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Prevalence and associated factors of fatigue among breast cancer patients in Malaysia—A prospective study

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ABSTRACT

The aim of this study was to determine the prevalence and factors associated with fatigue among breast cancer patients in Malaysia. This study was a prospective observational study and data were collected from medical records of Hospital Kuala Lumpur, University of Malaya Medical Center, and National Cancer Institute in the period between July 2019 and April 2020. The incidence of fatigue was determined by detecting whether or not fatigue developed during the course of chemotherapy. Severity of fatigue was determined by the Brief Fatigue Inventory scale after informed written consent was obtained. A chi-squared test was used to analyze the correlations between categorical variables, and logistic regression was used to evaluate the associations of risk factors with the presence of cancer-related fatigue. Out of a total population of 576 breast cancer patients, 292 had met the inclusion criteria and fatigue occurred at a rate of 58.9%. Our findings indicated that age, body mass index, smoking, number of chemotherapy regimens, fluorouracil, epirubicin, and cyclophosphamide were all associated with the presence of fatigue among breast patients ($p < 0.05$). This study finds that the prevalence of fatigue in breast cancer patients was high and suggests that effective management of both demographic and clinical factors may reduce fatigue severity and improve the overall health status of cancer patients.

INTRODUCTION

Fatigue is the most popular and unfavorable symptom in cancer patients with prevalence rates from 10% to 90% (Karthikeyan *et al*., 2018). The increase in the incidence of fatigue has been associated with reduced treatment response and quality of life of breast cancer patients (Muthanna *et al*., 2021). However, improvements in the quality of life of cancer patients have fallen short of expectations because of cancer-related fatigue (CRF), one of the most common cancer-related symptoms (Berger *et al*., 2010; Muthanna *et al*., 2021). Specific subgroups of patients are more likely to develop fatigue during the course of the disease. The prevalence of fatigue among cancer patients is very high. Karthikeyan *et al*. (2018) reported that the prevalence of CRF could reach up to 98.3% after receiving chemotherapy. In addition, Phillips *et al*. (2013) reported that the incidence of CRF during the course of treatment ranges from 25% to 99%, depending on the type of treatment received the patient population and assessment methods. The higher incidence of moderate to severe fatigue (30%–60%) may lead to treatment discontinuation (Bower, 2014).

Till today, the etiology of fatigue in cancer patients is associated with various factors that may play a significant role in

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its incidence. These factors include cancer type, stage of disease, and management (Fabi *et al*., 2017; Mao *et al*., 2018). Some researchers have reported that the incidence of CRF are associated significantly with increased levels of inflammatory cytokines, such as IL-6, tumor necrosis factor (TNF), IL-1 receptor antagonist (IL-1RA), and especially IL-8, a significant factor of pain and fatigue in cancer patients (Reyes-Gibby *et al*., 2013). Moreover, Inglis *et al*. (2010) and Mao *et al*. (2018) concluded that demographic factors, such as body mass index (BMI) (obesity), played an important role in the incidence of fatigue among cancer patients. In addition, Tabrizi and Alizadeh (2017) studied CRF in 150 breast cancer patients and recommended that future studies must evaluate additional variables related to fatigue following breast cancer treatment and their impact on the quality of life over time.

The National Comprehensive Cancer Network (NCCN) and the American Society of Clinical Oncology guidelines recommend screening fatigue in cancer patients before management. Both guidelines advise all healthcare clinicians to routinely screen and assess all cancer patients for the presence of fatigue from time of diagnosis onward, including after completion of primary treatment. In addition, both guidelines advise all cancer patients to be screened for fatigue at least once annually as clinically indicated. Screening must be documented using quantitative or semiquantitative assessment tools. This study used Brief Fatigue Inventory (BFI) to assess and evaluate fatigue severity in cancer patients. The advantages of the BFI scale are that it meets the requirement of a rapidly administered scale compared to other tools in which the time required to complete and fill their items makes them difficult to use for clinical screening or for outcome measures in clinical trials. In addition, the items of the BFI scale are easily understood with simple language and fast to complete (takes up to 8–10 minutes), which make it the best tool for measuring fatigue severity among cancer patients (Shuman-Paretsky *et al*., 2014).

The purpose of this study was to evaluate the prevalence and factors associated with increased severity of CRF among breast cancer patients in Malaysia and to provide a basis for future CRF management.

MATERIALS AND METHODS

Study design

This study used a prospective observational and multicenter design. Participants were collected randomly from the oncology department and daycare of Hospital Kuala Lumpur (HKL), University of Malaya Medical Center (UMMC), and National Cancer Institute (NCI) according to the inclusion criteria in the period between July 2019 and April 2020. The inclusion criteria included the following: (a) diagnosis with breast cancer at any stage; (b) age 18 years or above; (c) nonanemic; (d) ECOG scale ≥2; (e) no cognitive impairment; and (f) able to sign the consent form. Exclusion criteria included anemic patients with Hb < 12 g/dl, patients receiving other types of treatment, such as radiotherapy, surgery, or hormonal therapy, or those in their first cycle, those with mental or cognitive disorders, and patients who are unwilling to sign the consent form.

Sample size determination

Sample size was calculated using Raosoft online sample size calculator. Calculation was based on 50% response distribution, 5% margin of error, and 95% confidence interval (CI). The online software foundation is based on widely utilized descriptive studies sample size estimation formula proposed and cited by Sathian *et al*. (2010). Setting the response distribution to 50% is the most conservative assumption (Raosoft Inc.). The incidence of CRF was found to be in the range of 10%–90% (Karthikeyan *et al*., 2018) among breast cancer patients; thus, for this range, the sample size fell between 95 and 201 patients for fatigue cases. These numbers were derived based on an estimated total population of 125–420 breast cancer patients attending hospitals regularly. The total number of patients in the final calculated sample size was 292 patients (172 fatigued and 120 nonfatigued).

Sampling techniques

Data were collected from the three major hospitals. First, HKL is a large government hospital in Malaysia that serves as a tertiary and referral hospital in Kuala Lumpur. It has approximately 11,300 employees and 2,300 beds. Second, the UMMC in Kuala Lumpur has approximately 1,617 beds and serves as a teaching hospital for the University of Malaya. Third, the NCI is a government cancer treatment facility in Putrajaya, Selangor. It has approximately 252 beds and is specifically designed to provide specialized facilities for cancer patients.

The oncology units and daycare departments of those patients who met the inclusion criteria were identified using their medical records. A 1-year review of adults receiving chemotherapy cancer treatment revealed more than 9,000 cases in the oncology units of the 3 cancer centers.

About 576 cancer patients received monthly follow-up treatments and additional types of treatment, including radiotherapy, surgery, and hormonal therapy, and 292 patients were sampled during the study period using a simple random sampling technique and/or a systematic sampling technique (Fig. 1).

Data collection

Patients who experienced fatigue were identified based on the BFI scale and Eastern Cooperative Oncology Group (ECOG) Performance Status (ECOG PS), as recorded in their medical files. The severity of fatigue was assessed by the BFI scale: 0–3 = mild, 4–7 = moderate, and 7–10 = severe (Banipal *et al*., 2017). The patients were then briefed on the background of the study and given a consent form to sign once they agreed to participate. The researchers instructed patients on how to fill out the questionnaire, and the patients then did so accordingly.

Demographic data (including age, gender, ethnicity, BMI, marital status, employment status, and social status, e.g., smoking and alcohol consuming) and clinical data (including cancer stage, chemotherapy dose delay, dose reduction, type, and number of chemotherapy) were collected and analyzed either from medical files or supplied by the patients themselves. Age groups were categorized as elderly (≥55 years) and nonelderly (<55 years). Marital status was classified as married and unmarried. Ethnicity was categorized as Malay, Indian, Chinese, and others. Patients were classified according to their BMI as normal (BMI kg/m^2 < 25), overweight (BMI kg/m^2 25–30), and obese (BMI kg/m^2 > 30). Cancer stages were divided into four categories: stage I, stage II, stage III, and stage IV. The number of chemotherapy regimens was divided into two categories: single and combination regimen. Dose delay is defined as a chemotherapy dose that is delayed for more

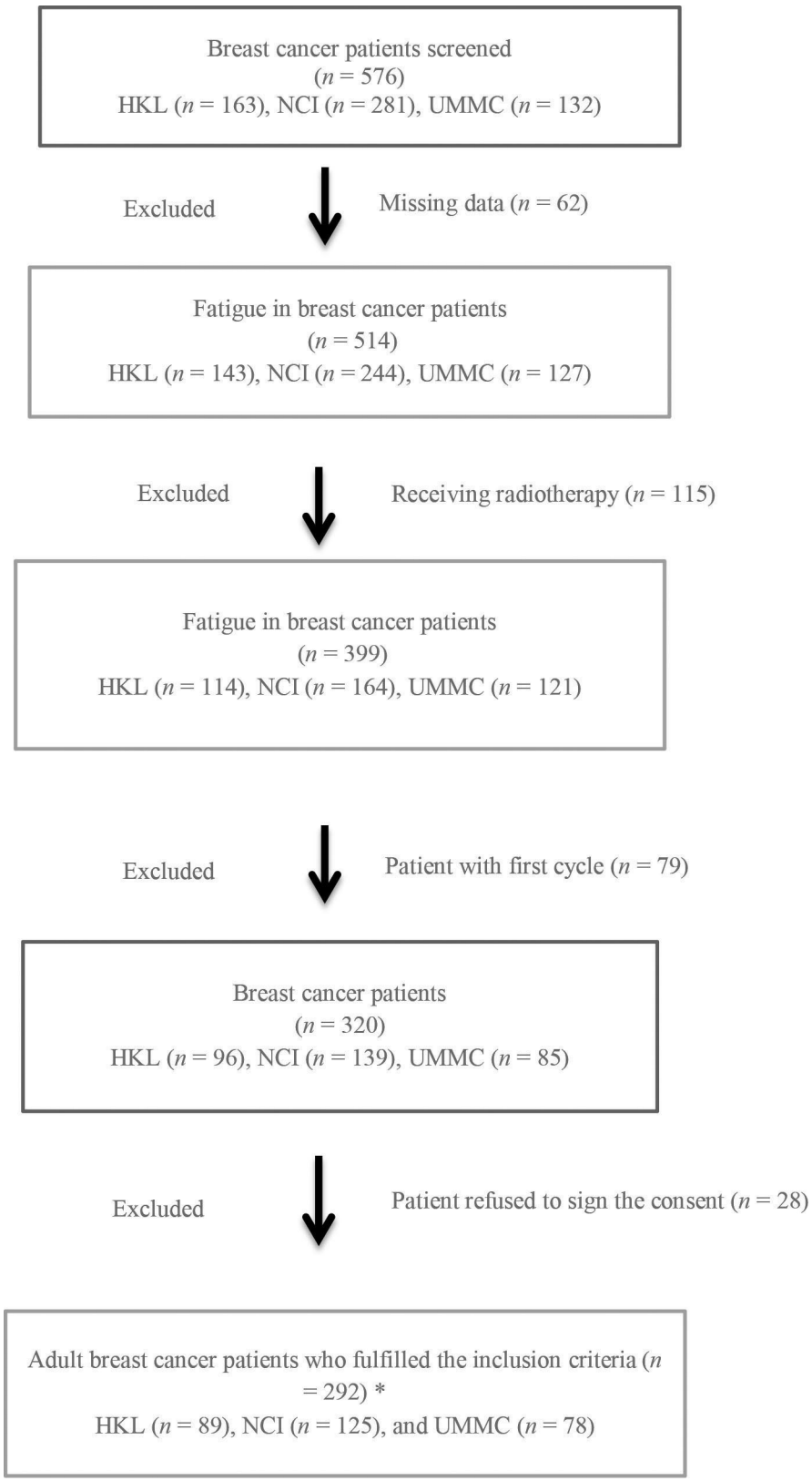

Figure 1. Adult patients with breast cancer screened during the study period. *Muthanna et al. (2022).

than 7 days (Family *et al*., 2016), and dose reduction is defined as a dose reduction of at least 10% at any consecutive cycle (Denduluri *et al*., 2018; Liutkauskiene *et al*., 2018).

Brief Fatigue Inventory

The BFI is a tool used to screen, detect, and assess the severity of daily fatigue among cancer patients. BFI was initially

developed by Mendoza *et al*. (1999). BFI is available in many other languages, including English (Catania *et al*., 2013; Mendoza *et al*., 1999). It includes nine questions, and the first three questions assess the "now," "usual," and "worst" levels of fatigue during the past 24 hours. The severity of fatigue was determined by the first three items using a score of 0 (no fatigue) to 10 (fatigue as bad as you can imagine). BFI is also recommended by the NCCN guidelines for screening, assessing, and reevaluating fatigue among cancer patients. The cut-off score for clinically significant fatigue was 4 (Berger *et al*., 2010). The internal consistency and reliability (Cronbach's α) of the first three questions in the Malay version was 0.85 (Muhamad *et al*., 2018). The following six questions were used to assess and detect the interference between fatigue and daily activities, such as the ability to walk, mood, work, life enjoyment, and connectivity with other people. In this setting, only the first three questions to identify the severity of fatigue among breast cancer patients were used. The scale was measured as 0 = no interfere and 10 = complete interference (Shuman-Paretsky *et al*., 2014).

Ethics approval

Ethical clearance and protocols of this study were obtained and approved by the Research Ethics Committee of the Clinical Research Centre of Universiti Teknologi MARA (REC/392/19), HKL (HCRC.IIR-2019-07-163), Institute Kanser Negara (IKN/500-5/1/25 JId 4 (18), UMMC, and the Medical Research Ethical Centre (NMRR -18-3902-45218). The researchers followed the principles of the Helsinki Declaration and Malaysian Good Clinical Practice Guidelines.

Statistical analysis

The data were analyzed by using Statistical Package for the Social Sciences software, version 23. The mean and standard deviation (SD) were used as descriptive statistics to present the demographic and clinical data in this study. Regression analysis is used to examine the association between independent and outcome variables, and chi-squared tests were used to examine the association between categorical and ordinal variables. We examined how variables (e.g., age, BMI, and ethnicity) affected the associations between independent and outcome variables.

There are three steps taken in analyzing the factors associated with fatigue. First, the association between the risk factors of fatigue and observed fatigue incidence (fatigue/nonfatigue) was examined using the chi-squared analysis for categorical data. Second, all factors with a p-value < 0.05 significance level, in the chi-square or Fisher's exact tests, were entered into a stepwise logistic regression analysis. Third, only risk factors with a statistically significant p-value were examined. The adjusted odds ratio, 95% CI, and p-value were all included in the results of logistic regression analyses. The level of significance was set as $p < 0.05$.

RESULTS

Patient characteristics

Table 1 presents clinical and demographic data for the 292 patients who were included in this study. As shown, the incidence of fatigue was 58.9% (172/292). Out of 292 respondents enrolled in the study, 119 of them (40.1%) were referred to the NCI hospital, followed by 93 to HKL (31.8%) and 80 to UMMC (27.4%). Malays and Chinese ethnicities made up more than 81% (n = 239) of the participants. Approximately 90% (n = 261) of them were married. The majority of participants (n = 180; 61.6%) were ≥55 years old, with a mean age of 52.77 years (SD = 10.25 years). With regard to social status, the majority of respondents were not smokers (n = 231, 79.1%) and only 41 (14%) patients consumed alcohol. In addition, 174 (59.6%) patients had a normal BMI (<25 kg/m^2), followed by overweight (BMI = 25–30 kg/m^2) and obese (35.6%, 104) patients. Furthermore, most of the respondents were working (n = 177, 60.6%).

In terms of clinical characteristics, the majority of respondents (n = 124; 42.5%) were at stage III and about 151 (51.7%) were prescribed a combination of chemotherapy regimens. Regarding type of chemotherapy data, about 105 (36%) and 54 (18.5%) patients received fluorouracil, epirubicin, and cyclophosphamide (FEC) and fluorouracil, epirubicin, cyclophosphamide, and docetaxel (FEC-T) regimens, respectively. The distributions of sociodemographic and clinical data of the participants are shown in Table 1.

Prevalence of CRF

Of the total number of patients enrolled in the study, 172 (58.5%) experienced clinically significant fatigue. In addition, 123 (71.5%) had moderate fatigue, 43 (25%) had mild fatigue, and 6 (3.5%) had severe fatigue. The average mean of the BFI score was 4.65 ± 1.14 (mean ± SD).

As shown in Table 2, 69 (61.6%) and 51 (28.3%) breast cancer patients, aged <55 years and ≥55 years, respectively, were observed to have fatigue. With regard to ethnicity, approximately 45.6% (n = 77) of the fatigue patients were Malay, followed by Chinese (38.6%, n = 27) and Indians (35.9%, n = 14). Considering chemotherapy data, about 66% (n = 93), 51.4% (n = 54), and 57.4% (n = 31) of the breast cancer patients receiving a combination of chemotherapy regimens, FEC, and FEC-T were affected with fatigue, respectively (Table 2).

Factors associated with CRF prevalence

Table 2 shows the associations between potential risk factors and incidence of CRF. In chi-squared and Fisher's exact test analyses, increasing age, increased BMI, social status, advanced cancer stages, and number or type of chemotherapy regimens were significantly associated with a higher incidence of CRF ($p < 0.05$). Other factors, such as ethnicity, marital status, and dose reduction, were not significantly correlated to the prevalence of CRF. Taking all the significant points of the results from chi-squared and run logistic regression analysis, the results of the logistic regression (Table 3) showed that elderly breast cancer patients aged >55 years were 5.4 times more likely to develop fatigue compared to nonelderly patients. In addition, overweight patients (BMI = 25–30 kg/m^2) were 3.4 times more likely to induce high levels of CRF compared to normal BMI patients. Furthermore, smoker patients were at a high risk of developing CRF compared to nonsmoker breast cancer patients. Moreover, participants who consumed alcohol were 8.16 times less likely to suffer from fatigue compared to those who did not consume alcohol. With regard to chemotherapy data, those who received

Table 1. Demographic and clinical data of the 292 patients included in the study.[a]

Variable		*N* (%)
Hospital name[a]	HKL	93 (31.8%)
	UMMC	80 (27.4%)
	NCI	119 (40.1%)
BFI score mean	4.65 ± (SD 1.14)	
Fatigue prevalence	Fatigue	172 (58.9%)
	Nonfatigue	120 (41.1%)
Fatigue severity (BFI score)	Mild (1–3)	43 (25%)
	Moderate (4–6)	123 (71.5%)
	Severe (7–10)	6 (3.5%)
Mean age	52.77 (SD 10.25)	
Age (years)	≥55	180 (61.6%)
	<55	112 (38.4%)
Ethnicity[a]	Malay	169 (57.9%)
	Indian	39 (13.4%)
	Chinese	70 (24%)
	Others	14 (4.8%)
Marital status	Married	261 (89.4%)
	Unmarried	31 (10.6%)
BMI kg/m^2	Normal (<25)	174 (59.6%)
	Overweight (25–30)	104 (35.6%)
	Obese (>30)	14 (4.8%)
Employment status[a]	Employed	177 (60.6%)
	Unemployed	115 (39.4%)
Smoking status	Smoking	61 (20.6%)
	Nonsmoking	231 (79.1%)
Alcohol consuming	Consumers	41 (14%)
	Nonconsumers	251 (86%)
Menopausal status	Pre	92 (31.5%)
	Post	200 (68.5%)
Stage of breast cancer[a]	Stage I	22 (7.5%)
	Stage II	81 (27.7%)
	Stage III	124 (42.5%)
	Stage IV	65 (22.3%)
Number of chemotherapy regimens[a]	Single	141 (48.3%)
	Combination	151 (51.7%)
Chemotherapy dose reduction	Reduced	51 (17.5%)
	Not reduced	241 (82.5%)
FEC	Received	105 (36%)
	Not received	187 (64%)
FEC-T	Received	54 (18.5%)
	Not received	238 (81.5%)

[a] Muthanna *et al*. (2022).
FEC: fluorouracil, epirubicin, and cyclophosphamide; FEC-T: fluorouracil, epirubicin, cyclophosphamide, and docetaxel.

a combination chemotherapy regimen and FEC were 21.29 times and 6.13 times more and less likely to induce CRF, respectively (Table 3).

DISCUSSION

CRF is by far the most notable medical issue in breast cancer patients receiving chemotherapy, and majority of the cancer patients experience fatigue during the course of antineoplastic therapy. Despite increasing evidence about fatigue induced by multiple chemotherapeutic drugs as well as how CRF affects quality of patient care, identifying its prevalence and factors associated with its intensity among breast cancer patients is still neglected and remains a challenge. Previous studies adequately explained the prevalence and predictors of fatigue among cancer patients, but not among breast cancer patients receiving only chemotherapy. The purpose of this study was to determine the prevalence and factors associated with CRF among breast cancer patients undergoing chemotherapy. This study correctly identified the sociodemographic and clinical aspects associated with increased fatigue prevalence in breast cancer patients. In general, our observations show that CRF is common among breast cancer patients and is strongly associated with sociodemographic determinants (such as increasing age, overweight, nonsmoking, and alcohol consuming) and clinical variables (such as number of chemotherapy regiments and type of antineoplastic). Other variables, such as ethnicity, marital status, employment status, and cancer stage, were not associated with intensity of CRF in breast cancer patients.

In this study, 58.9% of 292 breast cancer patient's experienced clinically significant fatigue. Sociodemographic clinical factors were included in the logistic regression analysis, yet only increased age, overweight BMI, social status, e.g., smoking and nonalcohol consumers, combination of chemotherapy regimens, and FEC were associated significantly with the prevalence of CRF. Meanwhile, other factors, such as marital status, ethnicity, employment status, cancer stage, and dose reduction, showed no association with CRF. Fatigue is one of the most distressing symptoms experienced by cancer patients and associated significantly with the decline in the Health Related Quality of Life (HRQOL) (Muthanna *et al*., 2021).

Our findings determined that the prevalence of fatigue among breast cancer patients referred to the oncology departments of NCI, HKL, and UMMC was very high. CRF was prevalent in 42.8% of the patients at NCI, 30.5% at HKL, and 26.7% at UMMC.

Several studies have reported a high incidence of CRF among cancer patients in which their findings were similar to our study. A recent meta-analysis was conducted by Al Maqbali *et al*. (2020), which included 129 studies and covered a period between 1993 and 2020. The main aim was to identify the prevalence of fatigue in cancer patients. Their results indicated that the overall prevalence of CRF was 49% increased among cancer stages, and 62% and 51% among chemotherapy. On the other hand, our results were lower than many studies (Gullett *et al*., 2019; Sathian *et al*., 2010) which used the BFI scale to assess fatigue severity and indicated that the prevalence of fatigue in cancer patients was 74% and 83%, respectively. Moreover, our data were higher than Fabi *et al*. (2017) and Tian *et al*. (2016), who reported that the incidence of CRF was 49% and 52.1%, respectively. The discrepancies in these findings may refer either to the objectives of study, tools used, or methodology, e.g., inclusion and exclusion criteria. The current study used the BFI scale to assess fatigue severity, with a cut-off of 4.

Table 2. Association between fatigue incidence and demographic and clinical factors.

Variable		Fatigue		*p*-value**
		Without fatigue frequency, *n* (%)	With fatigue frequency, *n* (%)	
Age (years)	<55	69 (61.6%)	48 (38.4%)	0.001
	≥55	51 (28.3%)	129 (71.7%)	
Ethnicity	Malay	77 (45.6%)	92 (54.4%)	0.10
	Indian	14 (35.9%)	25 (64.1%)	
	Chinese	27 (38.6%)	43 (61.4%)	
	Others	2 (14.3%)	12 (85.7%)	
BMI kg/m^2	Normal (<25)	97 (55.7%)	77 (44.3%)	0.001
	Overweight (25–30)	20 (19.2%)	84 (80.8)	
	Obese (>30)	3 (21.4%)	11 (78.6%)	
Marital status	Married	104 (39.8%)	157 (60.2%)	0.29
	Unmarried	16 (51.6%)	15 (48.4%)	
Smoking	Smoking	15 (24.6%)	46 (75.4%)	0.005
	Nonsmoking	105 (45.5%)	126 (54.5%)	
Employment status	Employed	86 (48.6%)	91 (51.4%)	0.001
	Unemployed	34 (29.6%)	81 (70.4%)	
Alcohol consumer	Consuming	29 (70.7%)	12 (29.3%)	0.001
	Nonconsuming	91 (36.3%)	160 (63.7%)	
Cancer stage	Stage I	5 (22.7%)	17 (77.3%)	0.036*
	Stage II	29 (35.8%)	52 (54.2%)	
	Stage III	62 (50%)	62 (50%)	
	Stage IV	24 (36.9%)	41 (63.1%)	
Number of regimens	Single	93 (66%)	48 (34%)	0.001
	Combination	27 (17.9%)	124 (82.1%)	
Dose reduced	Reduced	23 (45.1%)	28 (54.9%)	0.629
	Not reduced	97 (40.2%)	144 (59.8%)	
FEC	Received	54 (51.4%)	51 (48.6%)	0.007
	Not received	66 (35.3%)	121 (64.7%)	
FEC-T	Received	31 (57.4%)	23 (42.6%)	0.009
	Not received	89 (37.4%)	149 (62.6%)	

** Chi-squared analysis. $p < 0.05$ indicated a level of significance.
* Fisher's exact test. $p < 0.05$ indicated a level of significance.

Our data showed that increased age was a factor that may aggravate CRF. As mentioned by Giacalone *et al*. (2013) and Su *et al*. (2011), the relationship between CRF and age would be highly detected among elderly patients ≥65 years old, who are considered highly vulnerable to cancer. In general, aging results in the deterioration of the physiological and biological system. While there is no known threshold age, it is considered that deterioration of the biological systems begins from about the age of 45–50 years (Weinert, 2000). Alteration of the circadian time-keeping system and physiology of sleep homeostasis often results in fatigue (Dawson *et al*., 2011).

Moreover, our findings indicated that overweight patients were at high risk of developing CRF. According to the logistic regression analysis, overweight patients were 3.4 times more likely to develop fatigue than nonobese breast cancer patients. Our findings are in line with those of Mao *et al*. (2018) and Inglis *et al*. (2010), who established a statistically significant relationship between obesity and CRF. Overweight increases the risk of fatigue by increasing the risk of conditions that cause fatigue as a common symptom, such as diabetes or sleep apnea. Carrying more weight and experiencing joint or muscle pain can lead to or exacerbate fatigue (Rowe *et al*., 2017). Moreover, low-grade chronic inflammation makes overweight people feel tired, which explains why obese individuals express fatigue. The abdominal fat cells produce cytokines that increase sleepiness and reduce energy, leading to fatigue (Sweatt *et al*., 2018). Additionally, being overweight means being more likely to carry more weight, being more likely to have joint and muscle pain, and being more likely to have a condition where fatigue is a common symptom. Diabetes and sleep apnea are some of the risk factors of fatigue (McVinnie, 2013).

In this study, smoking showed a significant association with clinically significant fatigue, in accordance with previous research (Peppone *et al*., 2011). Smokers have a lower lung capacity than that of nonsmokers and less oxygen in the lungs

Table 3. Type of relationship between fatigue incidence and demographic and clinical factors.

Variables	Fatigue incidence				
	b	OR	CI (95%)		*p*-value*
			Lower	Upper	
Age					
Young age <55 years	Reference				
Elderly ≥55 years	1.69	5.42	2.58	11.39	0.001
BMI kg/m^2					
Normal (<25)	Reference				
Overweight (25–30)	1.24	3.44	1.55	7.62	0.002
Obese (>30)	1.29	3.63	3.63	0.67	0.135
Smoking status					
Smoker	Reference				
Nonsmoker	−1.18	0.31	0.11	0.84	0.021
Alcohol consuming					
Consuming	Reference				
Nonconsuming	2.1	8.17	2.31	28.86	0.001
Number of regimens					
Single	Reference				
Combination	3.03	21.29	8.57	52.95	0.001
Chemotherapy type					
FEC-received	Reference				
FEC-not received	1.81	6.13	2.48	15.19	0.001

* Logistic regression analysis. $p < 0.05$ indicated a level of significance.

means less oxygen to the brain, muscles, and other body systems. Over time, this can easily lead to reduced respiratory function and produce fatigue.

We found that breast cancer patients who received a combination of chemotherapy were more likely to develop CRF than those who received only one chemotherapy regimen (Table 3). This was expected, given chemotherapy may suppress the bone marrow and decrease the number of RBCs which leads to developing CRF. This finding is in agreement with one trial which reported that breast cancer patients who received combinations of chemotherapy medications experienced more severe fatigue than those who received only one chemotherapy (paclitaxel) (Prigozin *et al*., 2010). In addition, our finding is in line with one study carried out by Abrahams *et al*. (2016), which reported that the prevalence rate of severe fatigue increases from 7% to 52%, after receiving a combination of chemotherapy regimens. Combined therapy regimens with two or more chemotherapy medications worsen fatigue than either modality given alone. Fatigue tends to worsen with subsequent cycles of chemotherapy, which suggests a cumulative dose-related toxic effect which in turn reduces the quality of life.

Finally, our data found that the type of chemotherapy regimen, e.g., FEC, associated significantly with CRF. Logistic regression analysis revealed that patients who were prescribed FEC were less likely to induce CRF compared to those who did receive FEC. This finding is in agreement with one study which concluded that CRF was associated significantly with FEC and could be treated with modafinil that reduced fatigue associated with FEC (Mahoney *et al*., 2013).

STRENGTHS AND LIMITATIONS

Strengths

1. This research was carried out at various hospitals. As a result, the outcomes could well be generalized to nations and used to enhance medical care at different cancer treatment facilities.
2. All breast cancer survivors who participated in this study were at various stages of the illness, resulting in a diverse research population.
3. Our findings are attributed to the relatively large populations, and several potential considerations, such as sociodemographic and clinical features, are included in the descriptive statistics.
4. This setting used the BFI as a screening tool to evaluate the severity of fatigue. BFI is valid, reliable, simple, contains items easy to understand, and can be completed fast (it takes up to 10 minutes). BFI only assesses one dimension (physical fatigue).

Limitations

1. The outcome of the social status analysis was not very fairly obvious due to the relatively small sample size of respondents. This could be due to the fact that the vast

majority of the participants were Muslims, and all of them were women, indicating the lower proportion of cigarette smoking and alcohol-related patients in the Muslim society. As a result, future research should include a larger sample size to verify the findings.

2. The criteria for inclusion may have resulted in sample bias since only participants who were interested in joining and who had undergone chemotherapy only were included. As a result, the study findings may not be applicable to all oncology patients undergoing other different kinds of anticancer therapy, e.g., radiotherapy, during this time period.
3. The scarcity of research about the incidence and determinants of CRF among breast cancer patients as well as treatment adherence.

Despite these limitations, our study adds insights into the current literature by investigating the occurrence and predictors of CRF in breast cancer patients undergoing chemotherapy, and it acts as a powerful evidence for more appropriate CRF intervention and control approaches.

CONCLUSION

Our study examined the clinical and demographic factors associated with the prevalence and incidence of fatigue in breast cancer patients. Many factors (e.g., increased age, obese, and type of chemotherapy) were associated significantly with the prevalence of CRF. Further research is needed into the guideline for treating CRF and whether or not it impacts the health status of the patient's well-being. Our study contributes to that effort by providing data that can be used to identify groups of patients at increased risk of CRF. For these groups, optimal cancer management should include effective fatigue treatment.

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CONFLICTS OF INTEREST

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AUTHOR CONTRIBUTIONS

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work. All the authors are eligible to be an author as per the international committee of medical journal editors (ICMJE) requirements/guidelines.

ETHICAL APPROVALS

Ethical clearance details are given in Materials and Methods section.

DATA AVAILABILITY

All data generated and analyzed are included within this research article.

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