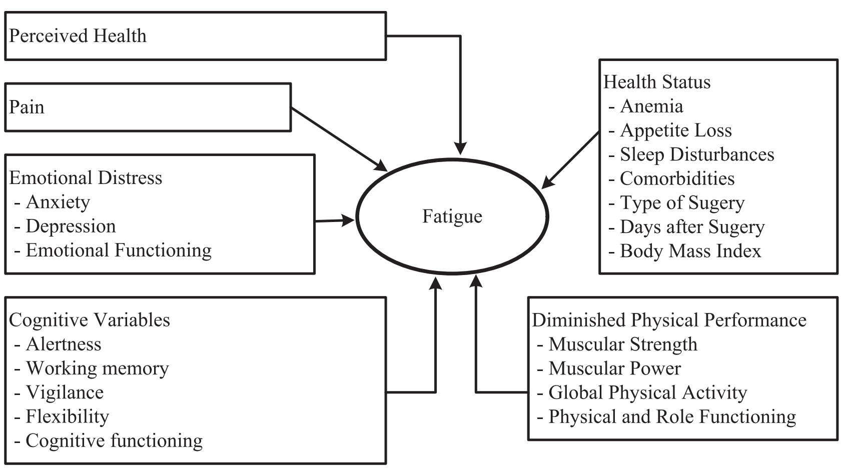

Figure 1. Examined contributors to cancer-related fatigue (model 1)

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sociodemographic data are reported in Table 1. Data regarding fatigue, emotional distress, physical activity level, muscular function, and cognitive function are presented in Table 2.

Procedure

A French ethical committee approved the study. After signing the informed consent, participants completed questionnaires assessing fatigue, emotional distress, and quality of life (QoL) and performed muscular and cognitive tests. Physiological and anthropometrical data were collected (e.g., weight, height, and hemoglobin concentration). All assessments were performed by one researcher according to standardized conditions following the instruments' manual guidelines. Blood analyses were conducted by specialized laboratories and delivered to the hospital.

Data were analyzed using partial least squares variance-based structural equation modeling (PLS-SEM) in order to model for simultaneous relationships among multiple constructs. PLS-SEM is intended to test for causal-predictive analysis in situations of high complexity but low theoretical information. It allows examination of complex relationships between latent variables (LVs), is less restrictive in terms of sample size, and provides a measurement model and a structural model [27]. PLS-SEM can be used in exploratory and confirmatory studies and is particularly suited for prediction [28]. Smart PLS (version 2.0 beta) statistical software was used for the data analysis [29].

Measures

Multidimensional Fatigue Inventory

The Multidimensional Fatigue Inventory (MFI) questionnaire is a 20-item self-report instrument developed by Smets, Garssen [30] to measure fatigue. The validated French version includes four dimensions: general fatigue, mental fatigue, reduced motivation, and reduced activity. Cronbach's alpha coefficient for the overall MFI was 0.93 and ranged from 0.68 to 0.92 for each subscale [31].

Table 1. Demographic and clinical data ($n = 60$)

Measures	Mean (standard deviation)
Age (years)	49.95 (10.03)
Body mass index (kg/m2)	25.03 (5.95)
Days after surgery	34.53 (11.44)
	n (%)
Cancer stage	
I	2 (3.2)
II	34 (54.8)
III	25 (40.3)
Surgery type	
Tumorectomy	21 (35)
Quadrantectomy	31 (51.7)
Mastectomy	8 (13.3)
Years of education	
<9	10 (16.7)
9–12	15 (25)
>12	35 (58.3)
Marital status	
Single with children	6 (10)
Couple without children	5 (8.3)
Couple with children	49 (81.7)

Attentional Performance Test [32]

Subtests of alertness (reaction time (RT), number of omissions, and errors), vigilance (RT, number of omissions, and errors), flexibility (performance-index, calculated using the median score of the RT, and the number of errors), and working memory (number of omissions, number of errors, and RT) were used to assess mental fatigue.

Global Physical Activity Questionnaire

Global Physical Activity Questionnaire is a 16-item self-report instrument designed to quantify physical activity.

Table 2. Descriptive statistics of study variables ($N = 60$)

Variable	Mean	Standard deviation
Physical/physiological evaluation		
Hemoglobin	12.89	1.02
Physical activity (METs)	1515.15	1855.79
Sit-to-stand (30 s)	16.26	4.64
Myotest muscular strength (%)	104.11	14.16
Myotest muscular power (%)	107.95	16.76
MFI-20		
Total score	40.65	14.90
Mental fatigue	10.91	4.70
Reduced physical activity	6.26	2.99
Reduced motivation	3.56	2.13
General fatigue	19.92	8.00
HADS		
Depression	3.95	3.30
Anxiety	9.05	3.50
EORTC-QLQ C30		
Cognitive function	88.33	16.89
Pain	23.06	23.98
Sleep problems	37.78	35.50
Fatigue	27.96	21.21
Appetite loss	8.89	16.08
Physical function	91.22	8.37
Role function	85.28	20.14
TAP		
Vigilance		
RT	568.72	93.23
Omissions	0.50	0.98
Errors	1.18	2.17
Working Memory		
RT	600.60	132.99
Errors	2.07	3.22
Omissions	3.00	2.44
Alertness		
Without signal (RT)	259.48	40.04
With signal (RT)	258.02	46.44
Flexibility	5.98	7.59

METs, Metabolic Equivalent of the Task; MFI, Multidimensional Fatigue Inventory; HADS, Hospital Anxiety and Depression Scale; EORTC-QLQ C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; TAP, Attentional Performance Test; RT, reaction time.

Intensity of physical activity is expressed in the Metabolic Equivalent of the Task, entailing the energetic cost of physical activities. This test's reliability and validity were confirmed [33].

Muscular test: vertical jump

Force and power were measured using the Myotest, a valid and reliable method for the assessment of vertical jumps [34] that has been used to assess fatigue in healthy individuals and athletes [35]. After warm-up, individuals are required to position both hands on the hips, keep their feet apart, and flex their knees at a 90° angle. At the signal, they are asked to perform 10 successive vertical jumps. The total score is determined by the ratio of the last three jumps over the first three jumps and represents the percentage of muscular resource (force and power) maintained during the task.

Muscular test: sit-to-stand

This test is an indirect and reliable measure of the lower limbs' strength. Patients are asked to position both hands on the hips and then perform the maximum flexion–extension to a set at a leg/thigh angle of 90°. The performance is expressed in number of repetitions/30 s. This functional test has been used to assess strength and fatigue in elderly people with cancer [17].

Hospital Anxiety and Depression Scale

Hospital Anxiety and Depression Scale is a 14-item self-report questionnaire commonly employed to assess anxiety and depression using a 4-point Likert scale [36]. The validated French version of the scale was used [37].

The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire

The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire is a 30-item self-report questionnaire designed to measure cancer-related QoL. It incorporates nine scales: functional domain scales (physical, role, cognitive, emotional, and social), symptom scales (fatigue, pain, nausea, and vomiting), and global health and QoL scale [38]. The French version was used.

Analyses

All variables were included in the PLS-SEM analysis as explanatory variables. The confidence intervals of the PLS-SEM coefficients were obtained by cross-validation, and the Q^2 index was calculated to measure the predictive power of the model. The best predictive model was obtained by maximizing the Q^2. PLS-SEM was performed following model 1 (Figure 1). It accounted for most contributors proposed by the NCCN model and included the aforementioned cognitive variables. First, all variables were included as CRF predictors. Bootstrapping was performed and only indicators, LVs, and paths that reached the significance level of 0.05 were retained. Then, the PLS algorithm was run, and indicators with loadings higher than 0.6 were retained.

Relations between LVs were examined. LVs, such as emotional distress and CRF, were created using parceling [39], considering that HADS and MFI are widely used, reliable, valid, and their dimensional structure has been extensively examined.

Results

The measurement model

Reliability results are given in Table 3. The measures are robust in terms of their internal consistency and reliability as indexed by the composite reliability. The composite reliability of the measures ranges from 0.77 to 0.94, exceeding the recommended threshold value of 0.70 [40]. Additionally, the Average Variance Extracted exceeded 0.50 for each measure, consistent with recommendations [41].

The discriminant validity of the measure scales are also reported in Table 3. The square roots of the Average Variances Extracted (shown in the matrix diagonals) are greater in all cases than the off-diagonal elements in their corresponding row and column, supporting discriminant validity at the LV level [28].

Convergent validity was tested by extracting the factor and cross-loadings of all indicator items to their respective LV (Table 4). All items loaded on their respective construct from a lower bound of 0.62 to an upper bound of 0.96 and more highly on their respective construct than on any other [28]. Furthermore, each item's factor loading on its respective construct was significant for all indicators

Table 3. Assessment of the measurement model and discriminant validity of variable constructs

Variable constructs	Composite reliability	AVE	1	2	3	4	5
1. Altered vigilance	0.77	0.63	**0.79**				
2. Distress	0.82	0.70	0.06	**0.84**			
3. CRF	0.87	0.63	0.37	0.67	**0.79**		
4. LPF	0.84	0.63	0.13	0.51	0.47	**0.80**	
5. Pain	0.94	0.89	0.12	0.25	0.42	0.50	**0.94**

AVE, Average Variance Extracted; CRF, cancer-related fatigue; LPF, low physical function.

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Table 4. Factor loadings (bolded) and cross-loadings

	Altered vigilance	Distress	CRF	LPF	Pain	Outer model T-statistics*
Reduced activity	0.23	0.39	**0.76**	0.35	0.59	0.001
Mental fatigue	0.32	0.59	**0.80**	0.31	0.16	0.001
General fatigue	0.31	0.63	**0.91**	0.61	0.46	0.001
Reduced motivation	0.30	0.50	**0.69**	0.15	0.09	0.001
HADS depression	0.16	**0.89**	0.66	0.46	0.20	0.001
HADS anxiety	-0.11	**0.77**	0.43	0.39	0.23	0.001
Pain 1 (QLQ 9)	0.03	0.23	0.36	0.38	**0.93**	0.001
Pain 2 (QLQ 19)	0.17	0.24	0.41	0.55	**0.96**	0.001
Loss of function 1 (QLQ 1)	0.19	0.29	0.37	**0.62**	0.41	0.01
Loss of function 2 (QLQ 6)	0.08	0.37	0.37	**0.91**	0.46	0.001
Loss of function 3 (QLQ 7)	0.05	0.54	0.38	**0.83**	0.34	0.001
Vigilance—reaction time	**0.69**	0.13	0.23	−0.01	−0.09	0.05
Vigilance—errors	**0.88**	−0.01	0.34	0.18	0.22	0.001

CRF, cancer-related fatigue; LPF, low physical function; HADS, Hospital Anxiety and Depression Scale; QLQ, Quality of Life Questionnaire.
*Significance level.

($p < 0.05$) The loadings, cross-loadings, and significant T-statistics support the convergent validity of these indicators as representing distinct LVs.

The structural model

Figure 2 shows the structural model's results. The R^2 values were 0.61 for CRF and 0.41 for LPF, respectively, indicating substantial and moderate-to-high explained variances [27]. All beta path coefficients were positive in the expected direction and statistically significant ($p < 0.05$). *Emotional distress*, *pain*, and *altered vigilance* had a significant influence on *CRF*. Also, emotional distress and pain had a significant influence on *LPF*. However, the relationship between LPF and CRF was weak and nonsignificant ($\beta = 0.01$; $p > 0.05$). Finally, altered vigilance did not influence LPF ($\beta = 0.07$; $p > 0.05$). The effect sizes of each path were calculated through F^2 values and were found to be moderate to substantial (Table 5).

Sociodemographic (marital status and years of education) and clinical variables (type of surgery and body mass index (BMI)) were included in the model, but their contribution was nonsignificant neither to fatigue nor to LPF ($p > 0.05$). Although age was not related to LPF ($p > 0.05$), it was significantly associated with fatigue ($\beta = 0.213$; $p < 0.05$) but had no significant impact on the explained variance of fatigue.

The model's predictive power was examined by calculating Q^2 indexes of CRF ($Q^2 = 0.35$) and LPF ($Q^2 = 0.25$). In both cases, results exceeded the recommended threshold value ($Q^2 > 0$), indicating an adequate predictive validity [27]. Although controversial, the goodness of fit index was derived (GoF = 0.60), indicating the model's moderate-to-good fit [27].

Discussion

The study examines contributing factors to fatigue and how these factors relate to each other in breast cancer patients who have undergone surgery only. A first model including all variables was tested (model 1, Figure 1). Variables showing no significant contribution were removed,

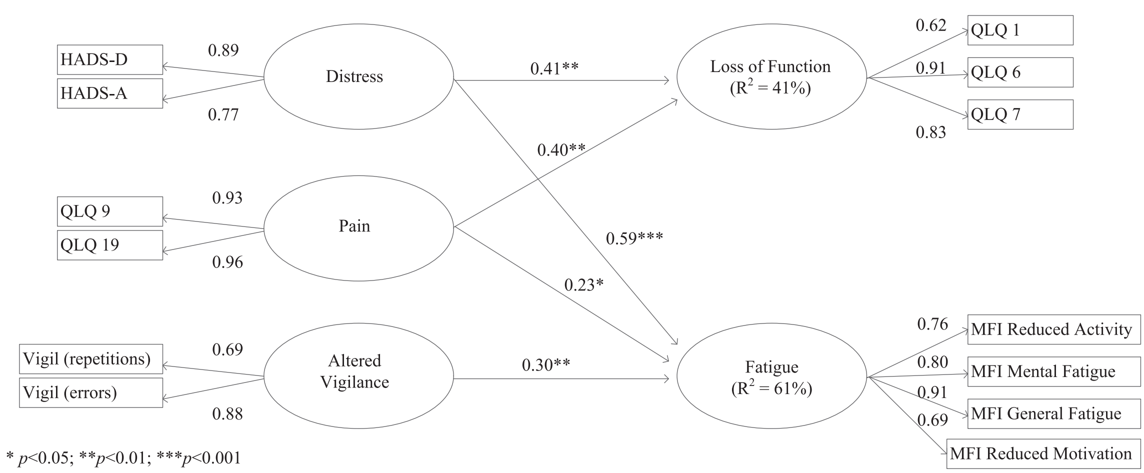

Figure 2. Structural model results (model 2)

Table 5. Effect sizes of the structural model paths

Paths	F2	Magnitude of the effect
Distress on CRF	0.72	Substantial
Pain on CRF	0.10	Moderate
Altered Vigilance on CRF	0.23	Moderate to high
Distress on LPF	0.26	Moderate to high
Pain on LPF	0.23	Moderate to high

CRF, cancer-related fatigue; LPF, low physical function.

leading to a more restrictive model (model 2, Figure 2). According to the results, CRF is associated with levels of emotional distress (depression and anxiety), pain, and diminished vigilance. Emotional distress and pain are also related to levels of LPF. However, LPF was not associated with CRF.

These results support previous findings showing that emotional distress has a significant impact on perceived CRF [9,42]. Furthermore, our findings indicate that fatigue also results from sustained levels of anxiety [9].

Likewise, pain influences fatigue levels, corroborating previous findings that show how pain in breast cancer patients after surgery is a common symptom associated with fatigue [43]. Pain and fatigue have been shown to be reciprocally related, suggesting the presence of a symptom cluster [44]. Although the current study did not assess the impact of CRF on pain, other studies have provided evidence in favor of a symptom cluster [10].

Pain and anxiety together have been found to correlate with fatigue in cancer patients prior to surgery and to contribute to postoperative fatigue [45]. This finding, along with our results, suggests that the synergy of pain and emotional distress relates to fatigue in patients undergoing surgery.

After a cancer diagnosis, the ability to cope with stress may be affected because of the multiple demands that patients must deal with, leading to overuse of the capacity of direct attention, necessary to solve problems, to carry out necessary tasks, and to manage fatigue [22]. Mental fatigue, a reduction in performance during tasks involving excessive and sustained mental effort, was examined through the vigilance task. The inverse relationship we found between vigilance and CRF has been previously reported [23,46]. Additionally, the tasks assessing working memory, flexibility, and alertness require less cognitive effort than the vigilance task, probably explaining why only vigilance entered the model [47]. Future studies assessing mental fatigue should use tasks involving more sustained effort.

Emotional distress and pain were also related to LPF. Three indicators accounted for LPF: difficulty performing strenuous physical efforts, daily tasks, and hobbies and leisure activities. Pain resulting from breast cancer surgery has shown to impact on daily activities such as household chores, carrying, and lifting [48]. Emotional distress was found to affect physical and role functioning [49] and has been implicated in both the development of fatigue and in physical dysfunction [50]. Additionally, pain and psychological distress altogether may contribute to functional impairment in acute and chronic illnesses [50].

The lack of association between LPF and fatigue was unexpected, and although the aim of the study was to examine predictors of fatigue alone, we decided to leave LPF given its relevance within the model. Moreover, physical performance, perceived health, and health status showed no influence on fatigue levels in this sample. Regarding physical performance, patients indicated adequate levels of physical functioning and health status. Hence, a particular level of diminished physical or health status may be required to constitute a CRF contributor. A diminished physical performance may result from chemotherapy and/or radiotherapy [51,52] but not from surgery alone [53]. It has been found that few patients undergoing breast surgery report severe problems in accomplishing household chores, self-care and grooming activities, and physical activities [53]. This lack of association may result from the tests used to assess muscular force and strength. The sit-to-stand test might not be sensitive enough to detect muscle fatigue, because it is commonly used with elderly patients [54], whereas our sample consisted of middle-aged women. Additionally, 10 repetitions in the vertical jump test may be insufficient to detect a decline in the muscles' force.

Medical variables such as type of surgery, days after surgery, number of comorbidities, hemoglobin level, appetite loss, sleep disturbances, and BMI had no effect on CRF or on physical functioning. Although most of these variables are linked to fatigue in breast cancer patients, women in our sample had generally adequate physical health status and most underwent conservative surgery. Perhaps, at this stage of the illness and treatment, psychological factors have a stronger contribution to fatigue than physical factors. Some studies suggest that certain symptoms following breast cancer surgery might be independent of the type of surgery [55] and can derived from factors others than cancer treatment-related variables [56].

As mentioned before, no significant levels of appetite loss or anemia were reported by the women in this study. Both problems are more common adverse effects during chemotherapy and radiotherapy [13,57] than after surgery only [20]. Also, women presented normal BMI scores. BMI is thought to predict CRF when it is equal to, or higher than, 25 kg/m^2 [24], probably explaining why this variable was not retained.

Sleep problems were not reported by women in our study, which may also explain why this factor was not retained. Previous studies have reported sleep problems even before other adjuvant treatments [3]. Prevalence estimates vary widely depending on the population under study, the illness trajectory, and assessment issues [58].

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Sleep disorders in breast cancer have been linked to fatigue and emotional distress [59]. However, it is possible that sleep disorders have not yet fully developed at this phase of the treatment. Moreover, methodological issues might explain our results. Objective and subjective measures are commonly employed to examine sleep problems, with the former being more accurate [3]. In our study, only subjective measures derived from the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire were used, which might not be sensitive enough to detect low-severity sleep problems.

This study presents some limitations. First, its cross-sectional nature does not allow concluding on causal evidence. Second, the sample size may have influenced the results by limiting testing for more complex relationships. Third, more robust physiological and objective measures should be used in future studies to fully understand the development and contribution of physical factors to fatigue and their relation with psychological ones.

In summary, our findings indicate that emotional distress, altered vigilance capacity, and pain experience were associated with CRF in breast cancer women who have undergone surgery. Emotional distress and pain also influence LPF, which, in turn, does not impact CRF. At this phase of the treatment, physical and physiological consequences might not be severe enough to impact on fatigue perception, whereas emotional distress seems to be more significant. Distress may be related to recent diagnosis [42], surgery outcomes in terms of pain [44], physical and body image changes [60], and/or the immediacy of chemotherapy and other cancer-related life stressors [23]. Future research should further explore these aspects. We recommend this model be retested in subsequent phases of the treatment, when side effects are more pronounced and additional physiological and biological aspects are involved, probably leading to increased levels of CRF and LPF.

Our results suggest that efforts to improve these factors may contribute to relieve CRF after surgery and may also prevent increased levels of CRF during subsequent treatment phases. In order to preserve the well-being during the entire treatment, to maintain a healthy life-style, and to avoid fatigue and deconditioning, patients should receive support and instructions on how to better cope with emotional distress, cognitive overload, and pain.

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