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Fatigue With Systolic Heart Failure

Anne M. Fink, MS, RN, CCRN,

Predoctoral Fellow, Department of Biobehavioral Health Science, University of Illinois at Chicago

Shawna L. Sullivan, MS, ACNP,

Acute Care Nurse Practitioner, Department of Biobehavioral Health Science, University of Illinois at Chicago

Julie J. Zerwic, PhD, RN, and

Associate Professor and Interim Department Head, Department of Biobehavioral Health Science, University of Illinois at Chicago

Mariann R. Piano, PhD, RN

Professor, Department of Biobehavioral Health Science, University of Illinois at Chicago

Abstract

Background and Research Objective—Fatigue is one of the most prevalent symptoms in persons with systolic heart failure (HF). There remains insufficient information about the physiological and psychosocial underpinnings of fatigue in HF. The specific aims of this study were to (1) determine the psychometric properties of 2 fatigue questionnaires in patients with HF, (2) compare fatigue in patients with HF to published scores of healthy adults and patients with cancer undergoing treatment, and (3) identify the physiological (eg, hemoglobin, B-type natriuretic peptide, body mass index, and ejection fraction) and psychosocial (eg, depressed mood) correlates of fatigue in HF.

Subjects and Methods—A convenience sample of 87 HF outpatients was recruited from 2 urban medical centers. Patients completed the Fatigue Symptom Inventory, Profile of Mood States, and Short Form-36 Health Survey.

Results and Conclusions—Patients with HF and patients with cancer reported similar levels of fatigue, and both patient groups reported significantly more fatigue than did healthy adults. Physical functioning and hemoglobin categories explained 30% of the variance in Fatigue Symptom Inventory-Interference Scale scores, whereas depressed mood and physical functioning explained 47% of the variance in Profile of Mood States Fatigue subscale scores. Patients with HF experienced substantial fatigue that is comparable with cancer-related fatigue. Low physical functioning, depressed mood, and low hemoglobin level were associated with HF-related fatigue.

Keywords

fatigue; heart failure; hemoglobin

Fatigue With Systolic Heart Failure

Fatigue is one of the most prevalent symptoms in patients with systolic heart failure (HF).^{1,2} The prevalence of fatigue in HF ranges from 50% to 96%,^{1,3–6} and fatigue in this population is associated with poor quality of life,^{1,3,4,7} restricted physical activity,⁸ and worsening HF

prognosis.⁹ The National Institutes of Health has identified fatigue in chronic illness as a priority area of research because there remains limited knowledge about the physiological and psychosocial underpinnings of fatigue in chronic illnesses, such as HF.¹⁰

Using different types of fatigue assessment questionnaires in patients with HF, investigators have found that dyspnea,^{3,8} negative personality traits (eg, anger and hostility),⁸ low life satisfaction,^{1,3} sleep problems,^{3,8} and depressed mood^{2,8} were all associated with fatigue. Investigators have also examined demographic characteristics and found that being married,¹ being female, having low education, and being unemployed⁸ were associated with fatigue in patients with HF. Evangelista and colleagues,² however, found that neither patients' age nor sex was associated with Fatigue subscale scores on the Profile of Mood States (POMS). The relationships between fatigue and indirect measures of functional status, such as New York Heart Association (NYHA) classification and left ventricular ejection fraction (EF), have also been investigated. Data from some studies support an association between fatigue and NYHA classification,^{7,8,11} whereas data from other investigations have not indicated a significant correlation between fatigue and either NYHA classification² or EF.^{2,7}

Physiological correlates have received less attention in research about HF-related fatigue. Anemia has been implicated as one of the most common causes of cancer-related fatigue.¹² Anemia is a common comorbidity in patients with HF¹³; anemia is associated with worsening HF symptoms and functional status and with increased mortality in HF.¹⁴ To date, only 2 investigations have examined anemia and fatigue in patients with HF, and the findings are equivocal.^{7,11} To our knowledge, other physiological variables have not been examined in the setting of HF-related fatigue, such as B-type natriuretic peptide (BNP) or obesity. B-type natriuretic peptide is secreted by the ventricles in response to excessive ventricular stretch (eg, increased volume and pressure) and has become an established biomarker for exacerbation of chronic HF.¹⁵ The relationship between fatigue and BNP, however, is not known. In addition, obesity has been associated with fatigue in healthy adults¹⁶ and in individuals with obstructive sleep apnea,¹⁷ but the relationship between obesity and fatigue in HF has not been explored.

Aims

The aims of this study were to (1) determine the psychometric properties of 2 fatigue questionnaires in patients with HF and (2) compare fatigue levels in patients with HF with those of a healthy population and of patients undergoing treatment for cancer, a condition in which fatigue is very prevalent. A third aim was to determine whether clinical/physiological variables (eg, NYHA classification, EF, BNP, body mass index [BMI], and hemoglobin), psychosocial variables (eg, depressed mood), and physical functioning were correlated with fatigue severity in patients with HF.

Methods

Participants

A convenience sample of patients with systolic HF (N = 87) was recruited from 2 urban medical center outpatient HF clinics. Inclusion/exclusion criteria included a diagnosis of systolic HF for at least 1 year,¹⁸ blood pressure greater than 90/60 mm Hg and less than 180/100 mm Hg, heart rate of 50 to 100 beats/min, and the absence of acute/exacerbated HF signs and symptoms (eg, shortness of breath) for 3 months before enrollment in the study. Patients were able to read English and were alert and oriented.

Research Design

This study used a cross-sectional research design. Data on patients with HF were collected prospectively, and data from the healthy and cancer comparison samples were obtained from

published studies.^{19–21} The study was approved by the institutional review board, and all participants provided informed consent. Questionnaire data, as well as demographic characteristics, physiological parameters, and clinical variables, were collected during a scheduled outpatient visit.

Measures

Fatigue was measured using the Fatigue Symptom Inventory (FSI)-Interference Scale and the Fatigue and Vigor subscales of the POMS (POMS-F and POMS-V, respectively). The 13-item FSI was developed by Hann and colleagues²¹ to measure fatigue in patients with cancer. The FSI includes 13 quantitative questions, and each question is answered using an 11-point Likert-type scale (0, no interference to 10, extreme interference). Similar to others,^{21,22} in this study, we used questions 5 to 11, which are referred to as the FSI-Interference Scale, to measure the degree to which fatigue has interfered with patients' daily activities in the past week. Physical, cognitive, and emotional aspects of daily living are measured using this scale. Scores on the FSI-Interference Scale range from 0 to 10, with higher scores reflecting more interference from fatigue.

Although the FSI has not previously been used in patients with HF, we found that the FSI-Interference Scale items were appropriate in the context of HF; the FSI-Interference Scale is used to assess the degree to which fatigue interferes with physical activity, mood, and the ability to perform self-care activities. The FSI has been used to measure fatigue in patients with different cancer diagnoses, including cancers of the breast,^{21–23} liver,²⁴ colon, or prostate.²² The FSI has been used to quantify fatigue with chronic fatigue syndrome²⁵ and has also been tested with healthy adults.^{21,23} In noncardiac populations, the psychometric properties of the FSI-Interference Scale were adequate.^{21,22} An aim of this study was to evaluate the psychometric properties of the FSI-Interference Scale in a sample of patients with HF.

To test the validity of the FSI in this study, we also used the POMS-F and POMS-V. The POMS-F has been used in 2 recent studies of fatigue in HF.^{1,2} The POMS was initially developed for use in patients with psychiatric disorders.²⁶ More recently, the POMS-F has been used to measure fatigue with rheumatoid arthritis^{27,28} and with cancer.^{20–22,29,30} Like the FSI, the POMS-F and POMS-V have been used in healthy samples as well.^{19,26,27}

On the POMS, patients use a 5-point Likert scale to choose words or phrases that reflect feelings associated with fatigue or vigor. Scores on the 7-item POMS-F range from 0 to 28, with higher scores reflecting more fatigue. Similarly, scores on the 8-item POMS-V range from 0 to 32, with higher scores reflecting more vigor.²⁶ Internal consistency reliability for the POMS-F subscale has been adequate ($\alpha > .80$) in patients with HF.^{1,2}

Depressed mood was measured using the Depression subscale of the POMS (POMS-D). Similar to the other POMS subscales, a 5-point Likert-type scale is used to respond to items reflecting a depressed mood. Scores on the POMS-D range from 0 to 60, with higher scores reflecting a greater degree of depressed mood. As with the POMS-F and POMS-V, the psychometric properties of the POMS-D have been well established.²⁶

Physical functioning was measured using the Short Form-36 Health Survey (SF-36) Physical Functioning subscale. The physical functioning items are used to measure a patient's perceived limitations with performing vigorous activities (eg, running and lifting heavy objects), moderate activity (vacuuming), and other activities such as climbing stairs and bathing/dressing. The subscales of the SF-36 have been recognized for strong psychometric properties.^{31,32}

Statistical Analyses

Data were analyzed using SPSS version 15.0 (SPSS Inc, Chicago, Illinois). An α level of .05 was selected for statistical significance. To determine the internal consistency reliability of the measures, Cronbach α was calculated for each subscale (FSI-Interference Scale, POMS-F, POMS-V, POMS-D, and SF-36 Physical Functioning). To determine the degree of fatigue experienced in HF, the scores of patients with HF on the FSI-Interference Scale, POMS-F, and POMS-V were compared with published scores of patients with cancer undergoing active treatment with chemotherapy or radiation^{20,21} and of samples of healthy adults^{19,21} using analysis of variance and t tests. The fatigue scores of patients with HF (FSI-Interference Scale and POMS-F) were examined using analysis of variance and/or t tests to determine if scores differed according to sex, race, marital status, or hemoglobin categories. Similar to others,³⁰ the sample was divided into hemoglobin categories of low (<11.0 mg/dL), moderate (11–12.99 mg/dL), and high (>13 mg/dL). Pearson correlations were calculated between the fatigue scores of patients with HF and their age, years diagnosed with HF, NYHA classification, EF, BNP, BMI, hemoglobin category, physical functioning (SF-36 Physical Functioning subscale), and depressed mood (POMS-D). Variables that were significant in these univariate analyses were then examined in a stepwise regression analysis to identify which variables were significant correlates of fatigue.

Results

Sample Characteristics

Participants ($N = 87$) were 21 to 89 years of age (mean, 57 years; SEM, 1.5 years). The duration of HF ranged from 1 to 16 years (mean, 5 years; SEM, 0.5 years), and participants were predominately NYHA class II or III (Table 1). Participants were also predominantly African American and female (Table 1). Hemoglobin levels were available for 79% of the patients enrolled. Fourteen patients had a hemoglobin level below 11.0 mg/dL (20%), 29 patients had hemoglobin levels of 11 to 12.99 mg/dL (42%), and 26 patients had hemoglobin levels greater than 13 mg/dL (38%). Other demographic and clinical/ physiological characteristics are shown in Tables 1 and 2.

Psychometric Properties of the FSI-Interference Scale and POMS Subscales

The psychometric properties of the FSI-Interference Scale and the POMS subscales were adequate in this sample. Scores were internally consistent for the FSI-Interference Scale ($\alpha = .93$), POMS-F ($\alpha = .90$), POMS-V ($\alpha = .90$), POMS-D ($\alpha = .93$), and SF-36 Physical Functioning subscale ($\alpha = .89$). As expected, FSI-Interference Scale scores were correlated with POMS-F scores ($r = 0.66$, $P = .01$) and inversely associated with POMS-V scores ($r = -0.28$, $P = .009$).

Distribution of Fatigue Subscale Scores

Most patients with HF reported “a little” or “moderate” levels of fatigue on both instruments (Table 3). The distribution of fatigue subscale scores for the FSI-Interference Scale and POMS-F is shown in Table 3.

Comparisons of Fatigue Scores Among Patients With HF, Patients With Cancer, and Healthy Adults

To gain a better perspective on the degree of fatigue experienced by patients with HF, we compared our findings to previously published scores for patients with cancer receiving chemotherapy.^{20,21} No significant differences were found in FSI-Interference Scale scores between patients with HF (mean, 2.9; SEM, 0.3) and patients with cancer²¹ (mean, 2.3; SEM, 0.2), and both patients with cancer and patients with HF reported significantly more interference from fatigue than did healthy adults¹⁹ (mean, 1.3; SEM, 0.1; $F = 9.0$, $P < .001$;

Figure 1). Similarly, on the POMS-F, no significant differences were found between patients with HF (mean, 9.9; SEM, 0.7) and patients with cancer²⁰ (mean, 11.4; SEM, 0.5), and both patients with HF and patients with cancer reported significantly more fatigue than did healthy individuals¹⁹ (mean, 7.3; SEM, 0.3; $F = 23.0$, $P < .001$; Figure 1). Consistent with the latter finding, we found significantly lower POMS-V scores in patients with HF (mean, 16.1; SEM, 0.7) compared with healthy adults¹⁹ (mean, 20.2; SEM, 0.3; $t = 4.8$, $P < .001$; Figure 1).

Correlates of Fatigue

FSI-Interference Scale—In the univariate analysis, FSI-Interference Scale scores were significantly correlated with depressed mood ($r = 0.43$, $P = .01$), hemoglobin categories ($r = -0.38$, $P = .01$), NYHA classification ($r = 0.29$, $P < .05$), and physical functioning ($r = -0.44$, $P = .01$). Participants with hemoglobin levels below 11.0 mg/dL had significantly higher FSI-Interference Scale scores (mean, 4.9; SEM, 0.8) compared with participants with hemoglobin levels above 13 mg/dL (mean, 2.0; SEM, 0.4; $F = 4.2$, $P = .02$). Scores on the FSI-Interference Scale did not differ according to sex, marital status, or race. Age, years diagnosed with HF, EF, BNP, and BMI were not correlated with FSI-Interference Scale scores. The significant univariate correlates for the FSI-Interference Scale were entered into a stepwise regression analysis. Physical functioning and hemoglobin categories were significant correlates in the multivariate model and explained 30% of the variance in FSI-Interference Scale scores (Table 4).

Profile of Mood States Fatigue Subscale—There was a significant correlation between POMS-F scores and depressed mood ($r = 0.64$, $P = .01$) and physical functioning ($r = -0.33$, $P = .01$). Also, POMS-F scores did not differ according to sex, marital status, or race. Age, years diagnosed with HF, NYHA classification, EF, BNP, hemoglobin categories, and BMI were not correlated with POMS-F scores. The significant univariate correlates for the POMS-F were entered into a stepwise regression analysis, and depressed mood and physical functioning explained 47% of the variance in POMS-F scores (Table 4).

Discussion

This was the first study to compare fatigue in patients with HF to fatigue reported by patients with cancer. During treatment, patients with cancer are known to experience profound fatigue. We found that the level of fatigue was similar in these 2 patient populations, indicating that patients with HF experience high and clinically significant levels of fatigue. Our findings are similar to those reported by Stephen¹ and Evangelista et al,² who, using the POMS-F, reported a high prevalence of fatigue among patients with HF. Recently, Smith et al,³³ using the Fatigue Assessment Scale, found that patients with HF reported significantly more fatigue compared with age-matched healthy controls (healthy control group, 9.2 ± 5.6 vs HF group, 16.5 ± 7.9). Our findings, along with those of others, continue to substantiate the prevalence and burden of fatigue among patients with HF.

Fatigue is a complex symptom, and measuring fatigue may require the use of instruments that address different functional and psychosocial manifestations of fatigue. In this study, we used 2 different questionnaires to measure fatigue. We choose the FSI and POMS because the FSI reflects the degree to which fatigue interferes with a person's daily activities and the POMS includes several subscales that measure the occurrence of different moods and attitudes. On the FSI-Interference Scale, we found that low hemoglobin level and limited physical functioning predicted fatigue. These findings are not surprising because several of the items on the FSI-Interference Scale are related to the ability to perform work and self-care, which may be hindered by the presence of anemia or limited physical function. In contrast, on the POMS-F, fatigue scores were predicted by depressed mood as well as limited physical

functioning. The items on the POMS-F reflect fatigue as a mood. For example, patients rate the degree to which they have felt listless, sluggish, exhausted, and weary. These concepts are closely related to the POMS-D items associated with depressed mood and to the SF-36 items that measure decreased physical functioning.

Our finding that depressed mood was a significant correlate of fatigue is consistent with findings reported by others.^{2,8} Depression and depressed mood are common in HF, although it remains incompletely understood why depression is so prevalent in this population and whether HF begets depression or whether depression begets HF.³⁴ For example, depression may occur in patients with HF as they develop functional limitations, or there may be shared pathophysiological mechanisms such as increased cytokine levels. In otherwise healthy individuals, increased cytokines have been implicated as a pathophysiologic mechanism for depression.³⁵ Cytokines, such as tumor necrosis factor α and interleukins, are increased in patients with HF. Although beyond the scope of this discussion, there is evidence to suggest that cytokines may alter the function/level of monoamine neurotransmitters and activate the hypothalamic-pituitary-adrenal axis, which is involved in the neurobiology of mood disorders.^{36,37} Also, fatigue is a common symptom of depression, and recently, Krum and Iyngkaran³⁴ suggested that the presence of fatigue may contribute to the diagnosis of depression. In HF, both depression and depressed mood are associated with higher mortality rates.^{38,39}

Consistent with Falk et al,¹¹ we found that low hemoglobin level was significantly correlated to the occurrence of fatigue. A reduction in hemoglobin (the iron-containing oxygen transport molecule) may result in muscle fatigue from inadequate oxygen delivery to the muscle. Statistical correlations between hemoglobin levels and scores on questionnaires, however, have not always been found in a variety of patient populations, including HF.^{7,40–43} For example, Schaefer et al⁷ did not find a significant correlation between hemoglobin levels and scores on the modified Fatigue Interview Schedule. Differences in sample demographics and the use of different instruments to measure fatigue may explain dissimilar findings regarding hemoglobin.

Consistent with Evangelista and colleagues,² we did not find a correlation between age and fatigue in patients with HF. Others have reported that cancer-related fatigue is equally prevalent in older and younger patients with cancer, suggesting that age is not correlated with fatigue. Higher levels of fatigue have been found in women with HF⁸ and in patients with HF who are married,¹ but we did not find a relationship between fatigue and female sex or between fatigue and being married.

We did not find EF, BNP, or BMI to be correlates of fatigue on either the FSI-Interference Scale or the POMS-F. With regard to EF, our findings are similar to those of Evangelista and colleagues, who also did not find a correlation between fatigue and EF. In HF, EF is not consistently correlated with physical functioning or with NYHA classification. To date, there have been no investigations of the relationship between BNP levels and HF-related fatigue. N-terminal proBNP and BNP are established biomarkers for exacerbation of chronic HF, and increased BNP levels reflect increased intracardiac filling pressures.⁴⁴ Higher levels of N-terminal proBNP are associated with increased risk of death and hospital admission related to de-compensated HF.⁴⁵ Even though our mean BNP level was 303 ± 37 pg/mL, our sample was a stable outpatient group of patients with HF; the majority were NYHA classification II/III. In a meta-analysis of 4 studies examining the relationship between BNP and functional status, Abdulla and colleagues⁴⁶ found that increased BNP was usually not correlated to poor functional status. However, it remains possible that, in patients with more severe HF (NYHA classification IV), increased BNP levels may be correlated with fatigue.

Fatigue with obesity has been attributed to metabolic and physiological factors such as insulin resistance and increased levels of cytokines.⁴⁷ In healthy adults¹⁶ and in individuals with obstructive sleep apnea, greater BMI values were correlated with fatigue.¹⁷ We did not find a correlation between BMI and fatigue in HF. We obtained height and weight data from the medical record and used those values to calculate BMI. According to Shirley and colleagues,⁴⁸ BMI as an estimate of body weight may have limitations in people who are edematous, those who have lost muscle mass (eg, elderly patients), individuals who are of extreme height, or those who have disproportionate limbs in relationship to trunk radius. Therefore, we recommend that BMI and fatigue be reexamined in a prospective manner.

Study Limitations

Limitations of this study include the small sample size and the lack of prospective data on a healthy control group and cancer group. Also, the patients with HF in this study were predominantly from a minority population, which may limit the generalizability of the findings. Another limitation relates to the use of multivariate analyses and the inability to determine causality or the direction of the relationships between the variables. For example, it is unclear whether depressed mood causes fatigue or whether fatigue leads patients with HF to experience a depressed mood. Despite these limitations, we believe that this study provides important information about fatigue and HF and highlights how reduced physical functioning, low hemoglobin level, and depressed mood are important correlates of fatigue.

Conclusion

In summary, we demonstrate that fatigue is prevalent in patients with HF, and the severity is comparable to that in patients with cancer actively undergoing chemotherapy or radiation therapy. Our findings underscore the importance and burden of fatigue in HF and the need to further investigate potential mechanisms that underlie fatigue in HF, such as anemia, depressed mood, and limited physical functioning. Further research will lead to the development of tailored and evidence-based interventions to treat HF-related fatigue.

What's New and Important

- HF patients experience substantial fatigue that is comparable to cancer-related fatigue.
- Depressed mood, low hemoglobin and limited physical functioning may be related to fatigue in HF.
- Our findings underscore the need to further investigate potential mechanisms that underlie fatigue in HF. This will lead to the development of tailored and evidence-based interventions to treat HF-related fatigue.

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FIGURE 1.

Comparisons of fatigue scores among patients with heart failure, patients with cancer, and healthy adults. Scores on the POMS Vigor subscale for patients with cancer were not available from the literature. * $P < .001$. FSI indicates Fatigue Symptom Inventory Interference Scale; POMS, Profile of Mood States.

Sample Demographics**TABLE 1**

Sex	
Male	44%
Female	56%
Race	
African American	77%
White, Non-Hispanic	15%
Hispanic/Latino	5%
Other	3%
Marital status	
Single	51%
Married/long-term relationship	29%
Divorced/separated/widowed	20%
Education	
<High school	30%
>High school	70%
Employment	
Employed	28%
Retired	30%
Unemployed/disabled	42%
New York Heart Association classification	
I	19%
II	41%
III	38%
IV	2%
Medications	
ACE inhibitors	63%
Angiotensin receptor blocker	23%
β -Blockers	98%
Calcium channel blockers	15%
Digoxin	35%
Diuretic	81%
Lipid-lowering agents	59%

Abbreviation: ACE, angiotensin-converting enzyme.

TABLE 2
Clinical and Physiological Variables

Hemoglobin, mg/dL	12.3 ± 0.2
BMI, kg/m ²	33.5 ± 1.1
BMI ≥30 kg/m ²	46
Ejection fraction, %	27 ± 1.6
B-type natriuretic peptide, pg/mL	303 ± 36.7
Blood urea nitrogen, serum, mg/dL	20 ± 1.7
Creatinine serum, mg/dL	1.5 ± 0.1
Systolic pressure, mm Hg	120.7 ± 2.2
Diastolic pressure, mm Hg	70.1 ± 1.2
Heart rate, beat/min	72.3 ± 1.7
Comorbidities	
Dysrhythmia	54
Diabetes mellitus	36
Hyperlipidemia	55
Hypertension	70
Thyroid disease	14
Pulmonary disease (COPD, asthma)	24
Renal insufficiency	15
Depressed mood (POMS-D)	21 ± 5
Physical functioning (SF-36)	9.5 ± 10

Abbreviations: BMI, body mass index; COPD, chronic obstructive pulmonary disease; POMS-D, Profile of Mood States Depression subscale; SF-36, Short Form-36 Health Survey.

Values are mean ± SEM or percentage of total sample.

TABLE 3
Distribution of Figure Subscale Score

Score Ranges	% of Sample
FSI-Interference Scale	
None (0)	11.9
A little (0.1–3.9)	54.8
Moderate (4–7.9)	28.5
Extreme (>7.9)	4.8
POMS-F	
None (0)	3.4
A little (1–6)	38.0
Moderate (7–13)	34.5
Quite a bit (14–20)	17.2
Extreme (>20)	6.9

Abbreviations: FSI, Fatigue Symptom Inventory; POMS-F, Profile of Mood States Fatigue subscale.

To compare the distribution of POMS-F scores with the FSI-Interference Scale, we arbitrarily designated the following for each question: a score of 0, no fatigue; 0.1–3.9, a little fatigue; 4–7.9, moderate fatigue; and >7.9, extreme fatigue.

TABLE 4
Stepwise Regression Analysis for Determinants of Fatigue

Predictors	β	R^2 Change	t	P
FSI-Interference Scale scores				
Physical functioning	-0.39	0.20	-3.8	<.001
Hemoglobin categories	-0.37	0.13	-3.5	.001
Full model information: $R^2 = 0.30$, $F_{2,65} = 15.5$, $P < .001$				
POMS-F scores				
Depressed mood	0.61	0.42	7.6	<.001
Physical functioning	-0.24	0.06	-3.0	.003
Full model information: $R^2 = 0.47$, $F_{2,85} = 37.8$, $P < .001$				

Abbreviations: FSI, Fatigue Symptom Inventory; POMS-F, Profile of Mood States Fatigue subscale.