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ORIGINAL ARTICLE

Higher levels of stress and different coping strategies are associated with greater morning and evening fatigue severity in oncology patients receiving chemotherapy

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Abstract

Purpose A cancer diagnosis and associated treatments are stressful experiences for most patients. Patients' perceptions of stress and their use of coping strategies may influence fatigue severity. This study extends our previous work describing distinct profiles of morning (i.e., Very Low, Low, High, and Very High) and evening (i.e., Low, Moderate, High, and Very High) fatigue in oncology patients by evaluating for differences in stress and coping strategies among these fatigue classes.

Methods This longitudinal study evaluated for changes in morning and evening fatigue in oncology patients ($n = 1332$) over two cycles of chemotherapy (CTX). Patients completed measures of cumulative exposure to stressful life events (SLEs) (i.e., the Life Stressor Checklist-Revised), general stress (i.e., Perceived Stress Scale [PSS]), cancer-specific stress (i.e., Impact of Event Scale-Revised [IES-R]), and coping strategies (i.e., Brief Cope). Differences among the latent classes were evaluated using analyses of variance, Kruskal-Wallis, or chi-square tests.

Results Patients in both the Very High morning and evening fatigue classes reported higher numbers of and a higher impact from previous SLEs and higher PSS scores than the other fatigue classes. The IES-R scores for the Very High morning fatigue class met the criterion for subsyndromal PTSD. Patients in the Very High evening fatigue class used a higher number of engagement coping strategies compared with the Very High morning fatigue class.

Conclusions Our findings suggest that interventions to reduce stress and enhance coping warrant investigation to decrease fatigue in patients undergoing CTX.

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Introduction

A cancer diagnosis and associated treatments are stressful experiences for most patients [1]. Stress initiates a cascade of pathways in the peripheral and central nervous systems that activates the autonomic nervous system (ANS) and/or the hypothalamic-pituitary-adrenal (HPA) axis to maintain homeostasis [2]. Cognitive and emotional feedbacks from the cortical and limbic areas of the brain modulate the activity of hypothalamic and brain stem structures directly controlling ANS and HPA activity [2, 3]. Fatigue is an adaptive response to acute stress that conserves energy and maintains homeostasis [3]. With repeated stressful events or cumulative exposure to stressful life events (SLEs), the ANS and HPA experience increased allostatic load resulting in increased fatigue severity [4].

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Fatigue is the most common and debilitating symptom experienced by oncology patients during chemotherapy (CTX). Inter-individual variability in fatigue severity is influenced by demographic, clinical, psychological, behavioral, and biological characteristics [5]. In prior work [6, 7], we described four classes of oncology patients ($N =$ 1332) with distinct profiles of morning and evening fatigue severity, and demographic, clinical, and co-occurring symptom characteristics that distinguished among these classes. Using clinically meaningful cutoff scores for the Lee Fatigue Scale (i.e., 3.2 for morning and 5.6 for evening), we labeled the four distinct morning (i.e., Very Low, Low, High, and Very High) [6] and four distinct evening (i.e., Low, Moderate, High, and Very High) [7] fatigue profiles derived using latent profile analysis (LPA; see Supplemental Figure 1).

Patients' perceptions of stress and their use of coping strategies may influence fatigue severity during CTX. Differences in the perception and evaluation of external events create variability in ANS and HPA activity levels, resulting in variable levels of perceived stress [3] that may influence inter-individual variability in fatigue severity. While higher levels of perceived stress were associated with greater fatigue severity [8–15], the majority of these studies were cross-sectional and evaluated only women with breast cancer [8–10, 13–15].

Coping encompasses a broad range of cognitive and behavioral responses to stress to maintain homeostasis [16]. Patients can use multiple coping strategies based on their appraisal of the internal (e.g., acceptance) and external (e.g., social support systems) resources available to them to reduce, master, or tolerate stress [16]. In addition, lifetime exposure to stressful experiences (e.g., physical or sexual assault) and current life stressors (e.g., cancer diagnosis and treatment) influence coping [16]. Coping is often described in terms of the use of engagement (e.g., actively doing something to alter the stressor) or disengagement (e.g., avoidance) strategies [16–18]. In the four studies that examined the association between coping and fatigue during CTX, greater fatigue severity was associated with disengagement coping [19, 20], while lower fatigue severity was associated with engagement coping [21, 22], However, these studies did not examine the impact of cumulative exposure to SLEs on coping and fatigue. One study found that increased exposure to SLEs was associated with greater fatigue severity in women with breast cancer; however, the effects of coping were not evaluated [23]. Given the paucity of research on the relationships between stress and coping and fatigue, the purpose of this study was to evaluate for differences in cumulative exposure to SLEs, general stress, cancer-specific stress, and coping strategies among our previously identified morning [6] and evening [7] fatigue classes.

Methods

Patients and settings

These analyses used data from a longitudinal study that evaluated the symptom experience of oncology patients receiving CTX [24]. Written informed consent was obtained from English literate patients ≥ 18 years of age who had received one or two cycles of CTX for a diagnosis of breast, gastrointestinal, gynecological, or lung cancer within the 4 weeks prior to enrollment and were scheduled for at least two additional CTX cycles. Patients were recruited from seven different sites that included community-based oncology programs and Comprehensive Cancer Centers. Of the 2234 patients approached, 1343 consented to participate (60.1% response rate). Patients' main reason for refusal was feeling overwhelmed with their CTX treatment. Additional methodological details are described elsewhere [6, 7].

Instruments

Fatigue measures

The 18-item Lee Fatigue Scale (LFS) is designed to assess physical fatigue and energy [25]. Each item was rated on a 0 to 10 numeric rating scale (NRS). Fatigue scores were calculated as the mean of the 13 fatigue items. Higher scores indicate greater fatigue severity. Using separate LFS questionnaires, patients rated each item based on how they felt within 30 min of awakening (i.e., morning fatigue) and prior to going to bed (i.e., evening fatigue). The LFS has established cutoff scores for clinically meaningful levels of fatigue (i.e., ≥ 3.2 for morning fatigue, ≥ 5.6 for evening fatigue) [26]. The LFS has well-established validity and reliability and is easy to administer [25]. In our study, Cronbach's alphas were 0.96 for morning and 0.93 for evening fatigue.

General stress measures

The Life Stressor Checklist-Revised (LSC-R) is a 30-item inventory of lifetime exposure to stressful, potentially traumatic events (e.g., physical assault, death of a loved one) [27]. The total LSC-R score was obtained by summing the number of events endorsed (possible range is 0–30, with 30 indicating that the patient experienced all of the events). If the patient endorsed an event, they indicated how much that stressor affected their life in the past year, using a 1 ("not at all") to 5 ("extremely") scale. These responses were averaged to yield a mean "affected" score. The LSC-R has good to moderate test-retest reliability and criterion-related validity in diverse populations [28].

The 14-item Perceived Stress Scale (PSS) is a measure of perceived stress according to the degree that life

circumstances are appraised as stressful over the previous 4 weeks [29]. Each item was rated on a 0 ("never") to 4 ("very often") scale. Total scores were summed after reversing the seven positive items' scores and can range from 0 to 56. A higher score indicates greater stress. The PSS has well-established validity and reliability [29]. In our study, its Cronbach's alpha was 0.85.

Cancer-specific stress measure

The 22-item Impact of Event Scale-Revised (IES-R) is used to measure cancer-related stress [30]. Patients rated each item based on how stressful each potential event was for them in the past week on a 0 (not at all) to 4 (extremely) scale. Three subscale (e.g., intrusion, avoidance, and hyperarousal) scores and a total score were calculated [30]. The total score can range from 0 to 88. A clinical cutoff score of 33 represents probable post-traumatic stress disorder (PTSD), and scores of ≥ 37 suggest high levels of post-traumatic symptoms [30]. The IES-R has well-established validity and reliability [30]. In this sample, its Cronbach's alpha was 0.91.

Coping strategy measure

The 28-item Brief Cope scale measures patients' use of various engagement and disengagement coping strategies [31]. For each strategy, patients rated the level of strategy use using a 4-point Likert scale that ranged from 1 ("I haven't been doing this at all") to 4 ("I have been doing this a lot"). Higher scores indicate greater use of each coping strategy. Fourteen total dimensions, represented by two items each, were evaluated using this instrument (with their respective Cronbach's alphas): self-distraction (0.46), active coping (0.75), denial (0.72), substance use (0.87), use of emotional support (0.77), use of instrumental support (0.77), behavioral disengagement (0.57), venting (0.65), positive reframing (0.79), planning (0.74), humor (0.83), acceptance (0.68), religion (0.92), and self-blame (0.73). The Brief Cope has well-established validity and reliability in oncology patients [32].

Study procedures

The study was approved by the Institutional Review Board at each study site. A research team member approached eligible patients during their first or second CTX cycle to discuss participation and obtain written informed consent. Depending on the length of their CTX cycle, patients completed the fatigue questionnaires in their homes, a total of six times over two CTX cycles (i.e., before CTX administration, approximately 1 week after CTX administration, approximately 2 weeks after CTX administration). Due to the potentially sensitive nature of LSC-R items, patients were given three options for its completion: in person with a research team member, over the telephone, or on their own. Patients were reminded that they could refuse to answer questions that caused discomfort.

Data analysis

Data were analyzed using SPSS version 22 (IBM, Armonk, NY). Descriptive statistics and frequency distributions were calculated for the stress and coping measures. As previously reported [6, 7], LPA was used to identify patient subgroups with distinct morning or evening fatigue profiles over the six assessments. We used the identified profiles in these analyses. Differences in general and cancer-specific stress scores and coping strategies scores among the classes were evaluated using analyses of variance, Kruskal-Wallis, or chi-square tests with Bonferroni-corrected post hoc contrasts (i.e., $p < .008$ [0.05/6]).

Results

Sample characteristics

In terms of differences in demographic and clinical characteristics among the latent classes [6, 7], in brief, the overall sample was predominantly female, white, and college educated. Compared with the other fatigue classes, patients in both the Very High morning and evening fatigue classes were younger and reported a higher comorbidity burden. Patients in the Very High morning fatigue class were more likely to live alone and had a higher body mass index. Patients in the Very High evening fatigue class were more likely to be female, have childcare responsibilities, and have a lower functional status.

Morning fatigue

Differences in cumulative life stress and general stress

In terms of cumulative life stress, significant differences were found among the morning fatigue classes for both the number and impact of SLEs (Table 1). Compared with the Very Low and Low classes (i.e., 5.2 and 5.4, respectively), patients in the High and Very High classes reported a higher number of SLEs (i.e., 6.4 and 8.5, respectively). An identical pattern of differences in the impact of SLEs was found among the morning fatigue classes. Compared with the High class, patients in the Very High class reported a higher number and a higher impact of SLEs. In terms of general stress, across the four classes, as the profiles of morning fatigue severity increased, PSS scores increased (i.e., Very Low < Low < High < Very High; Table 1).

Table 1 Differences in general and disease-specific stress scores among the morning and evening fatigue latent classes

Stress measures	Morning fatigue latent classes				Statistics	Evening fatigue latent classes				Statistics
	Very Low (0)261 (19.6%) Mean (SD)	Low (1)403 (30.2%) Mean (SD)	High (2)528 (39.6%) Mean (SD)	Very High (3)141 (10.6%) Mean (SD)		Low (0)186 (14.0%) Mean (SD)	Moderate (1)230 (17.2%) Mean (SD)	High (2)479 (36.0%) Mean (SD)	Very High (3)437 (32.8%) Mean (SD)	
LSC-R—number of SLEs	5.2 (3.6)	5.4 (3.4)	6.4 (4.1)	8.5 (4.6)	$F = 17.85, p < .001$, 0 and 1 < 2 and 3; 2 < 3	5.1 (3.3)	5.9 (3.7)	5.6 (3.9)	7.1 (4.3)	$F = 10.68, p < .001$, 0, 1, and 2 < 3
LSC-R—impact of SLEs	8.7 (8.6)	9.6 (9.2)	13.4 (11.4)	19.3 (14.7)	$F = 25.84, p < .001$, 0 and 1 < 2 and 3; 2 < 3	8.2 (6.8)	12.0 (10.3)	10.7 (9.8)	14.8 (13.5)	$F = 12.55, p < .001$, 0 < 1; 0, 1, and 2 < 3
Perceived Stress Scale	13.5 (6.2)	16.5 (7.1)	20.6 (7.6)	26.0 (8.3)	$F = 111.11, p < .001$, 0 < 1 < 2 < 3	14.1 (7.1)	17.2 (8.1)	18.2 (7.2)	21.4 (8.5)	$F = 41.52, p < .001$, 0 < 1, 2, and 3; 1 and 2 < 3
IES-R—avoidance	0.7 (0.6)	0.9 (0.6)	1.0 (0.7)	1.3 (0.8)	$F = 20.48, p < .001$, 0 < 1, 2, and 3; 1 and 2 < 3	0.8 (0.7)	1.0 (0.6)	1.0 (0.7)	1.0 (0.7)	$F = 2.65, p = .047$, 0 < 3
IES-R—intrusion	0.6 (0.5)	0.8 (0.6)	1.0 (0.7)	1.5 (0.8)	$F = 70.77, p < .001$, 0 < 1 < 2 < 3	0.6 (0.6)	0.8 (0.7)	0.9 (0.7)	1.1 (0.8)	$F = 21.34, p < .001$, 0 < 1, 2, and 3; 1 and 2 < 3
IES-R—hyperarousal	0.3 (0.4)	0.5 (0.5)	0.8 (0.7)	1.3 (0.9)	$F = 103.94, p < .001$, 0 < 1 < 2 < 3	0.4 (0.4)	0.6 (0.6)	0.6 (0.6)	0.8 (0.8)	$F = 25.97, p < .001$, 0 < 1, 2, and 3; 1 and 2 < 3
IES-R—total score	12.0 (9.3)	16.3 (10.3)	21.2 (13.4)	29.9 (15.9)	$F = 75.32, p < .001$, 0 < 1 < 2 < 3	13.4 (10.4)	17.8 (12.5)	18.8 (12.3)	21.7 (14.6)	$F = 17.65, p < .001$, 0 < 1, 2, and 3; 1 and 2 < 3

IES-R, Impact of Event Scale-Revised; LSC-R, Life Stressor Checklist-Revised; SD, standard deviation; SLEs, stressful life events

Differences in cancer-specific stress

For the intrusion and hyperarousal subscale and total scores of the IES-R, the post hoc contrasts were significant in the following pattern: Very Low < Low < High < Very High. For the avoidance subscale, compared with the Very Low class, patients in the Low, High, and Very High classes reported higher scores (Table 1).

Differences in coping

Significant differences were found among the morning fatigue classes in the frequency of use of eight of the fourteen (57%) coping strategies (Table 2). Compared with the Very Low class, patients in the Very High class were less likely to use active coping and more likely to use denial. Compared with the Very Low class, patients in the High class were less likely to use acceptance. Compared with the Low class, patients in the High class were more likely to use instrumental support. Compared with the Very Low class, patients in the Low, High, and Very High classes were more likely to use self-distraction. Compared with the Very Low class, patients in the High and Very High classes were more likely to use behavioral disengagement. Compared with the Very Low, Low, and High classes, patients in the Very High class were more likely to use venting. Compared with the Very Low and Low classes, patients in the High and Very High classes were more likely to use self-blame. No significant differences were found among the morning fatigue classes in the use of planning, positive reframing, humor, religion, emotional support, and substance use.

Evening fatigue

Differences in cumulative life stress and general stress

In terms of cumulative life stress, compared with the Low, Moderate, and High classes, patients in the Very High class reported a higher number of SLEs (i.e., 5.1, 5.9, 5.6, and 7.1, respectively; Table 1). In terms of the impact of SLEs, compared with the Low, Moderate, and High classes, patients in the Very High class reported higher SLE impact scores (i.e., 8.2, 12.0, 10.7, and 14.8, respectively; Table 1). In addition, compared with the Low class, patients in the Moderate class reported higher SLE impact scores. In terms of general stress, compared with the Low class, patients in the other three evening fatigue classes reported higher PSS scores. In addition, compared with the Moderate and High classes, patients in the Very High class reported higher PSS scores (Table 1).

Differences in cancer-specific stress

Compared with the Low class, patients in the Very High class reported higher IES-R avoidance scores. Compared with the Low class, patients in the Moderate, High, and Very High classes reported higher intrusion, hyperarousal, and IES-R total scores. In addition, compared with the Moderate and High classes, patients in the Very High class reported higher intrusion, hyperarousal, and IES-R total scores (Table 1).

Differences in coping

Significant differences were found among the evening fatigue classes in the frequency of use of eight of the fourteen (57%) coping strategies (Table 2). Compared with patients in the other three classes, patients in the Very High class were more likely to use planning, emotional support, instrumental support, and self-blame. Compared with the Low class, patients in the High and Very High classes were more likely to use humor and self-distraction. Compared with the High and Very High classes, patients in the Moderate class were more likely to use religion. Compared with the Low and Moderate classes, patients in the High and Very High classes were more likely to use venting. Compared with the other three classes, patients in the Very High class were more likely to use self-blame. No significant differences were found among the evening fatigue classes in the use of active coping, positive reframing, acceptance, denial, substance use, and behavioral disengagement.

Discussion

This study extends our previous work identifying patients with morning [6] and evening [7] fatigue profiles to include associations with cumulative life stress, cancer-specific stress, and coping. While previous research found associations between childhood SLEs and increased risk for greater fatigue severity in women with breast cancer [8], our study is the first to evaluate the impact of SLEs on fatigue severity in a sample of patients with heterogeneous cancer diagnoses. Compared with the other three classes, patients in both the Very High morning and evening fatigue classes reported higher numbers of and higher impact from previous SLEs. The increased allostatic load associated with cumulative SLEs [4] is a plausible explanation for these associations. For example, higher levels of and higher impact from SLEs increased the risk of experiencing chronic pain [33], as well as fatigue and depression [34]. These findings suggest that SLEs in oncology patients may be associated with increased risk for multiple co-occurring symptoms and warrant further study.

Given that higher cumulative life stress was associated with increased allostatic load in healthy adults and in patients with irritable bowel syndrome [35], our findings of higher PSS

Table 2 Differences in Brief Cope scores among the morning and evening fatigue latent classes

Coping strategies	Morning fatigue				Statistics	Evening fatigue				Statistics
	Very Low (0) 261 (19.6%) Mean (SD)	Low (1) 403 (30.2%) Mean (SD)	High (2) 528 (39.6%) Mean (SD)	Very High (3) 141 (10.6%) Mean (SD)		Low (0) 186 (14.0%) Mean (SD)	Moderate (1) 230 (17.2%) Mean (SD)	High (2) 479 (36.0%) Mean (SD)	Very High (3) 437 (32.8%) Mean (SD)	
Active coping	6.3 (1.7)	6.0 (1.7)	6.0 (1.6)	5.6 (1.7)	$F = 4.81$, $p = .002$, 0 > 3	5.9 (1.9)	5.9 (1.7)	6.0 (1.6)	6.1 (1.6)	$F = 1.05$, $p = .370$
Planning	5.2 (1.9)	5.1 (1.9)	5.4 (1.7)	5.4 (1.8)	$F = 2.27$, $p = .079$	4.9 (2.0)	5.2 (1.9)	5.2 (1.7)	5.7 (1.7)	$F = 11.66$, $p < .001$, 0, 1, and 2 < 3
Positive reframing	5.3 (2.0)	5.3 (2.0)	5.6 (1.9)	5.4 (2.0)	$F = 1.94$, $p = .122$	5.3 (2.1)	5.5 (1.9)	5.4 (2.0)	5.5 (1.9)	$F = 0.34$, $p = .793$
Acceptance	6.9 (1.3)	6.7 (1.4)	6.7 (1.3)	6.7 (1.4)	$F = 2.85$, $p = .037$, 0 > 2	6.8 (1.4)	6.8 (1.3)	6.6 (1.3)	6.8 (1.3)	$F = 1.45$, $p = .228$
Humor	4.2 (2.1)	4.3 (2.0)	4.3 (1.8)	4.6 (2.2)	$F = 1.20$, $p = .310$	3.9 (2.0)	4.2 (2.0)	4.3 (1.9)	4.6 (2.0)	$F = 5.48$, $p = .001$, 0 < 2 and 3
Religion	4.9 (2.3)	4.9 (2.4)	5.2 (2.2)	5.1 (2.3)	$F = 1.27$, $p = .283$	5.1 (2.4)	5.5 (2.3)	4.8 (2.3)	5.0 (2.3)	$F = 5.24$, $p = .001$, 1 > 2 and 3
Using emotional support	6.3 (1.7)	6.3 (1.7)	6.3 (1.6)	6.3 (1.6)	$F = 0.03$, $p = .993$	6.1 (1.9)	6.2 (1.8)	6.3 (1.6)	6.6 (1.5)	$F = 5.49$, $p = .001$, 0, 1, and 2 < 3
Using instrumental support	5.3 (1.8)	5.1 (1.8)	5.5 (1.7)	5.4 (1.8)	$F = 2.66$, $p = .047$, 1 < 2	5.0 (1.9)	5.2 (1.9)	5.2 (1.7)	5.7 (1.7)	$F = 8.60$, $p < .001$, 0, 1, and 2 < 3
Self-distraction	5.2 (1.9)	5.5 (1.8)	5.5 (1.5)	5.7 (1.5)	$F = 3.80$, $p = .010$, 0 < 1, 2, and 3	5.1 (1.9)	5.4 (1.7)	5.5 (1.6)	5.7 (1.6)	$F = 6.28$, $p < .001$, 0 < 2 and 3
Denial	2.3 (0.9)	2.5 (1.1)	2.5 (1.1)	2.7 (1.4)	$F = 3.76$, $p = .011$, 0 < 3	2.4 (1.0)	2.6 (1.2)	2.5 (1.0)	2.5 (1.2)	$F = 0.75$, $p = .522$
Venting	3.5 (1.6)	3.8 (1.6)	4.1 (1.6)	4.7 (1.8)	$F = 17.56$, $p < .001$, 0, 1, and 2 < 3, 0 < 2 and 3; 1 < 3	3.4 (1.5)	3.6 (1.5)	3.9 (1.5)	4.5 (1.8)	$F = 25.60$, $p < .001$, 0 and 1 < 2 and 3; 2 < 3
Substance use	2.2 (0.6)	2.2 (0.7)	2.3 (0.8)	2.3 (0.8)	$F = 1.00$, $p = .390$	2.2 (0.7)	2.2 (0.6)	2.3 (0.8)	2.3 (0.8)	$F = 1.78$, $p = .150$
Behavioral disengagement	2.1 (0.5)	2.2 (0.7)	2.3 (0.8)	2.5 (0.9)	$F = 7.33$, $p < .001$, 0 < 2 and 3; 1 < 3	2.3 (0.9)	2.3 (0.9)	2.2 (0.6)	2.3 (0.8)	$F = 1.66$, $p = .174$
Self-blame	2.4 (0.8)	2.6 (1.0)	3.1 (1.3)	3.6 (1.7)	$F = 38.71$, $p < .001$ 0 and 1 < 2 and 3; 2 < 3	2.4 (0.9)	2.8 (1.2)	2.8 (1.2)	3.1 (1.4)	$F = 13.83$, $p < .001$, 0 < 1, 2, and 3; 0, 1, and 2 < 3

SD, standard deviation

Table 3 Comparison of the stress measures and coping strategies associated with membership in the highest morning and evening fatigue classes compared with the lowest morning and evening fatigue classes

Characteristics	Very High morning fatigue	Very High evening fatigue
Stress measures		
LSC-R—number of SLEs	↑	↑
LSC-R—impact of SLEs	↑	↑
Perceived Stress Scale	↑	↑
IES-R—avoidance	↑	↑
IES-R—intrusion	↑	↑
IES-R—hyperarousal	↑	↑
IES-R—total score	↑	↑
Coping strategies		
Engagement		
Active coping	↓	
Planning		↑
Using emotional support		↑
Using instrumental support		↑
Disengagement		
Avoidance	↑	
Denial	↑	
Self-blame	↑	↑
Emotion-based		
Venting	↑	↑
Other subscales		
Self-distraction	↑	↑
Humor		↑
Religion		↓

↑ = Higher score for the highest morning and evening fatigue classes compared with the lowest classes

↓ = Lower score for the highest morning and evening fatigue classes compared with the lowest classes

IES-R, Impact of Event Scale-Revised; *LSC-R*, Life Stressor Checklist-Revised; *SLEs*, stressful life events

The coping strategies of positive reframing, acceptance, religion, and substance use are not included in the table because no significant differences were found between the highest morning and evening fatigue latent classes compared with the lowest classes

scores in the Very High morning and evening fatigue classes, compared with the other classes, suggests that this mechanism may occur in oncology patients. Equally important, PSS scores were associated with greater fatigue severity in adults with rheumatoid arthritis, fibromyalgia, and inflammatory bowel disease [36] and unexplained chronic fatigue [37]. Because these conditions and fatigue associated with cancer share inflammation as a common underlying mechanism, future studies need to examine the additive or synergistic effects of stress and inflammatory mechanisms on fatigue severity.

A cancer diagnosis and its treatment(s) are significant stressors, with 20% of patients reporting cancer-related subsyndromal PTSD [1]. The IES-R total score for patients in the Very High morning fatigue class (i.e., 29.9) meets the criterion for subsyndromal PTSD [30]. This finding is consistent with previous reports of greater fatigue severity being associated with higher IES-R total scores in patients with Cushing's disease [38] and survivors of Middle East respiratory syndrome [39]. While the patients in the Very High evening fatigue class had IES-R total scores below the clinically meaningful cutoff for subsyndromal PTSD (i.e., IES-R total score of 21.7), their scores were significantly higher than those of the other three evening fatigue classes, which suggests that cancer-specific stress is a risk factor for greater evening fatigue severity. Given the negative impact of fatigue on oncology patients receiving CTX [40], the higher scores on the avoidance, intrusion, and hyperarousal subscales of the IES-R are not unexpected. Our findings suggest that interventions to decrease cancer-specific stress (e.g., yoga [41]) may decrease fatigue severity.

In terms of the impact of coping strategies on fatigue, in older oncology patients (i.e., > 70 years), disengagement coping strategies were associated with higher fatigue severity [42]. In contrast, engagement coping strategies mediated fatigue's impact during [42] and after [42, 43] cancer treatment completion. In studies that explored the perceptions of effective coping strategies for fatigue in patients with chronic obstructive pulmonary disease [43] and end-stage kidney disease

(ESKD) [44], both groups valued clinicians' acknowledgment of fatigue variability, support to deal with the impact of fatigue in their daily lives, and active participation in individualizing interventions [43, 44].
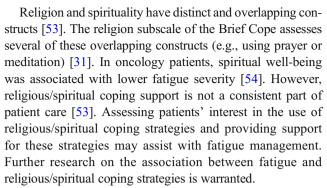
Noticeable similarities and differences were apparent in the coping strategies used by patients in the Very High morning and Very High evening fatigue classes (Table 3). Patients in the Very High evening fatigue class identified using engagement coping strategies more frequently than patients in the Very High morning fatigue class. One possible explanation for this difference in the use of engagement coping strategies may be the impact of morning compared with evening fatigue. In healthy adults, awakening refreshed without fatigue is considered "normal" [45]. Therefore, a patient may not actively plan or seek support when they expect to feel less fatigued in the morning. Educating patients about diurnal variability in fatigue and its potential impact on daily activities may increase the use of engagement coping strategies.

The finding that both the Very High morning and evening fatigue groups used self-blame as a coping strategy is consistent with prior research that identified self-blame as a predictor of fatigue in new parents [46], as well as in patients with melanoma [47], multiple sclerosis [48], and breast cancer [49]. In contrast, self-compassion was identified by patients with ESKD as an effective intervention to decrease their self-blame when they needed to ask for support to cope with their fatigue [44]. Teaching self-compassion may support patients to use more engaged coping behaviors for their stress and fatigue.

As an emotion-based coping strategy, venting refers to focusing on and expressing negative feelings [17]. While not evaluated in oncology patients, venting was found to increase patients' ability to cope with both positive and negative feelings about multiple sclerosis [48] and may warrant evaluation as a strategy for fatigue.

Our finding that patients in both the Very High morning and evening fatigue classes used self-distraction to cope with fatigue is not unexpected. Self-distraction was identified as an effective coping strategy for fatigue in oncology patients during CTX [20], in patients with ESKD [44], and in healthy working adults [50]. Self-distraction may be used to shift the focus from fatigue without eliminating or treating the symptom [50].

While using humor as a coping strategy was associated with decreased stress in women with breast cancer [51], it was not associated with decreased fatigue severity [49]. In general, humor is a personal experience, used in different ways and situations based on culture and gender [52]. Therefore, it is possible that the patients' personalities in the Very High evening fatigue class may have influenced their use of humor. The influence of personality characteristics on the use of various coping strategies to decrease fatigue warrants additional investigation.

Religion and spirituality have distinct and overlapping constructs [53]. The religion subscale of the Brief Cope assesses several of these overlapping constructs (e.g., using prayer or meditation) [31]. In oncology patients, spiritual well-being was associated with lower fatigue severity [54]. However, religious/spiritual coping support is not a consistent part of patient care [53]. Assessing patients' interest in the use of religious/spiritual coping strategies and providing support for these strategies may assist with fatigue management. Further research on the association between fatigue and religious/spiritual coping strategies is warranted.

Study limitations should be acknowledged. Patients were recruited at various times during their cancer treatment. Therefore, cancer-specific stress at diagnosis was not evaluated. Because the LSC-R is a retrospective evaluation, it is possible that the patients' current symptom experiences or cancer diagnosis and treatment influenced their memories of past events. While the subjective measures of stress are valid and reliable, future studies should examine associations between the severity of morning and evening fatigue and objective measures of stress (e.g., hair cortisol) as well as inflammatory genes and their expression and regulation. In addition, future studies should examine the extreme fatigue classes (i.e., Very Low morning versus Low evening, and Very High morning versus Very High evening) for differences in stress and coping strategies.

Despite these limitations, this longitudinal study with a large representative sample of oncology patients is the first to evaluate for associations among SLEs, general stress, cancer-specific stress, and the use various coping strategies and greater morning and evening fatigue severity during CTX. In addition, prior research has identified that higher levels of SLEs may decrease a patient's participation in health-related behaviors (e.g., physical activity) [55], which may affect adherence to exercise interventions prescribed to decrease fatigue severity. Additional studies are needed that evaluate the effect of stress management strategies and interventions targeted at the use of disengagement coping strategies to mitigate morning and evening fatigue.

Compliance with ethical standards

The study was approved by the Institutional Review Board at each study site. A research team member approached eligible patients during their first or second CTX cycle to discuss participation and obtain written informed consent.

Conflict of interest The authors declare that they have no conflicts of interest.

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