Distinct Profiles of Morning and Evening Fatigue Co-Occurrence in Patients During Chemotherapy

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Background: Morning and evening fatigue are distinct and distressing symptoms experienced during chemotherapy that demonstrate a large amount of interindividual variability.

Objectives: The objectives of this study were to identify subgroups of patients with distinct morning and evening fatigue co-occurrence profiles and evaluate for differences among these subgroups in demographic, clinical, and symptom characteristics and quality of life.

Methods: Oncology patients (n = 1,334) completed the Lee Fatigue Scale to self-report morning and evening fatigue, six times over two cycles of chemotherapy. Latent profile analysis was used to identify subgroups of patients with distinct morning and evening physical fatigue profiles.

Results: Four distinct morning and evening fatigue profiles were identified (i.e., Both Low, Low Morning + Moderate Evening, Both Moderate, and Both High). Compared to the Both Low profile, the Both High profile was significantly younger, less likely to be married or partnered, more likely to live alone, had a higher comorbidity burden, and lower functional status. The Both High profile had higher levels of anxiety, depressive symptoms, sleep disturbance, and pain and lower levels of quality of life.

Discussion: The variability in the morning and evening severity scores among the four profiles supports the hypothesis that morning and evening fatigue are distinct but related symptoms. Clinically meaningful levels of both morning and evening fatigue were reported by 50.4% of our sample, which suggests that the co-occurrence of these two symptoms is relatively common. Patients in Both Moderate and Both High profiles experienced an extremely high symptom burden that warrants ongoing assessments and aggressive symptom management interventions.

Key Words: cancer • chemotherapy • fatigue • latent profile analysis • quality of life

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Fatigue is a common symptom that limits oncology patients' daily activities (Berger et al., 2018). The severity of fatigue exhibits a large amount of interindividual variability associated with a variety of demographic, clinical, psychological, behavioral, and biological characteristics (Bower, 2019; Saligan et al., 2015). Person-centered analytic approaches (e.g., latent profile analysis [LPA]) allow for the characterization of patients with more severe fatigue to identify and target modifiable risk factors with individualized interventions. LPA is a person-centered analysis approach that uncovers patients' distinct "latent" (unobservable) characteristics to classify them into subgroups based on their experiences of fatigue.

In two previous studies, LPA was used to characterize groups of breast cancer patients undergoing chemotherapy with distinct average fatigue severity profiles (Huang et al., 2021; Whisenant et al., 2017). In one study (Whisenant et al., 2017), three fatigue classes were identified. The characteristics associated with membership in the highest fatigue class were receipt of doxorubicin and more time spent lying down. In another study (Huang et al., 2021), compared to the All Low fatigue class, the All High fatigue class had lower household income, more sedentary behavior, poorer sleep, and lower quality of life (QOL). These studies were homogenous in terms of cancer diagnosis and did not evaluate for diurnal variations in fatigue severity.

In two previous studies, separate LPAs to identify four distinct profiles for both morning (AM) fatigue (i.e., Very Low,

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Low, High, and Very High; Wright et al., 2019, 2020) and evening (PM) fatigue (i.e., Low, Moderate, High, and Very High; Wright et al., 2017, 2020). Common characteristics shared by patients in the separate Very High AM and Very High PM fatigue profiles were younger age; female gender; lower level of physical function; lower level of cognitive function; and having higher levels of depression, sleep disturbance, anxiety, and pain (Wright et al., 2017, 2019). The distinct characteristics associated with membership in the Very High AM fatigue profile included not being married or partnered, being unemployed, having a higher body mass index, not exercising regularly, and having a higher number of comorbid conditions (Wright et al., 2019). In contrast, membership in the Very High PM fatigue profile was associated with having higher educational attainment, having childcare responsibilities, and having a breast cancer diagnosis (Wright et al., 2017).

These prior studies suggest that AM and PM fatigue are distinct dimensions of physical fatigue (Kober et al., 2016; Wright et al., 2017, 2019, 2020). Characterizing patients who experience higher levels of both AM and PM fatigue may identify modifiable risk factors to develop personalized interventions to decrease both dimensions of fatigue. Therefore, as a logical extension of the separate LPA analysis of AM and PM fatigue (Kober et al., 2016; Wright et al., 2017, 2019, 2020), the purpose of this study was to identify subgroups of patients with distinct AM and PM fatigue co-occurrence profiles and evaluate for differences among these subgroups in demographic, clinical, and symptom characteristics, as well as QOL outcomes.

METHODS

Sample and Settings

Details about the parent study are published elsewhere (Miaskowski et al., 2014). In brief, eligible patients were ≥18 years of age; had a diagnosis of breast, gastrointestinal, gynecological, or lung cancer; had received chemotherapy within the preceding 4 weeks; were scheduled to receive at least two additional cycles of chemotherapy; were able to read, write, and understand English; and gave written informed consent. Patients were recruited from two comprehensive cancer centers, one Veterans Affairs hospital, and four community-based oncology programs. A total of 2,234 patients were approached during their first or second cycle of chemotherapy, and 1,343 consented to participate (60.1% accrual rate). The primary reason for declining to participate was being overwhelmed with their cancer treatment.

Study Procedures

The study was approved by the institutional review board at each of the study sites. After informed consent was obtained, patients completed questionnaires for a total of six times over two chemotherapy cycles (i.e., prior to chemotherapy administration, approximately 1 week after chemotherapy administration, and approximately 2 weeks after chemotherapy administration). A total of 1,334 patients who completed both the AM and PM fatigue measures were included in this analysis.

Measures

Demographic and Clinical Measures Patients completed a demographic questionnaire, the Karnofsky Performance Status (KPS) Scale, the Self-Administered Comorbidity Questionnaire (Sangha et al., 2003), the Alcohol Use Disorders Identification Test, and a smoking history questionnaire. The toxicity of each patient's chemotherapy regimen was rated using the MAX2 score (Extermann et al., 2004). Medical records were reviewed for disease and treatment information.

Fatigue Measures The 18-item Lee Fatigue Scale (LFS) was designed to assess physical fatigue and energy (Lee et al., 1991). Each item was rated on a 0–10 numeric rating scale (NRS). Total fatigue and energy scores are calculated as the mean of the 13 fatigue items and the five energy items, respectively. Higher scores indicate greater fatigue severity and higher levels of energy. Using separate LFS questionnaires, patients were asked to rate each item based on how they felt within 30 minutes of awakening (i.e., AM fatigue, AM energy) and before going to bed (i.e., PM fatigue, PM energy). The LFS has established cutoff scores for clinically meaningful levels of fatigue (i.e., ≥3.2 for AM, ≥5.6 for PM) and energy (i.e., <6.2 for AM energy, <3.5 for PM energy; Fletcher et al., 2008). In this study, the Cronbach's alphas were .96 and .93 for AM and PM fatigue, respectively, and .95 and .93 for AM and PM energy, respectively.

Other Symptom Measures In addition to diurnal variations in fatigue and energy, six common symptoms (i.e., trait anxiety, state anxiety, depression, attentional function, sleep disturbance, and pain) were assessed at enrollment using valid and reliable measures.

Spielberger State–Trait Anxiety Inventories (STAI-T and STAI-S) each has 20 items rated from 1 to 4. The summed scores for each scale can range from 20 to 80. The STAI-T measures a person's predisposition to anxiety as part of one's personality. The STAI-S measures how anxious a person is "right now" in a specific situation. Cutoff scores of ≥31.8 and >32.2 indicate high levels of trait and state anxiety, respectively (Spielberger et al., 1983). Cronbach's alphas for the STAI-T and the STAI-S were .92 and .96, respectively.

The 20-item Center for Epidemiological Studies–Depression (CES-D) Scale was used to evaluate the major symptoms of depression. A total score can range from 0 to 60, with scores of ≥16 indicating the need for individuals to seek clinical evaluation for major depression (Radloff, 1977). Cronbach's alpha for the CES-D total score was .89.

The 16-item Attentional Function Index was used to evaluate various dimensions of attentional function (i.e., effective action, attentional lapses, interpersonal effectiveness). A higher total mean score on a 0–10 NRS indicates greater

capacity to direct attention (Cimprich et al., 2011). Total scores are grouped into categories of attentional function (i.e., <5 low function, 5.0–7.5 moderate function, >7.5 high function; Cimprich et al., 2011). Cronbach's alpha for the Attentional Function Index total score was .93.

The 21-item General Sleep Disturbance Scale (GSDS) was designed to assess the quality of sleep. Each item was rated on a 0 (*never*) to 7 (*every day*) NRS. The GSDS total score is the sum of the seven subscale scores ranging from 0 (*no disturbance*) to 147 (*extreme sleep disturbance*; Lee, 1992). A GSDS total score of ≥43 indicates a significant level of sleep disturbance (Fletcher et al., 2008). Cronbach's alpha for the GSDS total score was .83.

The occurrence of pain was evaluated using the Brief Pain Inventory (Daut et al., 1983). Patients who responded yes to the question about having pain were asked to indicate if their pain was or was not related to their cancer treatment. Patients were categorized into one of four groups (i.e., no pain, only noncancer pain, only cancer pain, both cancer and noncancer pain). Patients rated the intensity of their worst pain using a 0 (*none*) to 10 (*excruciating*) NRS. Mean pain interference scores were calculated using the interference items on the Brief Pain Inventory.

Assessment of QOL QOL was evaluated using generic (i.e., Medical Outcomes Study–Short Form-12 [SF-12]) and disease-specific (i.e., Quality of Life Scale–Patient Version [QOL-PV]; Padilla et al., 1983) measures. The SF-12 consists of 12 questions about physical and mental health and overall health status. This instrument is scored into two components that evaluate physical (i.e., physical component summary [PCS] score) and mental (i.e., mental component summary [MCS] score) functioning. These scores can range from 0 to 100, with higher scores indicating a better QOL. The 41-item QOL-PV measures four dimensions of QOL (i.e., physical well-being, psychological well-being, social well-being, and spiritual well-being) and overall QOL. Each item is rated on a 0–10 NRS, with higher scores indicating a better QOL. Cronbach's alpha for the QOL-PV total score was .92.

Data Analysis

LPA was used to identify subgroups of patients (i.e., latent classes) with distinct AM and PM fatigue profiles using Mplus Version 8.4. LPA was done with the combined set of variables over time (i.e., using the AM and PM LFS scores obtained during the six assessments in a single LPA). This approach describes these two symptoms with two co-occurrence profiles over time.

To incorporate expected correlations among the repeated measures of the same variable and cross-correlations of the series of the two variables (i.e., AM and PM LFS scores), we included covariance parameters among measures at the same occasion and those that were one or two occasions apart. Covariances of each variable with the other at the same assessments were included in the model; autoregressive covariances were estimated with a lag of two with the same measures and a lag of one for each variable's series with the other variable. We limited the covariance structure to a lag of two to accommodate the expected reduction in the correlations introduced by two chemotherapy cycles within each set of three measurement occasions and to reduce model complexity (Jung & Wickrama, 2008). Model fit was evaluated to identify the solution that best characterized the observed latent class structure with the Bayesian Information Criterion (BIC), Vuong–Lo–Mendell–Rubin likelihood ratio test (VLMR) , entropy, and latent class percentages that were large enough to be reliable. Missing data were accommodated using the expectation–maximization algorithm, standard in Mplus.

After the latent classes were identified in Mplus, differences among the classes in demographic, clinical, and symptom characteristics, as well as QOL outcomes data, were evaluated with IBM SPSS (Version 28). Differences among the AM and PM fatigue classes in demographic, clinical, and symptom characteristics and QOL outcomes at enrollment were evaluated using parametric and nonparametric tests. A p-value of <.05 was considered statistically significant. Post hoc contrasts were done using a Bonferroni corrected p-value of .008 (i.e., .05/6 possible pairwise contrasts).

RESULTS

Results of the LPA

The four-class solution was selected because the BIC for that solution was lower than the BIC for the three-class solution (Supplemental Table 1, http://links.lww.com/NRES/A469). In addition, the VLMR was significant for the four-class solution, indicating that four classes fit the data better than three classes. Although the BIC was smaller for the five-class than the four-class solution, the VLMR was not significant for the five-class solution, indicating that too many classes were extracted.

The four AM and PM fatigue classes were named using the clinically meaningful cutoff scores for the LFS (Fletcher et al., 2008): Low AM + Low PM (i.e., Both Low, 23.5%), Low AM + Moderate PM (26.1%), Moderate AM + Moderate PM (i.e., Both Moderate, 38.8%), and High AM + High PM (i.e., Both High, 11.6%). As shown in Figure 1, the trajectories for AM + PM fatigue differed among the latent classes. For the Both Low and Both Moderate classes, the scores exhibited an increase at the second and fifth assessments (i.e., the week following the administration of chemotherapy). For the Low AM + Moderate PM class, whereas the AM fatigue scores exhibited an increase at the second and fifth assessments, the PM fatigue scores remained relatively stable over the six assessments. For the Both High class, both scores remained relatively stable over the six assessments.

Differences in Demographic and Clinical Characteristics

Compared to the Both Low and Low AM + Moderate PM classes, the other two classes were significantly younger, were less

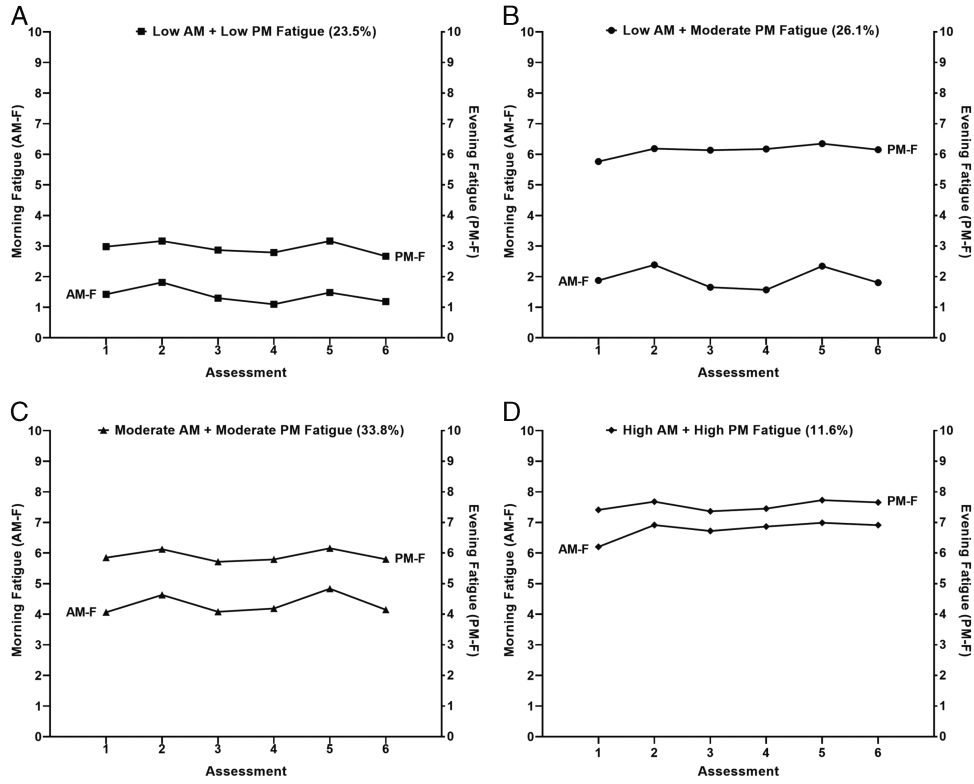

FIGURE 1. Changes in morning (AM) fatigue (AM-F, left *y*-axis) scores and evening (PM) fatigue (PM-F, right *y*-axis) scores over two cycles of chemotherapy for subgroups of oncology patients with Low AM + Low PM Fatigue (A), Low AM + Moderate PM Fatigue (B), Moderate AM + Moderate PM Fatigue (C), and High AM + High PM Fatigue (D).

likely to be married or partnered, had a higher level of comorbidity, and were more likely to be diagnosed with depression. Compared to the Both Low class, the Both Moderate and Both High classes had higher MAX2 scores and were more likely to have undergone previous cancer treatments. Compared to the Both Low class, the other three classes were less likely to have gastrointestinal cancer. Compared to the Low AM + Moderate PM class, the Both Moderate and Both High classes had a higher number of comorbidities and were more likely to be of Hispanic or mixed ethnic background (Table 1).

Differences in Symptom Measures

Compared to the Both Low and Low AM + Moderate PM classes, the other two classes had higher trait anxiety, state anxiety, depressive symptoms, worst pain intensity, and pain interference scores; had lower AM energy scores; and were more likely to report the occurrence of both cancer and noncancer pain. Compared to the Both Low class, the other three classes reported higher PM fatigue scores and lower PM energy levels. Although attentional function decreased across the four classes (i.e., 0 > 1 > 2 > 3), both sleep disturbance and AM fatigue scores increased (i.e., 0 < 1 < 2 < 3; Table 2).

Differences in QOL Outcomes

For the SF-12, compared to the Both Low and Low AM + Moderate PM classes, patients in the other two classes had significantly lower PCS and MCS scores. In addition, patients in the Both Moderate class had lower scores than patients in the Both High class (Table 3).

For the QOL-PV, physical well-being, psychological well-being, social well-being, and total QOL scores decreased across the four classes (0 > 1 > 2 > 3). For the spiritual well-being subscale, compared to the Both Low and Both Moderate classes, patients in the Both High class reported lower scores (Table 3).

DISCUSSION

This study builds on previous separate LPA analyses of AM (Wright et al., 2019, 2020) and PM (Wright et al., 2017, 2020) fatigue to provide new insights into how these two symptoms co-occur in patients over two cycles of chemotherapy. In addition, modifiable and nonmodifiable characteristics that place patients at increased risk for higher levels of co-occurring AM and PM fatigue were identified. Given the paucity of research on the co-occurrence of AM and PM fatigue, this discussion focuses on comparing the findings from this analysis with the prior separate LPAs of AM (Wright et al., 2019, 2020) and PM (Wright et al., 2017, 2020) fatigue (see Table 4) and the extant literature that evaluated average fatigue severity. These comparisons aim to describe common and distinct risk factors associated with higher risk profiles and the impact of co-occurring AM and PM fatigue on QOL outcomes.

TABLE 1. Differences in Demographic and Clinical Characteristics Among the Co-Occurring Morning and Evening Fatigue Profiles

	Both Low (0) 313 (23.5%)	Low AM + Moderate PM (1) 348 (26.1%)	Both Moderate (2) 518 (38.8%)	Both High (3) 155 (11.6%)	
Characteristic	**Mean (*SD*)**	**Mean (*SD*)**	**Mean (*SD*)**	**Mean (*SD*)**	**Statistics**
Age (years)	60.4 (12.3)	58.3 (11.8)	55.0 (12.5)	55.1 (11.4)	$F = 15.33$, $p < .001$ 0 and 1 > 2 and 3
Education (years)	16.0 (3.3)	16.6 (2.9)	16.1 (2.9)	15.9 (3.1)	$F = 3.19$, $p = .023$ No significant pw contrasts
Body mass index (kg/m^2)	25.9 (5.2)	25.7 (5.1)	26.4 (5.8)	27.3 (6.9)	$F = 3.13$, $p = .025$ 1 < 3
Karnofsky Performance Status score	85.6 (11.4)	83.1 (11.3)	77.1 (11.7)	71.0 (12.2)	$F = 71.47$, $p < .001$ 0 < 1 < 2 < 3
No. of comorbidities	2.3 (1.4)	2.1 (1.2)	2.5 (1.4)	2.9 (1.7)	$F = 13.10$, $p < .001$ 0 < 3, 1 < 2 and 3
SCQ score	4.8 (2.8)	4.8 (2.6)	5.8 (3.2)	7.1 (4.2)	$F = 26.33$, $p < .001$ 0 and 1 < 2 and 3
AUDIT score	2.8 (2.2)	3.2 (2.4)	2.9 (2.6)	3.0 (3.0)	$F = 1.21$, $p = .305$
Time since cancer diagnosis (years)	2.0 (4.1)	1.9 (3.8)	2.1 (4.1)	1.7 (2.9)	KW, $p = .076$
Time since cancer diagnosis (median)	.46	.39	.43	.45	
No. of prior cancer treatments	1.5 (1.5)	1.5 (1.5)	1.7 (1.5)	1.8 (1.5)	$F = 2.39$, $p = .067$
No. of metastatic sites including lymph node involvement	1.3 (1.2)	1.2 (1.2)	1.2 (1.3)	1.3 (1.2)	$F = .91$, $p = .433$
No. of metastatic sites excluding lymph node involvement	0.9 (1.0)	0.7 (1.0)	0.8 (1.1)	0.8 (1.1)	$F = .83$, $p = .478$
MAX2 score	0.16 (0.08)	0.18 (0.08)	0.18 (0.08)	0.18 (0.08)	$F = 4.41$, $p = .004$ 0 < 2 and 3
Hemoglobin (gm/dl)	11.6 (1.4)	11.6 (1.5)	11.5 (1.4)	11.4 (1.5)	$F = 1.01$, $p = .387$
Hematocrit (%)	34.8 (4.1)	34.7 (4.3)	34.4 (4.1)	34.2 (4.2)	$F = .951$, $p = .415$
	% (*n*)	**% (*n*)**	**% (*n*)**	**% (*n*)**	
Gender					
Female[a]	69.0 (216)	76.1 (264)	82.4 (427)	85.2 (132)	$\chi^2 = 26.00$, $p < .001$
Male	31.0 (97)	23.9 (83)	17.6 (91)	14.8 (23)	0 < 2 and 3
Race or ethnicity					$\chi^2 = 47.6$, $p < .001$
White	59.9 (185)	79.9 (275)	67.5 (345)	72.5 (111)	0 < 1; 1 > 2
Black	11.3 (35)	5.8 (20)	6.3 (20)	5.2 (8)	NS
Asian or Pacific Islander	16.8 (52)	9.0 (31)	14.1 (72)	6.5 (10)	0 > 1 and 3
Hispanic, mixed, or other	12.0 (37)	5.2 (18)	12.1 (62)	15.7 (24)	0 > 1; 1 < 2 and 3
Married or partnered (% yes)	68.9 (213)	72.3 (248)	59.0 (301)	55.6 (85)	$\chi^2 = 23.78$, $p < .001$ 0 and 1 > 2 and 3
Lives alone (% yes)	16.5 (51)	17.4 (60)	24.0 (122)	32.5 (50)	$\chi^2 = 20.74$, $p < .001$ 0 and 1 < 3
Child care responsibilities (% yes)	15.6 (48)	22.1 (75)	25.1 (127)	26.3 (40)	$\chi^2 = 11.75$, $p = .008$ 0 < 2
Care of adult responsibilities (% yes)	7.7 (22)	6.0 (19)	9.3 (43)	8.5 (12)	$\chi^2 = 2.88$, $p = .411$
Currently employed (% yes)	37.3 (115)	39.4 (135)	33.8 (174)	26.0 (40)	$\chi^2 = 9.42$, $p = .024$ 1 > 3
Income					
<$30,000+	18.0 (48)	6.8 (21)	21.2 (100)	34.5 (50)	KW, $p < .001$
$30,000 to <$70,000	24.3 (65)	18.3 (57)	21.7 (102)	19.3 (28)	0, 1 and 2 < 3
$70,000 to <$100,000	16.9 (45)	18.0 (56)	17.0 (80)	14.5 (21)	1 < 3
>$100,000	40.8 (109)	56.9 (177)	40.1 (189)	31.7 (46)	0 > 1
Specific comorbidities (% yes)					
Heart disease	7.0 (22)	3.7 (13)	6.2 (32)	5.2 (8)	$\chi^2 = 3.86$, $p = .276$
High blood pressure	35.1 (110)	29.3 (102)	28.8 (149)	26.5 (41)	$\chi^2 = 5.30$, $p = .151$

(continues)

TABLE 1. Differences in Demographic and Clinical Characteristics Among the Co-Occurring Morning and Evening Fatigue Profiles, Continued

Characteristic	Both Low (0) 313 (23.5%) Mean (*SD*)	Low AM + Moderate PM (1) 348 (26.1%) Mean (*SD*)	Both Moderate (2) 518 (38.8%) Mean (*SD*)	Both High (3) 155 (11.6%) Mean (*SD*)	Statistics
Lung disease	10.9 (34)	8.0 (28)	12.0 (62)	17.4 (27)	$\chi^2 = 9.74$, $p = .021$ 1 < 3
Diabetes	8.3 (26)	7.5 (26)	9.3 (48)	12.9 (20)	$\chi^2 = 4.11$, $p = .250$
Ulcer or stomach disease	4.2 (13)	4.3 (15)	5.4 (28)	5.8 (9)	$\chi^2 = 1.20$, $p = .754$
Kidney disease	1.3 (4)	1.4 (5)	1.2 (6)	2.6 (4)	$\chi^2 = 1.79$, $p = .618$
Liver disease	6.7 (21)	6.9 (24)	6.4 (33)	5.2 (8)	$\chi^2 = .582$, $p = .901$
Anemia or blood disease	9.3 (29)	12.1 (42)	12.5 (65)	18.1 (28)	$\chi^2 = 7.50$, $p = .058$
Depression	7.7 (24)	9.8 (34)	24.9 (129)	45.2 (70)	$\chi^2 = 124.65$, $p < .001$ 0 and 1 < 2 and 3; 2 < 3
Osteoarthritis	12.1 (38)	11.2 (39)	11.4 (59)	15.5 (24)	$\chi^2 = 2.18$, $p = .536$
Back pain	22.7 (71)	18.1 (63)	29.3 (152)	36.8 (57)	$\chi^2 = 25.56$, $p < .001$ 0 < 3;1 < 2 and 3
Rheumatoid arthritis	2.6 (8)	2.9 (10)	2.5 (13)	6.5 (10)	$\chi^2 = 6.82$, $p = .078$
Exercise on a regular basis (% yes)	74.4 (230)	78.2 (266)	68.6 (349)	53.4 (78)	$\chi^2 = 33.60$, $p < .001$ 0, 1, and 2 > 3; 1 > 2
Smoking, current or history of (% yes)	29.6 (91)	36.9 (127)	36.1 (183)	40.3 (62)	$\chi^2 = 6.50$, $p = .090$
Cancer diagnosis					$\chi^2 = 31.13$, $p < .001$
Breast	31.6 (99)	43.7 (152)	42.9 (222)	42.6 (66)	0 < 1 and 2
Gastrointestinal	42.2 (132)	28.4 (99)	25.7 (133)	26.5 (41)	0 > 1, 2, and 3
Gynecological	14.7 (46)	18.1 (63)	18.7 (97)	17.4 (27)	NS
Lung	11.5 (36)	9.8 (34)	12.7 (66)	13.5 (21)	NS
Type of prior cancer treatment					$\chi^2 = 27.83$, $p < .001$
No prior treatment	31.0 (94)	27.0 (92)	22.2 (112)	17.2 (26)	0 > 2 and 3
Only surgery, or CTX, or RT	34.3 (104)	44.3 (151)	44.0 (222)	45.7 (69)	NS
Surgery and CTX, or surgery and RT, or CTX and RT	24.8 (75)	15.5 (53)	20.0 (101)	19.2 (29)	0 > 1
Surgery and CTX and RT	9.9 (30)	13.2 (45)	13.7 (69)	17.9 (27)	NS
CTX cycle length					$\chi^2 = 7.61$, $p = .263$
14 days	47.3 (148)	39.4 (136)	41.5 (212)	38.6 (59)	
21 days	45.4 (142)	53.6 (185)	50.5 (258)	56.2 (86)	
28 days	7.3 (23)	7.0 (24)	8.0 (41)	5.2 (8)	
Emetogenicity of CTX					$\chi^2 = 8.09$, $p = .232$
Minimal/low	18.5 (58)	20.2 (70)	20.7 (106)	15.7 (24)	
Moderate	64.2 (201)	62.7 (217)	56.9 (291)	64.1 (98)	
High	17.3 (54)	17.1 (59)	22.3 (114)	20.3 (31)	
Antiemetic regimens					$\chi^2 = 15.09$, $p = .089$
None	6.5 (20)	7.4 (25)	8.2 (41)	4.0 (6)	
Steroid alone or serotonin receptor antagonist alone	20.8 (64)	21.2 (72)	19.7 (98)	20.8 (31)	
Serotonin receptor antagonist and steroid	52.4 (161)	49.3 (167)	45.1 (224)	42.3 (63)	
NK-1 receptor antagonist and two other antiemetics	20.2 (62)	22.1 (75)	27.0 (134)	32.9 (49)	

Note. Both Low = Low AM + Low PM; Both Moderate = Moderate AM + Moderate PM; Both High = High AM + High PM; *SD* = standard deviation; pw = pairwise; SCQ = Self-Administered Comorbidity Questionnaire; AUDIT = Alcohol Use Disorders Identification Test; KW = Kruskal–Wallis; NS = not significant; CTX = chemotherapy; RT = radiation therapy; NK-1 = neurokinin-1.

[a]Reference group for the post hoc comparisons.

TABLE 2. Differences in Symptom Characteristics Among the Co-Occurring Morning and Evening Fatigue Profiles

	Both Low (0) 315 (23.5%)	Low AM + Moderate PM (1) 348 (26.1%)	Both Moderate (2) 518 (38.8%)	Both High (3) 155 (11.6%)	
Symptom[a]	**Mean (*SD*)**	**Mean (*SD*)**	**Mean (*SD*)**	**Mean (*SD*)**	**Statistics**
Trait anxiety (≥31.8)	30.1 (8.5)	31.4 (7.6)	37.9 (9.9)	45.4 (11.5)	$F = 124.54$, $p < .001$ 0 and 1 < 2 and 3; 2 < 3
State anxiety (≥32.2)	28.6 (10.0)	30.1 (9.9)	36.2 (11.6)	45.8 (14.4)	$F = 98.93$, $p < .001$ 0 and 1 < 2 and 3; 2 < 3
Depressive symptoms (≥16.0)	7.7 (6.3)	9.0 (6.6)	15.3 (9.1)	24.1 (11.4)	$F = 173.60$, $p < .001$ 0 and 1 < 2 and 3; 2 < 3
Attentional function (<5.0 low, 5.0–7.5 moderate, >7.5 high)	7.5 (1.6)	7.0 (1.5)	5.8 (1.5)	4.7 (1.8)	$F = 1.49.25$, $p < .001$ 0 > 1 > 2 > 3
Sleep disturbance (≥43.0)	38.8 (16.1)	44.8 (16.9)	59.7 (16.9)	73.4 (16.5)	$F = 199.87$, $p < .001$ 0 < 1 < 2 < 3
Morning fatigue (≥3.2)	1.4 (1.3)	1.8 (1.4)	4.1 (1.7)	6.3 (2.3)	$F = 489.40$, $p < .001$ 0 < 1 < 2 < 3
Evening fatigue (≥5.6)	2.9 (1.7)	5.8 (1.6)	5.8 (1.6)	7.5 (1.5)	$F = 346.19$, $p < .001$ 0 < 1, 2, and 3; 1 and 2 < 3
Morning energy (≤6.2)	4.8 (2.7)	4.9 (2.2)	4.2 (1.8)	3.3 (2.2)	$F = 25.64$, $p < .001$ 0 > 1, 2, and 3; 1 and 2 > 3
Evening energy (≤3.5)	4.0 (2.1)	3.4 (2.0)	3.6 (1.9)	2.4 (1.9)	$F = 23.00$, $p < .001$ 0 > 1, 2, and 3; 1 and 2 > 3
	% (*n*)	**% (*n*)**	**% (*n*)**	**% (*n*)**	
Pain					$\chi^2 = 95.89$ $p < .001$
No pain	38.3 (118)	32.7 (112)	21.9 (111)	11.3 (17)	0 and 1 > 2 and 3; 2 > 3
Only cancer pain	20.8 (64)	28.3 (97)	29.0 147)	25.2 (38)	No significant pw contrasts
Only noncancer pain	20.1 (62)	17.5 (60)	13.2 (67)	11.9 (18)	No significant pw contrasts
Both cancer and noncancer pain	20.8 (64)	21.6 (74)	35.9 (182)	51.7 (78)	0 and 1 < 2 and 3; 2 < 3
For patients with pain	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	
Worst pain intensity score	5.3 (2.7)	5.4 (2.4)	6.3 (2.4)	7.3 (2.4)	$F = 20.98$, $p < .001$ 0 and 1 < 2 and 3, 2 < 3
Pain interference score	1.8 (1.8)	2.2 (2.1)	3.6 (2.4)	4.8 (2.9)	$F = 58.13$, $p < .001$ 0 and 1 < 2 and 3, 2 < 3

Note. Both Low = Low AM + Low PM; Both Moderate = Moderate AM + Moderate PM; Both High = High AM + High PM; *SD* = standard deviation; pw = pairwise.
[a]Clinically meaningful cutoff score.

Consistent with the prior analyses of AM and PM fatigue as single symptoms (Wright et al., 2017, 2019), four distinct co-occurring classes were identified. Across the four profiles identified in the joint analysis, the different levels and trajectories for the AM and PM fatigue severity scores support the hypothesis that AM and PM fatigue are distinct but related symptoms. Notably, 50.4% of this sample reported moderate to high levels of both AM and PM fatigue. This finding is consistent with a previous study that established clinically meaningful cut points for fatigue severity and found that 45% of patients undergoing active treatment reported moderate to severe levels of average fatigue (Wang et al., 2014).

Demographic and Clinical Characteristics

Across the previous (Wright et al., 2017, 2019) and current analyses, younger age and being female were the two

TABLE 3. Differences in Quality of Life Among the Co-Occurring Morning and Evening Fatigue Profiles

	Both Low (0) 315 (23.5%)	Low AM + Moderate PM (1) 348 (26.1%)	Both Moderate (2) 518 (38.8%)	Both High (3) 155 (11.6%)	
QOL scores	**Mean (*SD*)**	**Mean (*SD*)**	**Mean (*SD*)**	**Mean (*SD*)**	**Statistics**
			Medical Outcomes Study–Short Form-12		
Physical component summary score	45.4 (9.9)	43.7 (10.0)	38.9 (9.6)	34.8 (11.1)	$F = 51.37$, $p < .001$ 0 and 1 > 2 and 3; 2 > 3
Mental component summary score	53.7 (8.6)	52.5 (8.1)	46.8 (9.9)	38.6 (11.2)	$F = 107.80$, $p < .001$ 0 and 1 > 2 and 3; 2 > 3
			Multidimensional Quality of Life Scale–Patient Version		
Physical well-being	7.9 (1.4)	7.3 (1.4)	5.9 (1.5)	4.8 (1.7)	$F = 205.50$, $p < .001$ 0 > 1 > 2 > 3
Psychological well-being	6.6 (1.8)	5.9 (1.6)	5.0 (1.6)	3.8 (1.6)	$F = 127.78$, $p < .001$ 0 > 1 > 2 > 3
Social well-being	6.9 (1.8)	6.3 (1.7)	5.1 (1.8)	4.1 (1.9)	$F = 112.07$, $p < .001$ 0 > 1 > 2 > 3
Spiritual well-being	5.7 (2.2)	5.3 (2.0)	5.6 (2.0)	5.0 (2.0)	$F = 4.50$, $p = .004$ 0 and 2 > 3
Total QOL score	6.8 (1.3)	6.2 (1.2)	5.3 (1.2)	4.3 (1.2)	$F = 177.98$, $p < .001$ 0 > 1 > 2 > 3

Note. Both Low = Low AM + Low PM; Both Moderate = Moderate AM + Moderate PM; Both High = High AM + High PM; *SD* = standard deviation; QOL = quality of life.

demographic characteristics most often associated with membership in the higher AM and PM fatigue profiles. Previous work suggests that the association between younger age and higher fatigue severity (Bischel et al., 2016; Fisch et al., 2014) may be related to a "response shift" in older oncology patients' perceptions of symptom severity (Schwartz et al., 2006). However, additional research is warranted because older healthy adults report higher fatigue levels (Kocalevent et al., 2011). In addition, age-related changes in inflammatory processes, circadian rhythms, and stress responses may impact fatigue severity (Hardeland, 2019).

Given the high percentages of women with breast and gynecological cancers enrolled in this study, it is difficult to draw definitive conclusions regarding gender as a risk factor for membership in the higher fatigue profiles. In studies that evaluated gender differences in average fatigue severity in patients with gastrointestinal cancers, the results were inconsistent (Baussard et al., 2022; Thong et al., 2018). In contrast, women reported higher levels of average fatigue in studies of gender differences in fatigue severity in healthy individuals (Kocalevent et al., 2011) and patients with inflammatory bowel disease (Keightley et al., 2018) and multiple sclerosis (Hu et al., 2019).

Not being married or partnered were risk factors associated with membership in the Both High and Very High AM fatigue profiles. However, having childcare responsibilities was associated with membership in the Very High PM fatigue profile but not in the other two high profiles. Having a spouse or partner available to assist with routine activities and enhanced social support (e.g., housekeeping) may help mitigate these high fatigue levels.

Some differences in race/ethnicity, employment status, and income were noted across the current and prior analyses, which suggest that health disparities may influence fatigue severity (Alcaraz et al., 2020). The measures of social determinants of health in this study were limited to self-reported race and ethnicity, employment status, annual household income, and level of education. Additional research is needed to understand the impact of other social determinants of health (e.g., neighborhood, food insecurity) on fatigue severity.

The only two clinical characteristics associated with the higher fatigue severity profiles were being less likely to have a diagnosis of gastrointestinal cancer and having a lower functional status. In terms of cancer types, only one study found that patients with gastrointestinal cancers experienced less severe fatigue when compared to patients with breast and lung cancers

TABLE 4. Demographic, Clinical, and Symptom Characteristics Associated With Co-Occurring Morning and Evening Fatigue Profiles Compared to Separate Profiles of Very High Morning Fatigue or Very High Evening Fatigue

Characteristic	Both low	Low AM + Moderate PM	Both Moderate	Both High	Very High AM (Wright et al., 2019, 2020)	Very High PM (Wright et al., 2017, 2020)
			Demographic characteristics			
Younger age			◆	◆	◆	◆
Being female			◆	◆	◆	◆
Being White		◆				◆
Hispanic or mixed ethnicity			◆	◆		
Not being married or partnered			◆	◆	◆	
Living alone				◆	◆	
Having a higher income	◆	◆			◆	◆
Not currently employed	◆				◆	
Higher level of education						◆
Having childcare responsibilities			◆			◆
			Clinical characteristics			
Higher body mass index			◆	◆	◆	
Not exercising regularly			◆	◆	◆	
Lower functional status			◆	◆	◆	◆
Higher number of comorbidities			◆	◆	◆	
Higher SCQ score			◆	◆	◆	◆
Having a diagnosis of depression			◆	◆		
Having a diagnosis of lung disease				◆		
Having a diagnosis of depression				◆	◆	◆
Having a diagnosis of anemia or blood disease					◆	◆
Having a diagnosis of back pain				◆		
Having a diagnosis of breast cancer		◆	◆			◆
Having a diagnosis of gastrointestinal cancer	◆					
No prior cancer treatment	◆					
Surgery and CTX, or surgery and RT, or CTX and RT	◆					
			Symptom characteristics			
Higher trait anxiety			◆	◆	◆	◆
Higher state anxiety			◆	◆	◆	◆
Higher depressive symptoms			◆	◆	◆	◆
Lower attentional function				◆	◆	◆
Higher sleep disturbance				◆	◆	◆

(continues)

TABLE 4. Demographic, Clinical, and Symptom Characteristics Associated With Co-Occurring Morning and Evening Fatigue Profiles Compared to Separate Profiles of Very High Morning Fatigue or Very High Evening Fatigue, Continued

Characteristic	Both low	Low AM + Moderate PM	Both Moderate	Both High	Very High AM (Wright et al., 2019, 2020)	Very High PM (Wright et al., 2017, 2020)
Higher morning fatigue				◆	◆	◆
Higher evening fatigue				◆	◆	◆
Lower morning energy			◆	◆	◆	◆
Lower evening energy			◆	◆	◆	◆
Having cancer and non-cancer pain			◆	◆	◆	◆
Higher worst pain intensity			◆	◆	NR	NR
Higher pain interference			◆	◆	NR	NR
Quality of life outcomes						
Medical Outcomes Study–Short Form-12						
Lower physical component summary score			◆	◆	NR	NR
Lower mental component summary score			◆	◆	NR	NR
Quality of Life Scale–Patient Version						
Lower physical well-being			◆	◆	NR	NR
Lower psychological well-being			◆	◆	NR	NR
Lower social well-being			◆	◆	NR	NR
Lower spiritual well-being				◆	NR	NR
Lower total QOL score			◆	◆	NR	NR

Note. Both Low = Low AM + Low PM; Both Moderate = Moderate AM + Moderate PM; Both High = High AM + High PM; ◆ = association identified; SCQ = Self-Administered Comorbidity Questionnaire; CTX = chemotherapy; RT = radiation therapy; NR = not reported; QOL = quality of life.

(Batra et al., 2021). The reasons for these differences in fatigue severity across cancer types warrant additional investigation.

Functional status was assessed by asking patients to report their KPS score. Across the separate LPAs of AM (Wright et al., 2019) and PM (Wright et al., 2017) fatigue and the current study, the KPS scores among the patients with the lower (i.e., 85.6, 86.3, and 85.7, respectively) compared to the highest (i.e., 71.0, 70.7, and 76.4, respectively) fatigue profiles were very similar. However, the differences in KPS scores between the lower and higher fatigue profiles represent clinically meaningful decrements in functional status. These findings are consistent with previous studies that found that lower functional status was associated with higher levels of average fatigue in oncology patients (Thong et al., 2018), as well as in patients with heart failure (Conley et al., 2015) and other chronic conditions (Torossian & Jacelon, 2021). Maintenance of functional status is a high priority for both patients and clinicians. Ongoing functional status assessments and referrals to physical therapy are warranted to improve function and decrease fatigue severity.

Higher comorbidity burden and self-reported diagnosis of depression were associated with membership in the higher fatigue severity profiles. The Self-Administered Comorbidity Questionnaire score is a composite measure of comorbidity burden. It should be noted that the most common comorbid conditions reported by this sample (i.e., depression [Sunwoo et al., 2022] and back pain [Carlesso et al., 2021]) have demonstrated independent associations with fatigue in the general population. Although additional research is needed to evaluate the synergistic effects of multimorbidity on oncology patients' levels of fatigue, the optimal management of these comorbidities may decrease the severity of this symptom.

Several demographic and clinical characteristics in Table 4 were associated with one or two fatigue profiles. These modifiable characteristics (e.g., higher body mass index and lack of regular exercise) warrant confirmation in future studies.

Symptom Characteristics

Membership in the higher fatigue profiles was associated with significantly higher levels of anxiety, depression, sleep disturbance, and pain; lower levels of attentional function; and decrements in energy. These symptoms are known to co-occur with fatigue as a symptom cluster (George et al., 2020). Mounting evidence suggests that various neuroimmune interactions contribute to a higher symptom burden in oncology patients (Bower, 2019; Scheff & Saloman, 2021). Changes in inflammatory activity in the periphery and the central nervous system may contribute to fatigue and other symptoms. Additional research is needed to elucidate distinct and common underlying mechanisms for these co-occurring symptoms.

Previous studies that evaluated the occurrence of fatigue with these common symptoms have not evaluated the temporality (i.e., precedes, occurs simultaneously, or follows) of these associations (Whisenant et al., 2017, 2019). Therefore, whether one symptom drives the other symptoms' occurrence and severity is unclear. An increased understanding of the temporal relationships between/among multiple co-occurring symptoms is critical to developing interventions targeting the sentinel symptom.

QOL Outcomes

The extremely high symptom burden associated with the co-occurrence of AM and PM fatigue is evident in the statistically and clinically meaningful decrements in the PCS and MCS scores, as well as all but one of the subscales of the disease-specific QOL measure (Cohen's d = 0.2–0.5). For the Both Moderate and Both High classes, the PCS and MCS scores were below the cutoff of 50.0—the normative score for the general population.

Limitations

Several limitations warrant consideration. Because the characteristics associated with each profile were evaluated only at enrollment, how these associations change over time warrants evaluation in future studies. The inclusion of a more diverse sample would allow for a more detailed evaluation of the impact of social determinants of health on fatigue severity profiles. An evaluation of neuroimmune biomarkers would increase our knowledge of the potential mechanisms that underlie the relationships between fatigue and other common co-occurring symptoms. In addition, assessing patients' chronotypes may enable us to identify additional risk factors for diurnal variations in the various fatigue severity profiles. Despite these limitations, this study contributes to the growing body of evidence on diurnal variations in and interindividual variability in fatigue severity.

Conclusion

Future research needs to evaluate the relative contributions of stress and coping on these fatigue severity profiles because they may influence fatigue severity during chemotherapy, decreasing QOL. Given the impact of co-occurring AM and PM fatigue on QOL, the development of mechanistically based interventions need to be prioritized and evaluated in randomized clinical trials.

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REFERENCES

Alcaraz, K. I., Wiedt, T. L., Daniels, E. C., Yabroff, K. R., Guerra, C. E., & Wender, R. C. (2020). Understanding and addressing social determinants to advance cancer health equity in the United States: A blueprint for practice, research, and policy. *CA: A Cancer Journal for Clinicians*, *70*, 31–46. 10.3322/caac.21586

Batra, A., Yang, L., Boyne, D. J., Harper, A., Cuthbert, C. A., & Cheung, W. Y. (2021). Symptom burden in patients with common cancers near end-of-life and its associations with clinical characteristics: A real-world study. *Supportive Care in Cancer*, *29*, 3299–3309. 10.1007/s00520-020-05827-w

Baussard, L., Proust-Lima, C., Philipps, V., Portales, F., Ychou, M., Mazard, T., & Cousson-Gélie, F. (2022). Determinants of distinct trajectories of fatigue in patients undergoing chemotherapy for a metastatic colorectal cancer: 6-Month follow-up using growth mixture modeling. *Journal of Pain and Symptom Management*, *63*, 140–150. 10.1016/j.jpainsymman.2021.06.019

Berger, A. M., Mooney, K., Alvarez-Perez, A., Breitbart, W. S., Carpenter, K. M., Cella, D., Cleeland, C., Dotan, E., Eisenberger, M. A., Escalante, C. P., Jacobsen, P. B., Jankowski, C., LeBlanc, T., Ligibel, J. A., Loggers, E. T., Mandrell, B., Murphy, B. A., Palesh, O., & Pirl, W. F., National Comprehensive Cancer Network (2018). Cancer-related fatigue, Version 2.2015. *Journal of the National Comprehensive Cancer Network*, *13*, 1012–1039. 10.6004/jnccn.2015.0122

Bischel, L. E., Ritchie, C., Kober, K. M., Paul, S. M., Cooper, B. A., Chen, L. M., Levine, J. D., Hammer, M., Wright, F., & Miaskowski, C. (2016). Age differences in fatigue, decrements in energy, and sleep disturbance in oncology patients receiving chemotherapy. *European Journal of Oncology Nursing*, *23*, 115–123. 10.1016/j.ejon.2016.07.002

Bower, J. E. (2019). The role of neuro-immune interactions in cancer-related fatigue: Biobehavioral risk factors and mechanisms. *Cancer*, *125*, 353–364. 10.1002/cncr.31790

Carlesso, L. C., Tousignant-Laflamme, Y., Shaw, W., Larivière, C., & Choinière, M. (2021). Exploring pain phenotypes in workers with chronic low back pain: Application of IMMPACT recommendations. *Canadian Journal of Pain*, *5*, 43–55. 10.1080/24740527.2020.1870103

Cimprich, B., Visovatti, M., & Ronis, D. L. (2011). The attentional function index—A self-report cognitive measure. *Psycho-Oncology*, *20*, 194–202. 10.1002/pon.1729

Conley, S., Feder, S., & Redeker, N. S. (2015). The relationship between pain, fatigue, depression and functional performance in stable heart failure. *Heart & Lung*, *44*, 107–112. 10.1016/j.hrtlng.2014.07.008

Daut, R. L., Cleeland, C. S., & Flanery, R. C. (1983). Development of the Wisconsin Brief Pain Questionnaire to assess pain in cancer and other diseases. *Pain*, *17*, 197–210. 10.1016/0304-3959(83)90143-4

Extermann, M., Bonetti, M., Sledge, G. W., O'Dwyer, P. J., Bonomi, P., & Benson, A. B., 3rd (2004). MAX2—A convenient index to estimate the average per patient risk for chemotherapy toxicity; Validation in ECOG trials. *Eureropean Journal of Cancer*, *40*, 1193–1198. 10.1016/j.ejca.2004.01.028

Fisch, M. J., Zhao, F., O'Mara, A. M., Wang, X. S., Cella, D., & Cleeland, C. S. (2014). Predictors of significant worsening of patient-reported fatigue over a 1-month timeframe in ambulatory patients with common solid tumors. *Cancer*, *120*, 442–450. 10.1002/cncr.28437

Fletcher, B. S., Paul, S. M., Dodd, M. J., Schumacher, K., West, C., Cooper, B., Lee, K., Aouizerat, B., Swift, P., Wara, W., & Miaskowski, C. A. (2008). Prevalence, severity, and impact of symptoms on female family caregivers of patients at the initiation of radiation therapy for prostate cancer. *Journal of Clinical Oncology*, *26*, 599–605. 10.1200/JCO.2007.12.2838

George, M. A., Lustberg, M. B., & Orchard, T. S. (2020). Psychoneurological symptom cluster in breast cancer: The role of inflammation and diet. *Breast Cancer Research and Treatment*, *184*, 1–9. 10.1007/s10549-020-05808-x

Hardeland, R. (2019). Aging, melatonin, and the pro- and anti-inflammatory networks. *International Journal of Molecular Sciences*, *20*, 1223. 10.3390/ijms20051223

Hu, M., Muhlert, N., Robertson, N., & Winter, M. (2019). Perceived fatigue and cognitive performance change in multiple sclerosis: Uncovering predictors beyond baseline fatigue. *Multiple Sclerosis and Related Disorders*, *32*, 46–53. 10.1016/j.msard.2019.04.011

Huang, Q., Geng, Z., Fang, Q., Stinson, J., & Yuan, C. (2021). Identification of distinct profiles of cancer-related fatigue and associated risk factors for breast cancer patients undergoing chemotherapy: A latent class analysis. *Cancer Nursing*, *44*, E404–E413. 10.1097/NCC.0000000000000862

Jung, T., & Wickrama, K. A. S. (2008). An introduction to latent class growth analysis and growth mixture modeling. *Social and Personality Psychology Compass*, *2*, 302–317. 10.1111/j.1751-9004.2007.00054.x

Keightley, P., Reay, R. E., Pavli, P., & Looi, J. C. (2018). Inflammatory bowel disease-related fatigue is correlated with depression and gender. *Australasian Psychiatry*, *26*, 508–513. 10.1177/1039856218772245

Kober, K. M., Cooper, B. A., Paul, S. M., Dunn, L. B., Levine, J. D., Wright, F., Hammer, M. J., Mastick, J., Venook, A., Aouizerat, B. E., & Miaskowski, C. (2016). Subgroups of chemotherapy patients with distinct morning and evening fatigue trajectories. *Supportive Care in Cancer*, *24*, 1473–1485. 10.1007/s00520-015-2895-2

Kocalevent, R. D., Hinz, A., Brähler, E., & Klapp, B. F. (2011). Determinants of fatigue and stress. *BMC Research Notes*, *4*, 238. 10.1186/1756-0500-4-238

Lee, K. A. (1992). Self-reported sleep disturbances in employed women. *Sleep*, *15*, 493–498. 10.1093/sleep/15.6.493

Lee, K. A., Hicks, G., & Nino-Murcia, G. (1991). Validity and reliability of a scale to assess fatigue. *Psychiatry Research*, *36*, 291–298. 10.1016/0165-1781(91)90027-m

Miaskowski, C., Cooper, B. A., Melisko, M., Chen, L. M., Mastick, J., West, C., Paul, S. M., Dunn, L. B., Schmidt, B. L., Hammer, M., Cartwright, F., Wright, F., Langford, D. J., Lee, K., & Aouizerat, B. E. (2014). Disease and treatment characteristics do not predict symptom occurrence profiles in oncology outpatients receiving chemotherapy. *Cancer*, *120*, 2371–2378. 10.1002/cncr.28699

Padilla, G. V., Presant, C., Grant, M. M., Metter, G., Lipsett, J., & Heide, F. (1983). Quality of life index for patients with cancer. *Research in Nursing & Health*, *6*, 117–126. 10.1002/nur.4770060305

Radloff, L. S. (1977). The CES-D scale: A self-report depression scale for research in the general population. *Applied Psychological Measurement*, *1*, 385–401. 10.1177/014662167700100306

Saligan, L. N., Olson, K., Filler, K., Larkin, D., Cramp, F., Yennurajalingam, S., Escalante, C. P., del Giglio, A., Kober, K. M., Kamath, J., Palesh, O., & Mustian, K., Multinational Association of Supportive Care in Cancer Fatigue Study Group-Biomarker

Working Group (2015). The biology of cancer-related fatigue: A review of the literature. *Supportive Care in Cancer*, *23*, 2461–2478. 10.1007/s00520-015-2763-0

Sangha, O., Stucki, G., Liang, M. H., Fossel, A. H., & Katz, J. N. (2003). The Self-Administered Comorbidity Questionnaire: A new method to assess comorbidity for clinical and health services research. *Arthritis and Rheumatism*, *49*, 156–163. 10.1002/art.10993

Scheff, N. N., & Saloman, J. L. (2021). Neuroimmunology of cancer and associated symptomology. *Immunology & Cell Biology*, *99*, 949–961. 10.1111/imcb.12496

Schwartz, C. E., Bode, R., Repucci, N., Becker, J., Sprangers, M. A., & Fayers, P. M. (2006). The clinical significance of adaptation to changing health: A meta-analysis of response shift. *Quality of Life Research*, *15*, 1533–1550. 10.1007/s11136-006-0025-9

Spielberger, C. D., Gorsuch, R. L., Suchene, R., Vagg, P. R., & Jacobs, G. A. (1983). *Manual for the state-anxiety (Form Y) ("self-evaluation questionnaire")*. Consulting Psychologists Press.

Sunwoo, J. S., Kim, D., Chu, M. K., Yun, C. H., & Yang, K. I. (2022). Fatigue is associated with depression independent of excessive daytime sleepiness in the general population. *Sleep and Breathing*, *26*, 933–940. 10.1007/s11325-021-02448-3

Thong, M. S. Y., Mols, F., van de Poll-Franse, L. V., Sprangers, M. A. G., van der Rijt, C. C. D., Barsevick, A. M., Knoop, H., & Husson, O. (2018). Identifying the subtypes of cancer-related fatigue: Results from the population-based PROFILES registry. *Journal of Cancer Survivorship*, *12*, 38–46. 10.1007/s11764-017-0641-0

Torossian, M., & Jacelon, C. S. (2021). Chronic illness and fatigue in older individuals: A systematic review. *Rehabilitation Nursing*, *46*, 125–136. 10.1097/RNJ.0000000000000278

Wang, X. S., Zhao, F., Fisch, M. J., O'Mara, A. M., Cella, D., Mendoza, T. R., & Cleeland, C. S. (2014). Prevalence and characteristics of moderate to severe fatigue: A multicenter study in cancer patients and survivors. *Cancer*, *120*, 425–432. 10.1002/cncr.28434

Whisenant, M., Wong, B., Mitchell, S. A., Beck, S. L., & Mooney, K. (2017). Distinct trajectories of fatigue and sleep disturbance in women receiving chemotherapy for breast cancer. *Oncology Nursing Forum*, *44*, 739–750. 10.1188/17.Onf.739-750

Whisenant, M., Wong, B., Mitchell, S. A., Beck, S. L., & Mooney, K. (2019). Symptom trajectories are associated with co-occurring symptoms during chemotherapy for breast cancer. *Journal of Pain and Symptom Management*, *57*, 183–189. 10.1016/j.jpainsymman.2018.11.010

Wright, F., Cooper, B. A., Conley, Y. P., Hammer, M. J., Chen, L. M., Paul, S. M., Levine, J. D., Miaskowski, C., & Kober, K. M. (2017). Distinct evening fatigue profiles in oncology outpatients receiving chemotherapy. *Fatigue: Biomedicine, Health & Behavior*, *5*, 131–144. 10.1080/21641846.2017.1322233

Wright, F., Dunn, L. B., Paul, S. M., Conley, Y. P., Levine, J. D., Hammer, M. J., Cooper, B. A., Miaskowski, C., & Kober, K. M. (2019). Morning fatigue severity profiles in oncology outpatients receiving chemotherapy. *Cancer Nursing*, *42*, 355–364. 10.1097/NCC.0000000000000626

Wright, F., Kober, K. M., Cooper, B. A., Paul, S. M., Conley, Y. P., Hammer, M., Levine, J. D., & Miaskowski, C. (2020). Higher levels of stress and different coping strategies are associated with greater morning and evening fatigue severity in oncology patients receiving chemotherapy. *Supportive Care in Cancer*, *28*, 4697–4706. 10.1007/s00520-020-05303-5