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**Title**

Health status among long-term breast cancer survivors suffering from higher levels of fatigue: A cross-sectional study

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**Abstract**

**Purpose:** The aims of this study were to evaluate the health status of long-term breast cancer survivors (LTBCS) suffering from higher levels of fatigue, to highlight their needs, and to establish the key points of intervention support programs.

**Methods:** A cross-sectional observational study was conducted at the Sport and Health Joint University Institute (iMUDS) between September 2016 and July 2017 with 80 LTBCS that were classified into non-fatigued (≤3.9) or fatigued (≥4) according to the Piper Fatigue Scale (PFS) total score. The instruments used were the European Organization for Research and Treatment of Cancer Core 30 and its breast cancer (BC) module, the Visual Analog Scale (VAS), the Brief Pain Inventory (BPI), the Scale for Mood Assessment (EVEA), the International Fitness Scale (IFIS), and the Charlson Comorbidity Index.

**Results:** The analysis revealed that 41.2% of LTBCS were considered moderately fatigued and showed significantly higher levels for the categories of ‘nausea and vomiting’ (P=.005), ‘pain’, ‘dyspnea’ and ‘insomnia’ (P<.001), ‘appetite loss’ (P=.002), ‘financial difficulties’ (P=.010), ‘systemic therapy side effects’ (P<.001), ‘breast symptoms’ and ‘arm symptoms’ (P=.002), and ‘upset by hair loss’ (P=.016). In addition, LTBCS presented significantly higher levels of pain in the affected and non-affected arm, ‘sadness-depression’, ‘anxiety’, ‘anger/hostility’ (All: P<.001), and lower general physical fitness (P<.001). The rest of the variables did not show significant differences.

**Conclusion:** LTBCS suffering from higher levels of fatigue had lower QoL, higher level of pain, worse mood state, and lower physical fitness.

**Keywords**

Fatigue, Breast Cancer, Long-term survivorship, Quality of life

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**INTRODUCTION**

More effective therapies and early detection have led to an increased number of those transitioning from breast cancer (BC) patient to survivor [1]. Hence, BC survivorship has become a phase of continuous care of the cancer patient. Currently, the definition of Long-term breast cancer survivor (LTBCS) refers to someone who remains alive ≥5 years beyond cancer diagnosis [2]. In this sense, LTBCS must deal with an increase in the number of second tumors, recurrences, and physical and psychosocial side effects which may remain many years after the completion of the treatment or even for life. Among these ongoing sequels, one of the most common and debilitating is cancer-related fatigue (CRF) [3].

The pathophysiology of CRF is not fully elucidated. Previous studies have proposed various mechanisms of CRF pathophysiology including: proinflammatory cytokines [4], hypothalamic-pituitary-adrenal-axis disruption [5], or a defect in adenosine triphosphate [6]. Notwithstanding, recent research has found that distinct phenotypic characteristics and polymorphisms, diurnal cortisol dysregulation, or mitochondrial damage could also contribute towards the disruption of normal neuronal functions and result in the symptom of CRF [7-9]. Furthermore, CRF could appear during or after treatment and not only could it affect quality of life (QoL) [10], but it could also cause physical, emotional, and cognitive impairment [11]. Moreover, it is generally associated with factors such as comorbidities [12], reduced levels of physical activity [13], and loss of muscle mass or strength [3]. Thus, CRF is considered a multidimensional syndrome. Despite the fact that it is reported by a substantial majority during their initial treatment (surgery, radiation, and/or chemotherapy) [14], recent studies highlight CRF as a significant problem that may persist even 10 years after treatment for 1/3 of LTBCS [15] and that may increase the risk of rating low work ability by almost 11 times in comparison with cancer-free women [16].

Several studies have already highlighted how QoL, physical, emotional, and cognitive impairment could be related to CRF in LTBCS 5 years after the diagnosis [10, 12-14]. However, although studies have addressed these fatigue-related variables previously, there is still a need for more evidence in LTBCS. Interestingly, our research team found that 50% of BC survivors reported moderate fatigue within one year after their treatment, which was, besides, associated with higher levels of pain, depression, and lower body image [17]. Hence, it would indeed be very relevant to know if what was found in early survivorship is similar to the data obtained 5 years after the diagnosis, and thus to know the possibilities of approaching LTBCS.

Given the above, the aims of this cross-sectional study were to evaluate the health status of LTBCS suffering from higher levels of fatigue, to highlight their needs, and to establish the key points of intervention support programs.

**METHODS**

**Design**

Of 149 eligible LTBCS recruited from the University Hospital Complex of Granada between September 2016 and July 2017, we finally conducted a cross-sectional study with a cohort of 80 LTBCS because of the following reasons: being busy (n=25), living far (n=30), health (n=8), and other reasons (n=5). The sample size was estimated based on a similar previous study [13] in which 34% of the participants showed significant fatigue between 5-10 years after diagnosis. Considering the 149 LTBCS and a power of 80% (5% of significance), 75 BC survivors were needed in this study. Considering the potential loss of 5%, 79 participants were recruited.

LTBCS had to meet the following inclusion criteria: 1) being above the age of 18 and 2) having passed a period equal to or greater than 5 years after the diagnosis of stage I-IIIa BC at the time of the initial diagnosis. The participants who were unable to read or understand the assessments were excluded from the study. Those who were interested in participating were summoned by telephone to receive complete information on the project and answer any doubts. Later, in person, a physiotherapist member of the research team with more than three years of experience received the participants and they signed the written informed consents. The evaluations were carried out with a duration of approximately 30 minutes. The participants were divided into two groups following clinically significant fatigue criteria: non-fatigued (≤3.9) or fatigued (≥4), according to the value obtained for the *Piper Fatigue Scale (PFS)* total score [18-20]. Ethical approval for the study was granted by the Biomedical Research Ethical Committee of Granada (CEIm) (1038-N-16 I.P), and the study followed the Helsinki Declaration for biomedical research (14/2017) [21].

**Variables**

All the LTBCS were supervised during the assessment by an investigator of the research team with more than three years of experience in the evaluation of oncological patients.

***Cancer-Related fatigue***

The Spanish version of the PFS is a validated self-reported scale to assess CRF. It contains 22 items, and the scores range from 0 to 10 (0=none, 1-3=mild, 4-6=moderate, 7-10=severe) including four dimensions of subjective fatigue: ‘behavioral/severity’, ‘affective meaning’, ‘sensory’, and ‘cognitive/mood’ [18]. A total fatigue score is also calculated and higher scores indicate greater fatigue. A minimally important difference (i.e., a change of 2 points) on the PFS total score represents a clinically significant improvement in fatigue [18]. This tool has demonstrated a high reliability in BC survivors (Cronbach’s α .86) [22].

***Quality of life measures***

The *European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30)* Spanish version 3.0 was used to measure the QoL differences in LTBCS. The EORT QLQC-30, which has shown reliability in BC [23], includes both multi-item scales and single-item measures. They are composed of three symptom scales, five functional scales, a global health status scale, and six single items. The scores are transformed linearly to obtain a range of score from 0 to 100, with higher scores meaning a great response level. The *European Organization for Research and Treatment of Cancer Breast Cancer-Specific Quality of Life Questionnaire (EORTC QLQ-BR23)* is a BC module of EORTC QLQ-C30, and it contains 23 items assessing ‘body image’, ‘sexual functioning’, ‘future perspective’, ‘symptoms’, and ‘treatment side effects’. All of the items are rated on a four-point scale from 1 (not at all) to 4 (very much). The scoring procedure of the BR23 module is the same as that of EORTC QLQ-C30, and it has shown adequate reliability (Cronbach’s alpha ranged between .46 and .94) [24].

***Pain measures***

*The Visual Analog Scale (VAS)* is a linear scale with a length of 10 cm for subjective pain estimation. It ranges from 0 at one end (no pain) to 10 at the other end of the scale (the worst possible pain imaginable). Participants mark the level of pain that they feel in that moment for both arms. The VAS has been widely used and has previously shown to be a reliable and valid instrument for assessing pain with an intraclass correlation coefficient (ICC) 0.97 [25].

The Spanish version ofthe *Brief Pain Inventory (BPI)* abbreviated form contains the front and back body diagrams, four pain intensity/severity items, and seven pain interference items with daily activities. ‘Pain severity’ and ‘pain interference’ are obtained from mean scores. In the version we used, the ratings for pain were made for the previous 24 hours. The reliability between dimensions was good (Cronbach’s alpha range between .87 and .89) [26].

***Mood measures***

The Spanish version of the *Scale for Mood Assessment (EVEA)* evaluates four moods through 16 items (adjectives referring to mood states) divided into four categories: ‘sadness-depression’, ‘anxiety’, ‘anger/hostility’, and ‘happiness’. Item scores are evaluated with Likert scales ranging from 0 to 10, and the values per category are obtained from mean scores. The four EVEA categories have shown good reliability (Cronbach’s alpha range between .88 and .93) to assess positive and negative moods of a person at any moment [27].

***Fitness condition***

The Spanish version of the *International Fitness Scale (IFIS)* is a self-reported physical fitness questionnaire that includes ‘general physical fitness’, ‘cardiorespiratory fitness’, ‘muscular strength’, ‘speed/agility’, and ‘flexibility’ in comparison with a friend’s physical fitness. It is scored on a 5-point Likert-scale with five response possibilities (very poor, poor, average, good, and very good). The reliability of this test was Cronbach’s alpha .80 [28].

***Comorbidities measures***

The Spanish version of the *Charlson Comorbidity Index* is a method to predict mortality by classifying comorbid conditions. It consists of 17 comorbidities, with two subcategories. These comorbidities range from 1 to 6 for mortality risk and disease severity, which can be translated into a total score. The prediction of mortality in short follow-ups (˂ 3 years) is 0 points (12% mortality per year), 1-2 points (26%), 3-4 points (52%), and ≥ 5 points (85%). In long-term follow-ups (˃ 5 years) the prediction of mortality should be corrected with the age factor. This correction is made by adding a point to the index for each decade existing from 50 years onwards. The test has shown to be reliable 0.91 ICC [29].

**Analyses**

A statistical analysis was performed to examine differences in sociodemographic, medical, and clinical features using T-student tests for continuous variables and Chi-square for categorical variables. The Kolmogorov-Smirnov test was applied to check the hypothesis of normality for all variables (P>.05). The main analysis was tested using the analysis of covariance (ANCOVA) test, the groups served as the independent variable (non-fatigue or fatigue), and the QoL, pain, physical fitness, and mood parameters were used as dependent variables. Additionally, we considered the following covariates: age, educational level, tobacco consumption, recurrence, metastasis, and those sociodemographic variables that showed significant differences. The Mann-Whitney U test was used to analyze the differences when data have non-normal distribution. The Chi-square test was also used to determine between-group differences for comorbidities. Moreover, we estimated the between-group effect sizes (Cohen’s *d*) that were interpreted as follows: negligible (*d*= 0-0.19), small (*d*= 0.2-0.49), moderate (*d*= 0.5-0.79), and large (*d*=≥0.8) [30]. Missing data were not considered for the analysis and a complete case analysis with listwise deletion was used.

The Statistical Package for the Social Sciences (IBM SPSS Statistic for Windows, Armonk, NY, USA version 22.0) was used for data analysis, and the significance level set at (P˂.05) 95% confidence interval (CI).

**RESULTS**

No differences were observed in the demographic and clinical characteristics of the 80 subjects except for employment status (P=.036), alcohol consumption (P=.031), and type of treatment (P=.013). None of these variables showed significant differences when tested as covariates between groups. Following the criteria of fatigue [19-20], we observed non-fatigued (58.75%) (1.19±1.25) and fatigued (41.25%) (6.19± 1.50) LTBCS. The mean age in the non-fatigued group was 55.00 ± 8.69 years old while it was 53.97 ± 7.87 years old in the fatigued group. With regard to the non-fatigued group, 35 were married and 39 had no recurrence, whilst 21 were married in the fatigued group and 28 had no recurrence. The characteristics of the groups can be observed in **Table 1.**

***Quality of life***

The ANCOVA analysis revealed significant differences between groups in the following QLQ C30. ‘Physical functioning’ (F=33.69; P<.001), ‘role functioning’ (F=20.10; P<.001), ‘emotional functioning’ (F=24.55; P<.001), ‘cognitive functioning’ (F=23.62; P<.001), ‘social functioning’ (F=20.09; P<.001), and ‘global health status’ (F=52.35; P<.001) were higher in the non-fatigued group in comparison to the fatigued group. In contrast, ‘fatigue’ (U= 42.63; P<.001), ‘nausea and vomiting’ (U= 8.20; P=.005), ‘pain’ (U= 21.64; P<.001), ‘dyspnea’ (U=21.25; P<.001), ‘insomnia’ (F=14.36; P<.001), ‘appetite loss’ (U=8.64; P=.002), and ‘financial difficulties’ (U=9.21; P=.010) were higher in the fatigued group with respect to the non-fatigued group. ‘Constipation’ and ‘diarrhea’ did not show significant differences between groups (P>.05). Moderate-to-large effects were observed in ‘nausea and vomiting’, ‘appetite loss’ and ‘financial difficulties’, but particularly high values were found in ‘physical functioning’, ‘role functioning’, ‘emotional functioning’, ‘cognitive functioning’, ‘social functioning’, ‘fatigue’, ‘pain’, ‘dyspnea’, ‘insomnia’, and ‘global health status’ **Table 2.**

As for the QLQ-BR23, the analysis revealed significant differences between groups for the following areas: ‘body image’ (F=28.02; P<.001) and ‘future perspective’ (F=.005; P=.005), which were higher in LTBCS suffering from lower levels of fatigue in comparison to the fatigued group. However, ‘systemic therapy side effects’ (U=1.98; P<.001), ‘breast symptoms’ (U=9.04; P=.002), ‘arm symptoms’ (U=13.67; P=.002), and ‘upset by hair loss’ (U=1.94; P=.016) were higher in the fatigued group. There were no significant differences between groups in the ‘sexual functioning’ and ‘sexual enjoyment’ (P>.05). Small effects were observed in ‘systemic therapy side effects’ and ‘upset by hair loss’ as well as moderate-to-large effects were observed in ‘future perspective’ and ‘breast symptoms’, but we found particularly high values in the ‘body image’ and ‘arm symptoms’ variables **Table 2.**

***Pain***

The ANCOVA results revealed significant differences between groups in the VAS. LTBCS suffering from higher levels of fatigue showed more pain with respect to the other group for both the ‘affected’ (U= 21.04; P<.001) and the ‘non-affected arm’ (U= 17.33; P<.001). Large effects were observed in both ‘affected’ and ‘non-affected’ arms **Table 3.**

In addition, the analyses revealed significant differences between groups in the BPI. Thus, LTBCS suffering from higher levels of fatigue showed higher levels of ‘pain intensity’ (U=17.81; P<.001) and ‘pain interference’ (U=31.57; P<.001) than the other group. Large effects were observed in both ‘pain intensity’ and ‘interference’ **Table 3.**

***Mood State***

The ANCOVA analyses revealed significant differences between groups in The Scale for Mood Assessment (EVEA). LTBCS suffering from higher levels of fatigue showed higher levels of ‘sadness-depression’ (U=43.07; P<.001), ‘anxiety’ (U=39.98; P<.001), and ‘anger/hostility’ (U=28.59; P<.001) than the non-fatigued group. Furthermore, the analyses revealed significant differences between groups for ‘happiness’ (U=.06; P=.002). Hence, LTBCS suffering from lower levels of fatigue showed higher levels of ‘happiness’ compared with the fatigued group. Negligible effects were observed in ‘happiness’ but large effects were observed in the ‘sadness-depression’, ‘anxiety’, and ‘anger/hostility’ variables **Table 3.**

***Physical fitness level***

The ANCOVA analyses revealed significant differences between groups in all of the IFIS scales. In this regard, LTBCS suffering from lower levels of fatigue recognized themselves with higher levels of ‘general physical fitness’ (F=34.04; P<.001), ‘cardiorespiratory fitness’ (F=12.97; P<.001), ‘muscular strength’ (F=16.83; P<.001), ‘speed/agility’ (F=24.01; P<.001), and ‘flexibility’ (F=32.05; P<.001) than LTBCS who suffer from higher levels of fatigue. Large effects were observed in all of the IFIS variables **Figure 1.**

***Comorbidities***

The analyses did not reveal significant differences between groups in the Charlson Comorbidity Index (P=.093) **Table 3.**

**DISCUSSION**

Our results indicate that 5 years after the diagnosis, fatigue is still present in 41.2% of the sample, who also had a lower QoL, higher level of pain (including intensity and interference), worse mood state, and physical fitness. Furthermore, there was a 5-point difference of fatigue level between the non-fatigued (1.19±1.25) and the fatigued (6.19± 1.50) group. This is clinically significant because a change of 2 points is needed on the PFS total score to have a clinically significant improvement in fatigue [18]. To date, prior studies focused on CRF in LTBCS do not usually assess it from several domains and on the same sample. Therefore, to the best of our knowledge, this is one of the few studies to explore CRF in depth through numerous health domains and that used valid and reliable instruments. Our paper contributes not only to previous literature results, but also offers a global understanding of how LTBCS have very similar problems to short-term BC survivors that are not being treated and of how their global health status is affected. This highlights the need to create, by the health care systems and personnel, a clinical practice model that describes this reality and establishes guidelines for the assessment and treatment of this population group.

The prevalence of fatigue among LTBCS in our study is 7.2% higher than reported in a similar previous study, in which 34% of the participants showed significant fatigue 5-10 years after diagnosis [13]. Traditionally, fatigue has been considered one of the most common, debilitating, and troubling symptoms related mainly to BC treatment and early survivorship [3]. However, the prevalence of CRF from early to long-term survivorship still remains unclear because some authors, as Bower et al., found that fatigue decreased after 5-10 years after the diagnosis [31] and others, as Reinertsen et al., reported that fatigue increased after 7-10 years after the diagnosis [15]. Despite the fact that the course of fatigue is still not well elucidated, growing evidence suggests that fatigue not only does not disappear for a significant part of the LTBCS but it also co-occurs with other troublesome symptoms (physical and psychological), which in turn may lead to a lower QoL [32].

In this sense, our fatigued group showed significantly lower levels of ‘functioning’ and higher levels of ‘symptoms severity’ QLQ-C30, which is in line with previous results in LTBCS [10, 15]. Schmidt et al., concluded that although courses of fatigue varied widely between individuals, LTBCS with persisting long-term fatigue had significantly and markedly lower scores of ‘functioning’ and higher scores for ‘symptoms severity’ than other survivors and compared to the general population [10]. Furthermore, we found significant differences between the groups for QLQ-BR23. Our results showed that LTBCS who suffered from higher levels of fatigue also had lower scores of ‘functioning’ and higher scores for ‘symptoms severity’ compared to the other group. It has been found that fatigue in LTBCS is associated with higher severity pain [10, 15], poorer body image [33], and lower future perspective [34]. Although arm and breast symptoms could be long-term effects of surgery and therapy, they have also been previously reported as significant factors related to fatigue [35]. Hence, we speculate that intervention programs that tackle different aspects of QoL could have a positive influence on reducing fatigue in LTBCS.

On the one hand, our results regarding pain have also shown a significant difference between groups. LTBCS who suffered from higher levels of fatigue had 24.0% more pain in the ‘affected arm’ and 23.1% more pain in the ‘non-affected arm’ than the non-fatigued group. In addition, the fatigued group perceived that pain had more ‘intensity’ (21.8%) and more ‘interference’ (28.8%) compared to LTBCS who suffered from lower levels of fatigue. Yet, our findings of a significant increase in pain among LTBCS with persistent fatigue confirm the results of other studies, which have also observed a co-occurrence of fatigue and pain [10,15,33].

In this regard, the mechanism that has garnered the most empirical attention and support about why there is a co-occurrence of pain, fatigue, and depression, which is called “clustering of symptoms”, is an inflammatory reaction [36,37]. The release of proinflammatory cytokines, such as interleukin (IL)-6, IL-1, and tumor necrosis factor (TNF)-α, set off a complex neurochemical pathway in the brain that activates both the hypothalamic-pituitary-adrenal (HPA) axis and the sympathetic nervous system (SNS). This activation takes place concurrent with alterations in the neurotransmitter metabolism (e.g., serotonin, dopamine, norepinephrine) which are thought to be primarily responsible for the clustering of symptoms (pain, fatigue, and depression) [38]. Even so, most of the studies that have extended links between fatigue and inflammatory markers are focused mainly in early survivorship [39,40]. This is why further studies are needed to improve the knowledge about what happens with the clustering of symptoms and the implication of the HPA and the SNS ≥5 years after diagnosis in LTBCS.

Interestingly, our results further indicate that LTBCS who suffered from higher levels of fatigue showed higher levels of ‘depression’, ‘anxiety’, and ‘anger/hostility’ and lower level of ‘happiness’. In the existing literature, in addition to the alterations in the neurotransmitter metabolism [36,37], there is another alternative that involves direct effects from the individual hormones to the symptoms. For instance, persistent elevations in cortisol can produce severe fatigue, muscle weakness, and depression [41]. A possible explanation for our results could be the possibility of a cortisol increase, which may have contributed to higher levels of depression among our LTBCS. Nevertheless, this possibility should be confirmed in future studies by examining in greater detail whether altered cortisol levels could predict higher levels of depression in LTBCS.

On the other hand, we also observed that LTBCS who suffered from higher levels of fatigue showed lower self-reported physical fitness. The literature has previously suggested that people who suffer from more fatigue [39] are those who do less exercise. And those who do less exercise have a lower physical self-concept [42]. In addition, Mason et al. concluded that less than 40% of LTBCS met the United States physical activity guidelines (≥150 mins/week moderate or ≥75 mins/week vigorous activity) 5 years after the diagnosis [43]. Therefore, participating in multimodal therapeutic exercise programs could help LTBCS to improve not only their self-reported physical fitness but also QoL, body-image, emotional well-being, social functioning, anxiety, fatigue, and pain [44].

Finally, we expect to find significant differences in comorbidities among the groups because fatigue has been previously associated with shorter survival and increased mortality in cancer patients [45]. In addition, characteristics as age, stage of diagnosis, type of treatment, quality of treatment, and adherence are factors that may be associated with comorbidities [46], which could have influence and explain our results. Further studies are needed to improve the knowledge about this risk.

This study has several limitations that must be considered. Firstly, the fatigued cutoff points used in our study are accepted criteria [18-20], but the inclusion of other cutoff points could modify our results. Therefore, future studies are needed to support our findings. Secondly, having used more objective variables (although all the tests have been previously validated) could have strengthened our results.

Despite the aforementioned weaknesses, this study showed that ≥5 years after diagnosis fatigue is still present in 41.2% of the sample who also had several physical and psychological symptoms that still needed treatment and continue impairing QoL among LTBCS. Moreover, it is one of the few studies that could be helpful for the development of new clinical management strategies and practice models in LTBCS because it relates and leads to a better understanding of CRF simultaneously in several health domains in a very homogenous sample of LTBCS and uses several multidimensional and internationally validated and reliable instruments in cancer patients. Furthermore, this study includes effect size measures which complement and improve the methodological quality of the study, given the clinical value set to the P values.

So far, a variety of different intervention approaches have been used to treat cancer-related fatigue (e.g. physical activity, cognitive behavioral approaches, mindfulness, yoga, and acupuncture) with positive results in LTBCS [36]. However, and due to the complexity of this symptom, the next research generation should address the importance of identifying vulnerable individuals to develop and demonstrate the effectiveness of targeted and tailored multimodal interventions for every LTBCS.

**CONCLUSIONS**

The results of this study showed that more than 40% of LTBCS suffer from fatigue. What is more, those LTBCS who suffered from higher levels of fatigue had lower QoL, higher level of pain (including intensity and interference), worse mood state, and lower physical fitness, which may lead to a negative impact on their global health status. Therefore, the implementation of targeted and tailored multimodal programs that tackle not only fatigue from a physical point of view but also from a psychological approach could help improve the sequels that LTBCS still suffer many years from after diagnosis.

**COMPLIANCE WITH ETHICAL STANDARDS**

**Conflict of interests:** The authors declare that they have no conflict of interest.

**Ethical approval:** All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Ethical approval for the study was granted by the Biomedical Research Ethical Committee of Granada (1038-N-16 I.P) and the study followed the Helsinki Declaration for biomedical research (14/2017).

**Informed consent:** Informed consent was obtained from all the individual participants included in this study.

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**Figure 1. Physical fitness values between groups expressed as mean ± SD**

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**P<.001\*\*  
Analysis of covariance (ANCOVA)**

**Table 1. Demographic, Clinical and Medical Characteristic of the Groups**

|  |  |  |  |
| --- | --- | --- | --- |
| Characteristic | Fatigue | | *P* |
| Non-Fatigued (n=47) | Fatigued (n=33) |
| Mean Age ± SD, Years | 55.00±8.69 | 53.97±7.87 | .589 |
| Mean Time Since Diagnosis ± SD, Months | 89.97±30.28 | 91.18±28.11 | .856 |
| Mean Time Since The First Surgery ± SD, Months | 87.43±30.70 | 87.85±28.59 | .952 |
| Marital Status, n (%) |  |  |  |
| Married | 35 (74.4) | 21 (63.6) | .581 |
| Unmarried | 6 (12.7) | 6 (18.1) |
| Divorced | 2 (4.2) | 6 (18.1) |
| Widowed | 4 (8.5) | 0 (0) |
| Educational Level, n (%) |  |  |  |
| Primary School | 21 (44.6) | 13 (39.3) | .707 |
| Secondary School | 10 (21.2) | 8 (24.2) |
| University | 16 (34.0) | 12 (36.3) |
| Employment Status, n (%) |  |  |  |
| Housewife | 17 (36.1) | 8 (24.2) | **.036\*** |
| Currently working | 14 (29.7) | 3 (9.1) |
| Work leave | 12 (25.5) | 18 (54.5) |
| Can’t work because of disability | 4 (8.5) | 4 (12.1) |
| Tobacco Consumption, n (%) |  |  |  |
| Non-smoker | 25 (53.1) | 15 (45.4) | .824 |
| Smoker | 9 (19.1) | 10 (30.3) |
| Ex-smoker | 13 (27.6) | 8 (24.2) |
| Alcohol Consumption, n (%) |  |  |  |
| Non-consumption | 15 (31.9) | 15 (45.4) | **.031\*** |
| Monthly | 7 (14.8) | 12 (36.3) |
| Weekly | 23 (48.9) | 4 (12.1) |
| Daily | 2 (4.2) | 2 (6.0) |
| Recurrence, n (%) |  |  |  |
| No | 39 (82.9) | 28 (84.8) | .826 |
| Yes | 8 (17.0) | 5 (15.1) |
| Metastasis, n (%) |  |  |  |
| No | 40 (85.1) | 26 (78.7) | .470 |
| Yes | 7 (14.8) | 7 (21.2) |
| Type of treatment (%) |  |  |  |
| None | 0 (0) | 0 (0) | **.013\*** |
| Radiotherapy | 0 (0) | 2 (6.1) |
| Chemotherapy | 2 (4.3) | 5 (15.2) |
| Radiotherapy and Chemotherapy | 45 (95.7) | 26 (78.8) |
| Type of medication (%) |  |  |  |
| None | 14 (29.8) | 5 (15.2) | .080 |
| Tamoxifen | 16 (34.0) | 14 (42.4) |
| Other types | 17 (36.2) | 14 (42.4) |

**P˂.05\*  
NOTE. P values for between-groups differences were calculated using the *t* test for continuous variables and X² for categorical variables.  
n: Sample size  
SD: Standard deviation**

**Table 2. Quality of life values expressed as mean ± SD (95%CI)**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Variables | Fatigue | | *P* | Cohen’s  *D* |
| Non-fatigued (n=47) | Fatigued (n=33) |
| Functioning Scales QLQ-C30 |  |  |  |  |
| Physical Functioning | 90.92 ± 11.98  (95% CI 87.40-94.44) | 68.32 ± 22.58  (95% CI 60.32-76.33) | **<.001ᵃ** | 1.25 |
| Role Functioning | 90.42 ± 21.63  (95% CI 84.07-96.77) | 63.64 ± 31.86  (95% CI 52.34-74.93) | **<.001ᵃ** | 0.98 |
| Emotional Functioning | 79.07 ± 22.97  (95% CI 72.33-85.82) | 47.97 ± 33.20  (95% CI 36.20-59.75) | **<.001ᵃ** | 1.09 |
| Cognitive Functioning | 75.89 ± 25.01  (95% CI 68.54-83.23) | 44.95 ± 31.86  (95% CI 33.65-56.25) | **<.001ᵃ** | 1.08 |
| Social Functioning | 87.23 ± 24.13  (95% CI 80.15-94.32) | 54.55 ± 33.14  (95% CI 42.79-66.30) | **<.001ᵃ** | 1.13 |
| Symptom Scales QLQ-C30 |  |  |  |  |
| Fatigue | 21.04 ± 23.54  (95% CI 14.13-27.95) | 58.56 ± 27.68  (95% CI 48.77-68.40) | **<.001ᵇ** | 1.46 |
| Nausea and vomiting | 2.84 ± 10.02  (95% CI -.11-5.78) | 14.14 ± 24.34  (95% CI 5.51-22.77) | **.005ᵇ** | 0.61 |
| Pain | 26.24 ± 28.60  (95% CI 17.84-34.64) | 56.57 ± 28.85  (95% CI 46.34-66.79) | **<.001ᵇ** | 1.06 |
| Single Items QLQ-C30 |  |  |  |  |
| Dyspnea | 11.35 ± 21.17  (95% CI 5.13-17.56) | 40.40 ± 35.11  (95% CI 27.95-52.86) | **<.001ᵇ** | 1.00 |
| Insomnia | 39.01 ± 32.09  (95% CI 29.58-48.43) | 66.16 ± 30.76  (95% CI 55.26-77.07) | **<.001ᵃ** | 0.86 |
| Appetite Loss | 4.96 ± 16.99  (95% CI -.03-9.95) | 21.21 ± 32.08  (95% CI 9.84-32.59) | **.002ᵇ** | 0.63 |
| Constipation | 17.02 ± 23.96  (95% CI 9.91-24.14) | 34.34 ± 40.38  (95% CI 20.02 – 48.66) | .074ᵇ | 0.52 |
| Diarrhea | 7.09 ± 16.93  (95% CI 2.12-12.06) | 17.17 ± 30.18  (95% CI 6.46-27.87) | .083ᵇ | 0.41 |
| Financial Difficulties | 12.84 ± 24.59  (95% CI 5.62-20.06) | 35.35 ± 41.61  (95% CI 20.60-50.11) | **.010ᵇ** | 0.66 |
| Global Health Status QLQ-C30 |  |  |  |  |
| Global Health Status | 75.70 ± 17.71  (95% CI 70.51-80.91) | 44.94 ± 20.09  (95% CI 37.83-52.07) | **<.001ᵃ** | 1.62 |
| Functional Scales QLQ-BR23 |  |  |  |  |
| Body Image | 89.18 ± 19.26  (95% CI 83.53-94.84) | 60.10 ± 29.88  (95% CI 49.50-70.69) | **<.001ᵃ** | 1.16 |
| Sexual Functioning | 22.34 ± 21.50  (95% CI 16.03-28.65) | 19.19 ± 22.87  (95% CI 11.08-27.30) | .273ᵃ | 0.14 |
| Sexual Enjoyment | 21.27 ± 37.06  (95% CI 10.40-32.16) | 9.09 ± 37.52  (95% CI -4.21-22.39) | .119ᵃ | 0.33 |
| Future perspective | 64.54 ± 37.69  (95% CI 53.47-75.61) | 40.40 ± 35.12  (95% CI 27.95-52.86) | **.005ᵃ** | 0.66 |
| Symptom Scales QLQ-BR23 |  |  |  |  |
| Systemic Therapy Side Effects | 19.22 ± 20.12  (95% CI 13.32-25.13) | 41.97 ± 20.12  (95% CI 35.34-48.59) | **.000ᵇ** | 0.29 |
| Breast Symptoms | 18.79 ± 24.29  (95% CI 11.66-25.93) | 36.62 ± 28.49  (95% CI 26.52-46.72) | **.002ᵇ** | 0.67 |
| Arm Symptoms | 21.51 ± 22.98  (95% CI 14.76-28.26) | 45.79 ± 35.76  (95% CI 33.11-58.47) | **.002ᵇ** | 0.81 |
| Upset by hair loss | -13.83 ± 34.10  (95% CI -23.84- -3.81) | 4.03 ± 38,86  (95% CI -9.74-17.81) | **.033ᵇ** | 0.22 |

**P˂.05\* / P<.001\*\*  
ᵃ Analysis of covariance (ANCOVA)  
ᵇ Mann-Whitney U test   
Abbreviations: QLQ = Quality of Life Questionnaire, IC = Confidence Interval**

**Table 3. Pain, mood, and cormobidities values between groups.**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Variables | | Fatigue | | *P* | Cohen’s  *d* |
| Non-fatigued (n=47) | Fatigued (n=33) |
| VAS (cm), mean ± SD (95%CI) | |  |  |  |  |
| Affected Arm | | 1.32 ± 1.91  (95% CI .76-1.88) | 3.72 ± 2.79  (95% CI 2.73-4.72) | **<.001ᵃ** | 1.00 |
| Non-Affected Arm | | .51 ± 1.61  (95% CI .04-.98) | 2.82 ± 3.28  (95% CI 1.65-3.98) | **<.001ᵃ** | 0.89 |
| BPI, mean ± SD (95%CI) | |  |  |  |  |
| Intensity | | 1.38 ± 1.87  (95% CI .83-1.93) | 3.56 ± 2.74  (95% CI 2.59-4.53) | **<.001ᵃ** | 0.93 |
| Interference | | .84 ± 1.60  (95% CI .37-1.31) | 3.72 ± 2.96  (95% CI 2.67-4.77) | **<.001ᵃ** | 1.21 |
| EVEA, mean ± SD (95%CI) | |  |  |  |  |
| Sadness-Depression | | 1.51 ± 1.87  (95% CI .95-2.07) | 4.81 ± 2.57  (95% CI 3.89-5.74) | **<.001ᵃ** | 1.46 |
| Anxiety | | 1.73 ± 1.73  (95% CI 1.21-2.24) | 4.84 ± 2.62  (95% CI 3.90-5.79) | **<.001ᵃ** | 1.40 |
| Anger / Hostility | | 1.10 ± 1.42  (95% CI .68-1.52) | 3.73 ± 2.87  (95% CI 2.69-4.76) | **<.001ᵃ** | 1.16 |
| Happiness | | 6.17 ± 2.37  (95% CI 5.46-6.87) | 5.80 ± 9.20  (95% CI 2.49-9.12) | **.002ᵃ** | 0.06 |
| Charlson Comorbidity Index, n (%) | |  | | | |
| Index Score | Prediction of mortality per year |
| 0 | 12% | 42 (89.36) | 23 (69.70) | .093b |  |
| 1-2 | 26% | 4 (8.51) | 5 (15.15) | - |
| 3-4 | 52% | 0 (0) | 2 (6.06) |  |
| ≥5 | 85% | 1 (2.13) | 3 (9.09) |  |

**P˂.05\* / P<.001\*\*  
NOTE. P values for between-groups differences were calculated using the *t* test for continuous variables and X² for categorical variables.  
n: Sample size  
Abbreviations: VAS = Visual Analog Scale, BPI = Brief Pain Inventory, EVEA = Scale for Mood Assessment, IFIS = International Fitness Scale, CI= Confidence Interval**