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Risk Factors and Symptoms Associated with Pain in HIV-Infected Adults

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Abstract

Studies suggest that people living with HIV (PLWH) experience many unrelieved symptoms. The purposes of this study was to estimate the occurrence of pain in adult PLWH and to determine whether participants with pain differed from those without pain on selected demographic factors, clinical characteristics, symptoms of fatigue, sleep disturbance, anxiety, or depression. We conducted a descriptive, comparative, and correlational study of 317 PLWH seen at academic and community clinics in San Francisco. Participants completed a demographic questionnaire, the MSAS, the FSS, the GSDS, the POMS Tension-Anxiety subscale, and the CESD. Medical records were reviewed for clinical characteristics (i.e., disease and treatment information). A single item on pain from the MSAS was used to classify participants into those with and without pain. Pain was highly prevalent (55%)

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and was associated with immune status (CD4+ T cell count), race, and sleep disturbance, but not with age, sex, or symptoms of fatigue, depression, or anxiety.

Keywords

HIV; PLWH; pain; sleep disturbance; symptoms

While the treatment of PLWH has improved significantly, epidemiologic studies suggest that these patients experience a number of unrelieved symptoms, including pain, that limit their quality of life. Pain is consistently one of the most frequently reported symptoms in PLWH (Breitbart et al., 1996; Lee et al., in press; Vogl et al., 1999), with estimates ranging from 30% to 80% (Lebovits, Smith, Maignan, & Lefkowitz, 1994; Schofferman, 1988; Singer et al., 1993). Pain can be due to multiple causes including the disease itself or its consequences, treatments for HIV infection, or other chronic conditions. However, most of these pain studies evaluated HIV-infected patients with AIDS (Lebovits et al., 1994; Schofferman, 1988) or HIV-infected individuals in the terminal stages of the disease (Schofferman, 1988). A particular concern with these pain studies is that they no longer reflect PLWH in the present day given new treatment options and clinical care, which would be expected to impact the occurrence of symptoms in this population.

Clinical experience suggests that PLWH rarely present with a single symptom (Lee et al., in press; Vogl et al., 1999). Numerous studies have described individual symptoms such as fatigue (Lee, Portillo, & Miramontes, 2001; Lee et al., in press), depression (Lee et al., in press), or sleep disturbance (Lee et al., 2001; Lee et al., in press) in these patients. However, no studies have evaluated differences in the severity of fatigue, sleep disturbance, anxiety, or depression in PLWH with and without pain. This omission is clinically relevant given the fact that these symptoms are often synonymous with poorer functional status and quality of life in other chronic conditions including cancer (Portenoy et al., 1994), heart failure, and diabetes (Stewart et al., 1994). Moreover, associations between pain and age, sex, race, number of co-morbid conditions, and symptoms (e.g., fatigue, sleep disturbance, anxiety, depression) have been reported in patients with cancer (Kim, Dodd, Aouizerat, Jahan, & Miaskowski, 2008) and chronic obstructive pulmonary disease (Blinderman, Homel, Billings, Tennstedt, & Portenoy, 2009). However, no study has described these relationships in a sample of PLWH.

While pain in PLWH is recognized as a common problem (Breitbart et al., 1996; Vogl et al., 1999), the last study of its occurrence and description was published in 1993 (Dobalian, Tsao, & Duncan, 2004). This omission is significant because of differences in treatments for and demographics of PLWH. No study was found that examined the occurrence of and risk factors for pain in a large cohort of community-dwelling HIV-infected individuals. Therefore, the purposes of this study were to describe the occurrence of pain and risk factors for pain and to compare differences in fatigue, sleep disturbance, anxiety and depressive symptoms in HIV-infected participants with and without pain.

Methods

The Symptom and Genetic Study is an ongoing prospective, longitudinal study designed to identify biomarkers of the symptom experience of HIV-infected adults. This analysis evaluated data from the initial assessment of adults living with HIV in the San Francisco area. The protocol was approved by the Committee on Human Research (CHR) at the University of California, San Francisco (UCSF). All participants provided written informed consent prior to enrollment and signed a Health Insurance Portability and Accountability Act (HIPAA) release for the use of their protected medical information in research.

Participants and Settings

Adults were recruited using flyers posted at CHR-approved local HIV clinics and community sites, and study visits were conducted at the UCSF General Clinical Research Center. Eligible participants were English-speaking adults who were at least 18 years of age and who had been diagnosed with HIV at least 30 days prior to enrollment. Individuals were excluded if they currently used illicit drugs (as assessed by self-report and subsequent drug test), worked nights (i.e., at least 4 hours between 12 a.m. and 6 a.m.), reported having a diagnosed sleep disorder, bipolar disorder, schizophrenia, or dementia, or had been pregnant within the previous 3 months.

Measures

In addition to completing the demographic and symptom questionnaires, participants were screened for illicit drug use by a urine drug test at the beginning and end of the 3-day assessment. Data on demographic and clinical characteristics were obtained by self-report, including time since HIV diagnosis, prior AIDS diagnosis, and antiretroviral therapy (ART) regimen. CD4+ T cell count and viral load measures were obtained from the most recent lab report in the medical record. A demographic questionnaire provided information on age, sex, marital status, educational background, ethnicity, employment status, and number of co-morbid conditions (e.g., hepatitis, diabetes, asthma, hypertension).

The Memorial Symptom Assessment Scale (MSAS), which contains a list of 32 physical and psychological symptoms, is a self-report questionnaire designed to measure the multidimensional experience of symptoms (Portenoy et al., 1994) and has been used in studies of PLWH (Harding, Molloy, Easterbrook, Frame, & Higginson, 2006). Using the MSAS, patients were asked to indicate whether or not they had experienced each symptom in the previous week (i.e., symptom occurrence). If they had experienced the symptom, they were asked to rate its severity, frequency of occurrence, and distress. Symptom severity was measured using a 5-point Likert scale (i.e., 0 [*not at all*], 1 [*mild*], 2 [*moderate*], 3 [*severe*], 4 [*very severe*]). The patients' responses to the occurrence of pain were used to create the pain versus no pain groups. The reliability and validity of the MSAS is well established (Portenoy et al., 1994).

The Fatigue Severity Scale (FSS) was used to assess participants' levels of fatigue in the previous week (Krupp, LaRocca, Muir-Nash, & Steinberg, 1989). The FSS is comprised of 9 items that evaluate features of fatigue that are common in chronic disease (i.e., *Exercise brings on my fatigue*). Each item was rated on a numeric rating scale that ranged from 1 (*strongly disagree*) to 7 (*strongly agree*). The responses to the 9 items were averaged to yield a total score that could range from 1 (*no fatigue*) to 7 (*extreme fatigue*). A score of 2.3 is the norm in healthy individuals (Krupp et al., 1989). The FSS has well-established test-retest reliability and differentiated between patients with chronic disease and healthy adults. In this study, the Cronbach's alpha for the FSS was 0.91.

The General Sleep Disturbance Scale (GSDS; Lee et al., 2001) was used to assess perceived sleep quality and quantity in the previous week. The GSDS has 21 items that evaluate various aspects of sleep disturbance (i.e., quality and quantity of sleep, sleep onset latency, sleep maintenance, excessive daytime sleepiness, medication use). Each item was rated on a 0 (*never*) to 7 (*every day*) numeric rating scale. The 21 items were summed to yield a total score that could range from 0 (*no disturbance*) to 147 (*extreme disturbance*). Scores of 43 and higher indicate a clinically significant level of sleep disturbance. The GSDS has well-established validity and reliability in shift workers, pregnant women, and PLWH (Lee et al., 2001). In our study, the Cronbach's alpha coefficient for the GSDS was 0.83.

The Center for Epidemiological Studies-Depression Scale (CES-D; Radloff, 1977) was used to assess the frequency of depressive symptoms in the previous week. The CES-D consists of 20 items selected to represent major symptoms in the clinical syndrome of depression. Scores can range from 0 to 60 with scores of 16 and higher indicating the need for patients to seek clinical evaluation for major depression. The CES-D has well-established concurrent and construct validity. In this study, the Cronbach's alpha coefficient for the CES-D was 0.88.

The Profile of Moods State (POMS) Tension-Anxiety subscale (McNair, Lorr, & Droppleman, 1971) was used to assess anxiety in the previous week. The subscale has 9 items selected to represent the major symptoms of anxiety. Scores can range from 0 to 36, with 8.6 as the mean in HIV-infected outpatients (Illa et al., 2008). Only the Tension-Anxiety subscale was measured in this cohort. The POMS has well-established concurrent and construct validity. In this study, the Cronbach's alpha coefficient for the POMS subscale was 0.86.

Statistical Analyses

Data were analyzed using Stata® Version 8.0, and SPSS™ Version 13.0. Descriptive statistics were used to summarize the demographic and clinical characteristics of the sample and to calculate the occurrence of pain. Differences in demographic and clinical characteristics, as well as symptom severity scores were evaluated using Chi square, Fisher's Exact, Mann-Whitney, and independent samples *t* tests. A *p*-value < 0.05 was considered statistically significant. Square root transformations were sufficient to normalize skewed distributions for CD4+ T cell count, the CESD total score, and the POMS Tension-Anxiety subscale score.

Logistic regression analysis was used to determine the unique contributions of race/ethnicity, sex, age, clinical characteristics, and symptom measures to pain experience. Because males and transgender (22 male-to-female, 1 female-to-male) participants did not differ with respect to their report of pain, age, CD4+ T cell count, or race/ethnicity, their data were combined for subsequent analyses. Only those variables that were associated with the occurrence of pain in the bivariate analyses (*p* < 0.10) were retained in the multivariable analysis. Age and sex were controlled for in the model because numerous studies have shown a relationship between gender (Zingmond et al., 2003) and age (Rollman, 2003) and pain. An interaction term between sex and race was tested. Potential confounding between race, sex, and clinical characteristics was assessed. Age, sex, race, CD4+ T count ≤ 200 cells/mm³, and prior AIDS diagnosis were entered into the model. A backwards stepwise procedure was employed for model building. Each predictor retained in the final model was required to have a *p*-value ≤ 0.20. Model assumptions and fit were evaluated by examination of standardized Pearson residuals to identify outlying observations. Model fit was also assessed by the goodness of fit test.

Results

Sample Characteristics

A convenience sample of 350 adults with HIV was enrolled in this study over a 3-year period (April 2005 - December 2007). Three had incomplete symptom data, 29 were excluded after screening positive for illicit drug use (i.e., cocaine, amphetamine, ecstasy, methamphetamine, or phencyclidine), and one was excluded after being unable to submit a urine sample for screening. The sample was ethnically diverse and predominantly male, which reflected the local population of adult PLWH. Over half (62%) of the 78 women in the sample were African American. Given the low number of participants self-identifying as being of mixed race/ethnicity, Asian/Pacific Islander, Native American, or of another race/ethnicity than the options provided in the questionnaire, these individuals were collapsed into a single subcategory for analysis. Most participants had been living with HIV for many years; 71% were currently

receiving ART, 54% had an AIDS diagnosis, and most (75%) were receiving medical disability assistance.

Occurrence, Frequency, Severity, and Distress of Pain

A total of 175 participants (55%) indicated *yes* to the occurrence of pain on the MSAS. Of those with pain, 67% reported that it occurred *frequently* or *almost constantly* and 82% reported that it was *severe* or *very severe*. When asked how distressing their pain was in the last week, 58% described it as *quite a bit* or *very much* distressing.

Differences in Demographic and Clinical Characteristics

As shown in Table 1, no differences were found between the two pain groups on any of the demographic characteristics. With the exception of CD4+ T cell count, no differences were found in any of the clinical characteristics. Participants who reported pain had a significantly lower mean CD4+ T cell count ($p = .034$) and a larger proportion of those in pain had a CD4 + T cell count < 200 cells/mm³ ($p = .006$). Participants who reported pain also reported more co-morbid health problems ($p = .021$, Table 1).

Differences in Symptom Severity Scores

Differences in symptom severity scores between the pain and the no pain groups are summarized in Table 2. For the measurement of *sleep disturbance*, significant differences in mean total GSDS scores were found between the two groups ($p < .0001$). Participants with pain had significantly higher mean sleep disturbance scores (50.9 ± 20.8) than those without pain (37.2 ± 18.5). For the measurement of *fatigue*, significant differences in fatigue severity scores were found between the two pain groups ($p < 0.001$). Participants with pain had significantly higher mean fatigue scores (4.1 ± 2.3) than participants without pain (3.4 ± 2.2). For the measurement of *anxiety*, significant differences in mean POMS Tension-Anxiety subscale scores were found between the two pain groups ($p = .003$). Participants with pain had significantly higher anxiety scores (9.8 ± 7.4) than those without pain (7.3 ± 6.4). For the measurement of *depressive symptoms*, significant differences in mean CES-D scores were found between the two pain groups ($p < .0001$). Participants with pain had significantly higher CES-D scores (19.0 ± 10.7) than those without pain (14.2 ± 9.5).

Multivariate Analysis of Pain

Results of the regression analysis are presented in Table 3. After controlling for age (years), sex (male/transgender vs. female), race (non-Black vs. Black), and CD4+ T cell count ≤ 200 cells/mm³, every 10-point increase in GSDS score was associated with a 45% increase in the odds of reporting pain (OR = 1.45, 95% CI: 1.269, 1.661; $p < .001$). After controlling for age, race, GSDS total score, and sex, having a CD4+ T cell count ≤ 200 cells/mm³ was associated with a 307% increase in the odds of reporting pain (OR = 3.07, 95% CI: 1.476, 6.400; $p = 0.003$). After controlling for age, GSDS total score, sex, and CD4+ T cell count ≤ 200 cells/mm³, being Black was associated with a 48% decrease in the odds of reporting pain (OR = 0.52, 95% CI: 0.303, 0.897, $p = 0.019$).

Discussion

This study is the first to evaluate the occurrence of pain and differences in the severity of four common symptoms in the same sample of community-based PLWH with and without pain. Pain was reported by more than 55% of the sample, which is comparable to previous reports in PLWH but higher than the prevalence of chronic pain in the general population (Rustoen et al., 2004). In addition, regardless of pain group membership, the mean severity scores for sleep disturbance, anxiety, and depressive symptoms were above the established cutoffs for clinically

meaningful findings. Finally, the percentage of participants with clinically meaningful levels of all four symptoms is above the ranges that are common for fatigue (Krupp et al., 1989), sleep disturbance (Morin, LeBlanc, Daley, Gregoire, & Merette, 2006), anxiety (McNair et al., 1971), and depressive symptoms (Ohayon, 2007) in the general population.

Pain was reported by more than half (55%) of the participants in the study, and most (82%) of those who reported pain rated it as *severe* or *very severe*. This finding suggests that unrelieved pain is a significant problem for this population. Additional research is needed to determine the underlying causes, detailed characteristics, and functional outcomes associated with chronic pain in these individuals. While previous reports suggest that a variety of chronic pain conditions occur more frequently in women (Fillingim, King, Ribeiro-Dasilva, Rahim-Williams, & Riley, 2009), no sex differences were found in this study. This inconsistency may relate to the relatively small number of women in this study. In contrast, the finding that Blacks reported less pain than the other racial groups in this sample differs from prior reports in other chronic diseases (Cano, Mayo, & Ventimiglia, 2006), but it is consistent with previous reports in the HIV literature (Dobalian et al., 2004; Rotheram-Borus, 2000).

Several findings from the regression analysis are worth noting. The number of co-morbid health problems was not associated with pain group membership. While anxiety was found to mediate the relationship between pain and depressive symptoms in the regression analysis, as observed previously (Keller et al., 2008), this association was no longer significant after controlling for sleep disturbance (data not shown). Because only 13% of the variance in pain group membership was accounted for by total GSDS score, race, and immune status, additional risk factors need to be identified. However, while the precision of the point estimates for race and immune status were modest, the lower bound of each estimate suggests a clinically meaningful change in the odds of reporting pain. Of note, total GSDS score was the strongest predictor of pain group membership. This finding is consistent with recent literature that suggests that pain and sleep disturbance are interrelated (Moldofsky, 2001). The magnitude of this relationship may be underestimated in this cohort given the fact that individuals at risk for more severe sleep disturbance (e.g., illicit drug use, a diagnosed sleep disorder, nightshift workers, pregnant women) were excluded from this study.

An advantage of the symptom measures used in this study is their established cut-points for clinically meaningful differences. In comparison to the group without pain, a greater proportion of participants in the pain group rated the severity of the following symptoms above the established cut-point: sleep disturbance (cut-point ≥ 47 ; 44% in the group without pain vs. 66% in the group reporting pain, $p < .001$), and depressive symptoms (cut-point ≥ 16.0 ; 42% vs. 68%, $p < .001$). While cut-points for the POMS Tension-Anxiety subscale and the FSS are not established, the pain group had a greater proportion of individuals who rated the severity of their anxiety above the norm for HIV-infected individuals (Illa et al., 2008; norm ≥ 8.8 ; 47% vs. 66%, $p = .001$) and above the norm for healthy individuals for fatigue (cut-point ≥ 2.3 ; 41% vs. 59%, $p = .008$). In addition, differences in the severity of fatigue, sleep disturbance, depressive symptoms, and anxiety between the pain and no pain groups were also clinically meaningful based on calculation of effect sizes (i.e., Cohen's $d = 0.47$ for fatigue, $d = 0.70$ for sleep disturbance, $d = 1.46$ for depressive symptoms, $d = 1.49$ for anxiety; Norman, Sloan, & Wyrwich, 2003).

In our previous report on this cohort's symptom experience, a global symptom distress score was calculated using the MSAS (Lee et al., in press). Symptom distress was not related to age or CD4+ T cell count. However, having an AIDS diagnosis, being on ART, or being female was associated with higher levels of symptom distress. In addition, African American individuals reported lower levels of symptom distress than other racial/ethnic groups. In this study, which focused on pain, only some of the risk factors associated with global symptom

distress were associated with pain group membership. While having an AIDS diagnosis and taking ART were not significant factors, the direction of their associations with pain were concordant with global symptom distress.

A number of study limitations are worth noting. The generalizability of the findings may be limited to urban U.S. populations of HIV-infected individuals. The cross-sectional design precludes the ability to establish causal relationships among the associated symptoms. In the current study, only HIV disease-related ART medications were evaluated. Future studies need to evaluate the use of medications to relieve pain, fatigue, sleep disturbance, anxiety, and depression. Finally, the causes of pain in this cohort need to be determined. Additional research is warranted to determine the co-occurrence of multiple symptoms in PLWH, their impact on functional status and quality of life, as well as how these symptoms interact and change over time and in relationship to disease trajectory.

Clinical Implications

- Pain is a common symptom among people living with HIV infection, particularly in White patients with CD4+ T cell counts < 200/mm³.
- High risk patients warrant systematic pain assessments to determine the causes, severity, and impact of pain on functional abilities and quality of life.
- Clinicians need to assess patients for the co-occurrence of sleep disturbance, anxiety, and depression. Based on a comprehensive clinical assessment of these symptoms, an appropriate treatment plan can be initiated and evaluated.

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Table 1
Demographic Characteristics for the Total Sample and Differences in Demographic Characteristics Between the Two Pain Groups

Characteristic	TOTAL N = 317	No Pain n = 142 (44.8%)	Pain n = 175 (55.2%)	Test and Statistical Significance
Age in years, mean (SD)	45.3 (8.53)	44.4 (8.6)	45.7 (8.1)	$t = -1.4; p = .168$
Sex Male/Transgender Female	75.4% 24.6%	78.2% 21.8%	72.6% 27.4%	$p = .359^a$
Race/Ethnicity ^b Black/African American Hispanic/Latino White/Caucasian Mixed/Asian/Other	39% 10% 41% 10%	47% 9% 38% 7%	33% 11% 43% 13%	$\chi^2 = 7.8; p = .05$
Education Some High School or less High school Diploma or equivalent Some College College or Trade School Degree Post-college education	15% 30% 33% 18% 5%	13% 36% 30% 16% 4%	16% 25% 35% 19% 5%	$\chi^2 = 4.8; p = .304$
In a relationship	35%	36%	34%	$p = .723^e$
Have children	36%	35%	37%	$p = .725^e$
Household Monthly Income < \$1000 \$1000-\$1999 > \$2000	69% 22% 9%	71% 20% 9%	68% 23% 9%	$\chi^2 = .4; p = .833$
Employment Medical leave/disability Employed/Student Not Employed	75% 16% 9%	71% 20% 9%	78% 14% 9%	$\chi^2 = 2.2; p = .332$
Number of co-morbid health problems Time since HIV diagnosis in years Mean (SD) Range	1.1 (1.2) 12.1 (7.0) 1 – 27	0.9 (1.0) 11.5 (6.9) 1 – 26	1.3 (1.3) 12.5 (7.0) 1 – 27	$t = -2.3; p = .021$ $t = -1.4; p = .177$
AIDS diagnosis	52%	47%	57%	$p = .090^a$
On ART	71%	68%	73%	$p = .321^a$
CD+ T cell count cells/mm ³ (n = 302) % < 200 cells/mm ³ Mean $\pm$ SD ^b Range	17.3% 449 (265) 4 – 1740	10.4% 483 (270) 4 – 1740	22.8% 422 (260) 9 – 1246	$p = .006^a$ $t = 2.1; p = .034$
VL copies/mL (n = 295/317) % with detectable VL (copies/mL) Mean of detectable VL (copies/mL; n = 147) ^b Range of detectable VL	50% 43625 (104518) 50 – 500,000	n = 132 46% 45703 (102292) 75 – 500,000	n = 163 53% 42176 (106616) 50 – 500,000	$p = .293^a$ $t = 0.9; p = .342$

Note. ART = antiretroviral therapy; SD = standard deviation; VL = viral load

^a Fisher's Exact Test

^b Comparisons are based on square-root or log₁₀ transformed scores.

Table 2
Mean Symptom Scores for the Total Sample and Differences in Fatigue, Sleep Disturbance, Anxiety, and Depression Between the Two Pain Groups

Symptom Inventory	TOTAL <i>N</i> = 317 ^a	No Pain <i>n</i> = 142 (44.8%)	Pain <i>n</i> = 175 (55.2%)	Statistics
FSS Mean (<i>SD</i>) Range Median	3.8 (2.3) 1-9 3.9	3.4 (2.2) 1-6.6 3.4	4.1 (2.3) 1-9 4.3	<i>U</i> = 11079 <i>p</i> < .001
GSDS Total Score Mean (<i>SD</i>) Range Median	44.8 (20.9) 2-116 44.0	37.2 (18.5) 2-86 37.0	50.9 (20.8) 7-116 49.5	<i>t</i> = -6.127; <i>p</i> < .001
POMS Tension-Anxiety Score Mean (<i>SD</i>) Range Median	8.8 (7.2) 0-32 7.0	7.3 (6.4) 0-26 5.0	9.8 (7.4) 0-32 9.0	<i>t</i> = -3.022; <i>p</i> = .003
CESD Mean (<i>SD</i>) Range Median	16.9 (10.4) 0-57 15.0	14.2 (9.5) 0-46 12.0	19.0 (10.7) 0-57 18.0	<i>t</i> = -4.187; <i>p</i> < .001

Note. FSS = Fatigue Severity Scale; GSDS = General Sleep Disturbance Scale; CESD = Center for Epidemiological Studies – Depression; *SD* = standard deviation.

^a One participant in the group who reported experiencing pain in the previous week failed to complete the GSDS and CESD (*n* = 316).

Table 3

Multiple Logistic Regression Analysis of Pain

Predictor	Odds Ratio	Standard Error	95% CI	Z	p-value
GSDS	1.45	0.010	1.269, 1.661	5.43	<.001
CD4+ T cell count ≤ 200 cells/mm ³	3.07	1.150	1.476, 6.400	3.00	.003
Race	0.52	0.144	0.303, 0.897	-2.35	.019
Age	1.03	0.016	0.999, 1.061	1.90	.057
Sex	1.36	0.429	0.731, 2.524	0.97	.333

Note. Multiple logistic regression analysis of report of pain ($n = 301$). Predictors evaluated in the model included: sex (female vs. male/transgender), race (Black vs. not Black), CD4+ T cell count ≤ 200 cells/mm³, number of co-morbid conditions, age (years), FSS score, GSDS score (a 10-point increase in GSDS Total score), POMS Tension-Anxiety subscale score, and CES-D score. Interaction terms for sex and race, sex and CD4+ T cell count, and race and CD4+ T cell count were assessed (all $p > 0.200$). Overall model fit: Wald $\chi^2 = 55.15$, $p < .0001$; pseudo $R^2 = 0.13$. CI = confidence interval; GSDS = General Sleep Disturbance Scale; SD = standard deviation; FSS = Fatigue Severity Scale; CESD = Center for Epidemiological Studies – Depression; Profile of Moods States Tension-Anxiety subscale (POMS).