

# Distinct Morning and Evening Fatigue Profiles in Patients With Gynecologic Cancers Receiving Chemotherapy

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**OBJECTIVES:** To identify distinct morning and evening fatigue profiles in patients with gynecologic cancers and evaluate for differences in demographic and clinical characteristics, common symptoms, and quality-of-life outcomes.

**SAMPLE & SETTING:** Outpatients with gynecologic cancers (N = 233) were recruited before their second or third cycles of chemotherapy at four cancer centers in San Francisco Bay and New York.

**METHODS & VARIABLES:** The Lee Fatigue Scale was completed six times over two cycles of chemotherapy in the morning and in the evening. Latent profile analysis was used to identify distinct morning and evening fatigue profiles.

**RESULTS:** Four distinct morning and two distinct evening fatigue classes were identified. Common risk factors for morning and evening fatigue included younger age, higher body mass index, lower functional status, and higher comorbidity burden. Patients in the worst morning and evening fatigue classes reported higher levels of anxiety, depression, and sleep disturbance; lower levels of energy and cognitive function; and poorer quality of life.

**IMPLICATIONS FOR NURSING:** Clinicians can use this information to identify higher-risk patients and develop individualized interventions for morning and evening fatigue.

**KEYWORDS** chemotherapy; evening fatigue; morning fatigue; gynecologic cancer; quality of life  
**ONF, 52(2), E35–E57.**

**DOI** 10.1188/25.ONF.E35-E57

Although in the current authors' recent systematic review (Asakitogum et al., 2024) the grand mean prevalence rate for fatigue in patients with gynecologic cancers was 62.1%, reported rates ranged from 22% (Vittrup et al., 2021) to 90% (King et al., 2018). This range suggests that a large amount of interindividual variability exists in the experience of fatigue. Although fatigue is known to have a negative impact on patients' functional status and quality of life (QOL), most of the research on risk factors for and QOL outcomes associated with higher rates and severity of fatigue were evaluated in patients with breast cancer (Joly et al., 2019; Peterson & Ligibel, 2018) or patients with heterogeneous types of cancer (Bower, 2014; Ma et al., 2020; Thong et al., 2020).

## Diurnal Variations in and Risk Factors for Fatigue

Equally important, diurnal variations exist in the occurrence and severity of fatigue in patients with cancer, with lower levels occurring in the morning and higher levels in the evening (Dhruva et al., 2010, 2013; Kober, Cooper, et al., 2016; Lerdal et al., 2016; Lin et al., 2023; Miaskowski et al., 2008; Wright et al., 2015a, 2015b, 2017, 2019). However, no studies have evaluated diurnal variations in fatigue severity in patients with gynecologic cancers. In terms of demographic risk factors, higher levels of morning and evening fatigue were associated with being aged younger (Dhruva et al., 2010, 2013; Kober, Cooper, et al., 2016; Lin et al., 2023; Miaskowski et al., 2008; Wright et al., 2015a, 2017, 2019), being female (Dhruva et al., 2013; Kober, Cooper, et al., 2016; Lin et al., 2023; Wright et al., 2017, 2019), having a lower annual income (Kober, Cooper, et al., 2016; Lin et al., 2023; Wright et al.,

2017), and having childcare responsibilities (Dhruva et al., 2010, 2013; Kober, Cooper, et al., 2016; Lin et al., 2023; Wright et al., 2015b, 2017). Common clinical risk factors for both symptoms included having a lower functional status (Dhruva et al., 2013; Kober, Cooper, et al., 2016; Lin et al., 2023; Wright et al., 2015a, 2015b, 2017, 2019) and a higher comorbidity burden (Kober, Cooper, et al., 2016; Lin et al., 2023; Wright et al., 2015b, 2017, 2019), as well as a self-reported diagnosis of depression (Lin et al., 2023; Wright et al., 2017, 2019) and receipt of a higher number of cancer treatments (Lin et al., 2023).

Unique risk factors for morning fatigue included living alone (Lin et al., 2023; Wright et al., 2019), not being married or partnered (Kober, Cooper, et al., 2016; Lin et al., 2023; Wright et al., 2019), being unemployed (Lin et al., 2023), and not exercising regularly (Kober, Cooper, et al., 2016; Lin et al., 2023; Wright et al., 2019). In addition, these patients had a higher body mass index (BMI) (Dhruva et al., 2010; Kober, Cooper, et al., 2016; Wright et al., 2015a, 2019), were more likely to self-report diagnoses of anemia or blood disease (Lin et al., 2023; Wright et al., 2019) or back pain (Wright et al., 2019), and had received a lower number of cancer treatments (Kober, Cooper, et al., 2016). Unique risk factors for evening fatigue included having a higher level of education (Wright et al., 2015b, 2017), self-report of being White (Kober, Cooper, et al., 2016; Lin et al., 2023; Wright et al., 2015b, 2017), being more likely to self-report a diagnosis of high blood pressure (Wright et al., 2017), and having breast cancer (Kober, Cooper, et al., 2016; Wright et al., 2015b, 2017). These findings demonstrate that morning and evening fatigue are distinct symptoms. Carefully evaluating specific risk factors for increased fatigue in patients with gynecologic cancers could lead to earlier identification of high-risk patients.

### **Common Symptoms Associated With Fatigue**

Many studies evaluated for associations between diurnal variations in fatigue severity and other common symptoms in patients with cancer. Of note, higher levels of morning and evening fatigue were associated with higher symptom severity scores for depression (Dhruva et al., 2010, 2013; Lin et al., 2023; Miaskowski et al., 2008; Wright et al., 2015a, 2015b, 2017, 2019), sleep disturbance (Dhruva et al., 2010, 2013; Lin et al., 2023; Miaskowski et al., 2008; Wright et al., 2015a, 2015b, 2017, 2019), trait anxiety (Dhruva et al., 2010, 2013; Lin et al., 2023; Miaskowski et al., 2008; Wright et al., 2017, 2019), and state anxiety (Dhruva et al.,

2010, 2013; Lin et al., 2023; Miaskowski et al., 2008; Wright et al., 2015a, 2017, 2019). In addition, both symptoms were associated with significant decrements in cognitive function (Dhruva et al., 2013; Lin et al., 2023; Wright et al., 2017, 2019) and evening energy (Lin et al., 2023; Wright et al., 2017, 2019), as well as higher occurrence rates for cancer and noncancer pain (Dhruva et al., 2013; Wright et al., 2017, 2019) and higher worst pain and pain interference scores (Lin et al., 2023). Unique symptoms associated with higher morning fatigue scores were lower levels of morning energy (Lin et al., 2023) and higher levels of evening fatigue (Lin et al., 2023; Wright et al., 2019). Higher levels of morning fatigue was the unique symptom associated with higher levels of evening fatigue.

### **QOL and Fatigue**

Most of the studies that evaluated the relationships between average fatigue and QOL in patients with cancer found a negative correlation (Agarwal et al., 2020; Chen et al., 2018; Gupta et al., 2007; Liu et al., 2023; Pelzer et al., 2024; Ruiz-Casado et al., 2021). In terms of the associations between morning and/or evening fatigue and QOL outcomes, in the current authors' previous studies (Dhruva et al., 2013; Lin et al., 2023), higher levels of both morning and evening fatigue were associated with lower summary scores for the physical and mental components of SF-12® (Ware et al., 1996). In terms of a cancer-specific measure of QOL, except for the spiritual well-being subscale, higher levels of both morning and evening fatigue were associated with lower scores for all the other subscales of the Multidimensional Quality of Life Scale–Patient Version (MQOLS-PV) (Dhruva et al., 2013; Ferrell et al., 1995; Lin et al., 2023).

Although the findings summarized previously provide evidence of diurnal variations in the severity of fatigue and associations with other common symptoms and QOL outcomes, no studies evaluated the occurrence and/or severity of these two symptoms in patients with gynecologic cancers. Knowledge of common and distinct risk factors, and associations with other common symptoms, could be used to provide tailored interventions for patients with one or both symptoms. For example, if high levels of morning fatigue were associated with significant sleep disturbance, patients could be taught interventions to improve their sleep routines. Therefore, the purposes of this study, in a sample of patients with gynecologic cancers receiving chemotherapy (N = 233), were to identify subgroups of patients with distinct morning and evening fatigue profiles; evaluate for differences

among these subgroups in demographic, clinical, and symptom characteristics and QOL outcomes; and determine whether morning and evening fatigue are distinct symptoms.

Methods

Patients and Settings

The theoretical framework for the parent study was the theory of symptom management (Weiss et al., 2023). For the current study, the main concepts evaluated were the symptoms, experiences, and outcomes within the context of various person and health and illness characteristics. The current study is part of a larger longitudinal study that evaluated the symptom experience of outpatients with cancer receiving chemotherapy (Wright et al., 2015b). Patients were enrolled if they were aged 18 years or older; were able to read, write, and understand English; had a diagnosis of breast, gastrointestinal, gynecologic, or lung cancer; had received chemotherapy within the preceding four weeks; were scheduled to receive at least two additional cycles of chemotherapy; and gave written informed consent. Patients were recruited from two comprehensive cancer centers, one Veterans Affairs hospital, one public hospital, and four community-based oncology clinics in San Francisco Bay and New York. For this analysis, of the

1,343 patients enrolled, only patients with gynecologic cancers were included (n = 233).

Instruments

Demographic and Clinical Characteristics

Patients completed a demographic questionnaire that obtained information on age, ethnicity, marital status, living arrangements, education, employment status, and income. In addition, they completed the Karnofsky Performance Status Scale (KPS) (Karnofsky, 1977), the Self-Administered Comorbidity Questionnaire (Sangha et al., 2003), the Alcohol Use Disorders Identification Test (Bohn et al., 1995), 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.

Morning and Evening Fatigue and Energy 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). Fatigue and energy scores were calculated as the mean of the 13 fatigue items and 5 energy items. Higher scores indicate greater severity of fatigue and higher levels of energy. Patients were asked to rate each item based on how they felt within 30 minutes

TABLE 1. Morning and Evening Fatigue Latent Profile Solutions and Fit Indices

Model	LL	AIC	BIC	Entropy	VLMR
Morning fatigue					
1 class	-2,494.03	5,022.07	5,080.73	N/A	N/A
2 class	-2,366.67	4,781.34	4,864.16	0.78	254.73**
3 class	-2,305.19	4,672.39	4,779.37	0.84	122.95**
4 class <sup>a</sup>	-2,268.21	4,612.42	4,743.56	0.82	73.97*
5 class	-2,250.22	4,590.44	4,745.74	0.78	NS
Evening fatigue					
1 class	-2,312.56	4,659.12	4,717.71	N/A	N/A
2 class <sup>b</sup>	-2,168.86	4,385.71	4,468.43	0.87	287.41***
3 class	-2,125.02	4,312.04	4,418.89	0.77	NS

\* p < 0.05; \*\* p < 0.01; \*\*\* p < 0.00005

<sup>a</sup>The 4-class solution was selected for morning fatigue because the BIC for that solution was lower than the BIC for the 3-class and 5-class solutions. In addition, the VLMR was significant for the 4-class solution, indicating that 4 classes fit the data better than 3 classes.

<sup>b</sup>The 2-class solution was selected for evening fatigue because the BIC for that solution was lower than the BIC for the 1-class (enrollment) solution. In addition, the VLMR was significant for the 2-class solution, indicating that 2 classes fit the data better than only 1 class. Although the BIC was smaller for the 3-class solution than for the 2-class solution, the VLMR was not significant for the 3-class solution, indicating that too many classes were extracted.

AIC—Akaike information criterion; BIC—Bayesian information criterion; LL—log-likelihood; N/A—not applicable; NS—not significant; VLMR—Vuong–Lo–Mendell–Rubin likelihood ratio test for the K versus K-1 model

of awakening (i.e., morning fatigue and morning energy) and before going to bed (i.e., evening fatigue and evening energy). The LFS has established cutoff scores for clinically meaningful levels of fatigue (i.e., 3.2 or greater for morning fatigue, 5.6 or greater for evening fatigue) and energy (i.e., 6.2 or less for morning energy, 3.5 or less for evening energy) (Fletcher et al., 2008). Cronbach's alphas were 0.96 for morning fatigue and 0.93 for evening fatigue, and 0.95 for morning energy and 0.93 for evening energy.

### Symptom Measures

**Anxiety:** The 20 items on the Spielberger State-Trait Anxiety Inventory (STAI-S and STAI-T) were rated from 1 to 4 (Spielberger et al., 1983). The STAI-S measures a person's temporary anxiety response to a specific situation or how anxious or tense a person is "right now" in a specific situation. The STAI-T measures a person's predisposition to anxiety as part of one's personality. Cutoff scores of 31.8 or greater and 32.2 or greater indicate a high level of trait and state anxiety, respectively. Cronbach's alphas for the STAI-T and STAI-S were 0.92 and 0.96, respectively.

**Depression:** The 20-item Center for Epidemiological Studies Depression Scale evaluates the significant symptoms in the clinical syndrome of

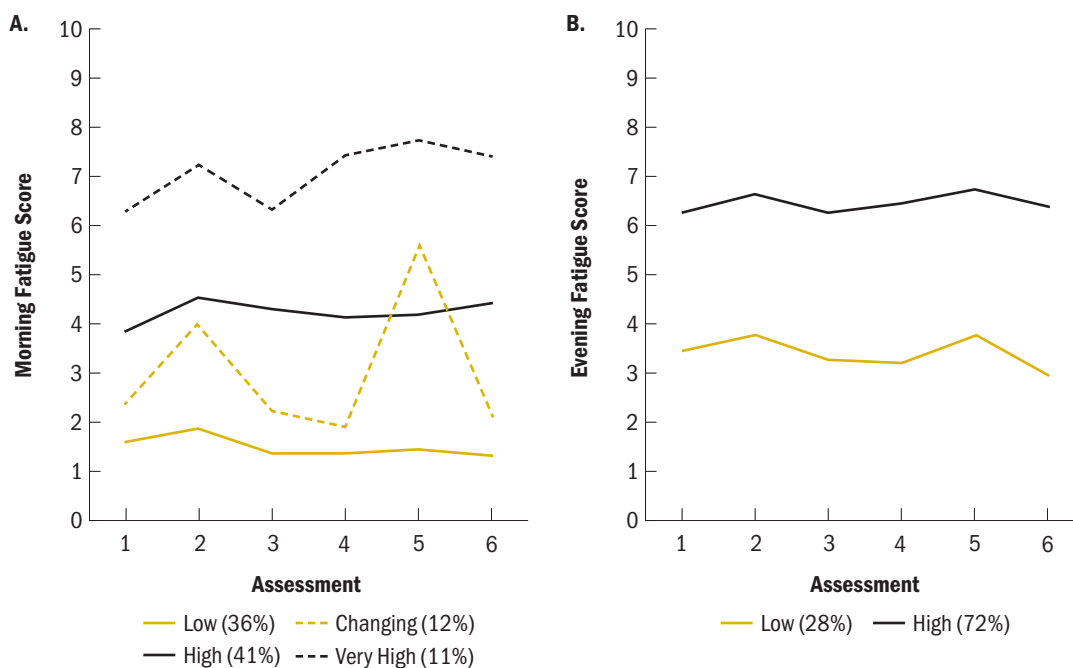
depression (Radloff, 1977). A total score can range from 0 to 60, with scores of 16 or greater indicating the need for individuals to seek clinical evaluation for major depression. Its Cronbach's alpha was 0.89.

**Sleep disturbance:** The 21-item General Sleep Disturbance Scale (GSDS) was designed to assess sleep quality in the past week (Lee, 1992). Each item was rated on a 0 (never) to 7 (every day) NRS. The GSDS total score is the sum of the 21 items that range from 0 (no disturbance) to 147 (extreme sleep disturbance). Higher total scores indicate higher levels of sleep disturbance. A GSDS total score of 43 or greater indicates a significant level of sleep disturbance (Fletcher et al., 2008). Its Cronbach's alpha was 0.83.

**Cognitive function:** The 16-item Attentional Function Index assesses an individual's perceived effectiveness in performing daily activities supported by attention and working memory (Cimprich et al., 2011). A higher total mean score on a 0–10 NRS indicates better cognitive function (Cimprich et al., 2011). Total scores are grouped into categories of attentional function (i.e., less than 5 = low function, 5–7.5 = moderate function, and greater than 7.5 = high function) (Cimprich et al., 2005). Its Cronbach's alpha was 0.93.

**Pain:** The occurrence of pain was evaluated using the Brief Pain Inventory (Daut et al., 1983). Patients

**FIGURE 1. Trajectories of Morning Fatigue for the 4 Latent Classes (A) and Trajectories of Evening Fatigue for the 2 Latent Classes (B)**



**TABLE 2. Differences in Demographic and Clinical Characteristics Among the Morning Fatigue Classes at Enrollment**

Characteristic	Low (0) (N = 84, 36%)		Changing (1) (N = 28, 12%)		High (2) (N = 95, 41%)		Very High (3) (N = 26, 11%)		Statistics
	$\bar{X}$	SD	$\bar{X}$	SD	$\bar{X}$	SD	$\bar{X}$	SD	
Age (years)	63.2	11.9	59.6	12.2	58.4	13.4	53.2	10.5	F = 4.96, p = 0.002 0 > 3
Education (years)	16.1	3	16.1	2.9	16	2.8	15.7	2.8	F = 0.1, p = 0.96
Body mass index (kg/m <sup>2</sup> )	26	5.6	27.2	6.2	28.1	6.5	29.9	8.6	F = 3.11, p = 0.027 0 < 3
AUDIT score	2.7	1.3	2.6	2.6	3.1	2.6	2.1	1	F = 0.99, p = 0.4
Karnofsky Performance Status Scale score	83.2	11.7	75	13.8	77.2	11.5	71	10.4	F = 8.62, p < 0.001 0 > 1, 2, and 3
Number of comorbidities (of 13)	2.1	1.1	2.2	1.3	2.6	1.5	2.9	1.9	F = 3.13, p = 0.027 No significant pairwise contrasts
Self-Administered Comorbidity Questionnaire score	4.5	2.3	5	2.7	6	3.5	7	4.7	F = 5.39, p = 0.001 0 < 2 and 3
Time since diagnosis (years)	2.3	3.3	1.5	2.7	2.1	4.1	1.4	2.1	KW = 7.2, p = 0.066
Number of prior cancer treatments	2	1.2	1.6	1	1.8	1.1	1.4	1	F = 2.3, p = 0.078
Number of metastatic sites including lymph nodes <sup>a</sup>	1.4	1.3	1.6	1.3	1.4	1.3	1.6	1.4	F = 0.18, p = 0.908
Number of non-lymph metastatic sites	1	1.1	1.1	1	1	1.1	1.3	1.3	F = 0.47, p = 0.705
MAX2 score	10.14	0.06	0.19	0.06	0.15	0.06	0.15	0.06	F = 6.7, p < 0.001 0 and 2 < 1
Characteristic	n	%	n	%	n	%	n	%	Statistics
<b>Self-reported race and ethnicity</b>									$\chi^2 = 7.56$ , p = 0.579
Asian or Pacific Islander	6	7	3	11	8	9	3	12	
Black	3	4	–	–	5	5	–	–	
Hispanic, mixed, or other	7	9	6	21	9	10	2	8	
White	66	81	19	68	71	76	20	80	
<b>Married or partnered</b>									
Yes	47	57	18	67	47	51	12	48	$\chi^2 = 2.72$ , p = 0.436
<b>Lives alone</b>									
Yes	24	29	5	19	35	38	13	50	$\chi^2 = 7.5$ , p = 0.058
<b>Currently employed</b>									
Yes	28	33	7	26	30	32	6	23	$\chi^2 = 1.37$ , p = 0.712
<b>Annual household income (\$)</b>									KW = 5.68, p = 0.128
< 30,000	9	12	5	19	18	21	6	25	

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**TABLE 2. Differences in Demographic and Clinical Characteristics Among the Morning Fatigue Classes at Enrollment (Continued)**

Characteristic	Low (0) (N = 84, 36%)		Changing (1) (N = 28, 12%)		High (2) (N = 95, 41%)		Very High (3) (N = 26, 11%)		Statistics
	n	%	n	%	n	%	n	%	
Annual household income (\$) (continued)									KW = 5.68, p = 0.128
30,000 to < 70,000	17	23	8	30	25	30	7	29	
70,000–100,000	15	20	2	7	16	19	2	8	
> 100,000	34	45	12	44	25	30	9	38	
Childcare responsibilities									
Yes	3	4	3	11	13	14	4	15	$\chi^2 = 6.21$ , p = 0.102
Eldercare responsibilities									
Yes	5	7	–	–	10	12	3	13	$\chi^2 = 4.74$ , p = 0.192
Past or current history of smoking									
Yes	27	33	10	36	32	34	10	39	$\chi^2 = 0.26$ , p = 0.968
Exercise on a regular basis									
Yes	64	77	18	67	67	71	12	50	$\chi^2 = 6.82$ , p = 0.078
Specific comorbid conditions									
Heart disease	6	7	1	4	4	4	2	8	$\chi^2 = 1.16$ , p = 0.762
High blood pressure	26	31	11	39	33	35	8	31	$\chi^2 = 0.81$ , p = 0.845
Lung disease	2	2	–	–	5	5	–	–	$\chi^2 = 3.45$ , p = 0.328
Diabetes	2	2	1	4	8	8	2	8	$\chi^2 = 3.52$ , p = 0.318
Ulcer or stomach disease	3	4	1	4	6	6	3	12	$\chi^2 = 2.71$ , p = 0.439
Kidney disease	1	1	1	4	5	5	–	–	$\chi^2 = 3.45$ , p = 0.328
Liver disease	3	4	1	4	1	1	–	–	$\chi^2 = 2.2$ , p = 0.533
Anemia or blood disease	8	10	5	18	18	19	6	23	$\chi^2 = 4.3$ , p = 0.231
Depression	7	8	7	25	26	27	12	46	$\chi^2 = 19.51$ , p < 0.001
									0 < 2 and 3
Osteoarthritis	16	19	3	11	14	15	6	23	$\chi^2 = 2.07$ , p = 0.557
Back pain	15	18	4	14	28	30	12	46	$\chi^2 = 11.11$ , p = 0.011
									0 < 3
Rheumatoid arthritis	4	5	–	–	1	1	1	4	$\chi^2 = 3.49$ , p = 0.336
Type of gynecologic cancer									$\chi^2 = 1.6$ , p = 0.0953
Ovarian	47	53	17	61	54	58	13	50	
Uterine	24	29	9	32	26	28	9	35	
Other	11	13	2	7	13	14	4	15	
Type of prior cancer treatment									$\chi^2 = 12.88$ , p = 0.168
No prior treatment	2	2	–	–	3	3	3	12	
Only surgery, CTX, or RT	43	51	20	74	47	51	14	56	
Surgery and CTX, or surgery and RT, or CTX and RT	33	39	6	22	33	36	6	24	
Surgery and CTX and RT	6	7	1	4	10	11	2	8	

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**TABLE 2. Differences in Demographic and Clinical Characteristics Among the Morning Fatigue Classes at Enrollment (Continued)**

Characteristic	Low (0) (N = 84, 36%)		Changing (1) (N = 28, 12%)		High (2) (N = 95, 41%)		Very High (3) (N = 26, 11%)		Statistics
	n	%	n	%	n	%	n	%	
Cycle length (days)									KW = 5.43, p = 0.143
14	4	5	1	4	5	5	3	12	
21	66	79	27	96	74	78	21	81	
28	14	17	-	-	16	17	2	8	
Emetogenicity of the CTX regimen									KW = 9.18, p = 0.027 0 < 1
Minimal/low	19	23	1	4	17	18	6	23	
Moderate	63	75	23	82	69	73	19	73	
High	2	2	4	14	9	10	1	4	
Antiemetic regimen									$\chi^2 = 9.88$ , p = 0.361
None	13	17	-	-	10	11	1	4	
Steroid alone or serotonin receptor antagonist alone	19	24	10	36	25	27	6	24	
Serotonin receptor antagonist and steroid	37	47	5	18	41	44	3	12	
NK-1 receptor antagonist and 2 other antiemetics	10	13	5	18	17	18	3	12	

<sup>a</sup>Total number of metastatic sites evaluated was 9.

AUDIT—Alcohol Use Disorders Identification Test; CTX—chemotherapy; KW—Kruskal-Wallis; NK-1—neurokinin-1; RT—radiation therapy

**Note.** Median time since diagnosis was 0.59 years for Low, 0.32 years for Changing, 0.55 years for High, and 0.43 years for Very High.

**Note.** Because of rounding, percentages may not total 100.

who responded “yes” to the question about having pain were asked to indicate whether 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, or both cancer and noncancer pain). Patients rated the intensity of their worst pain using a 0 (none) to 10 (excruciating) NRS. In addition, they rated pain’s level of interference with function.

#### QOL Measures

QOL was evaluated using general (e.g., SF-12) and disease-specific (e.g., MQOLS-PV) measures. The SF-12 consists of 12 questions about physical and mental health and overall health status. Scores for the individual items on the SF-12 range from 0 to 100. The instrument is divided into two components (e.g., physical component summary [PCS] and mental component summary [MCS] scores). Higher PCS and MCS scores indicate better QOL (Ware et al., 1996).

The 41-item MQOLS-PV assesses four domains of QOL (i.e., physical, psychological, social, and spiritual well-being) in patients with cancer and a total QOL score. Each item was rated on a 0–10 NRS, with higher scores indicating better QOL (Ferrell et al., 1995).

#### Study Procedures

The parent study was approved by the Committee on Human Research at the University of California, San Francisco, and the institutional review board at each study site. Written informed consent was obtained from all patients. Eligible patients were approached by a research staff member in the infusion unit to discuss participation in the study during their first or second cycle of chemotherapy. Depending on the length of their chemotherapy cycle, patients completed paper questionnaires in their homes a total of six times over two cycles of chemotherapy (i.e., before chemotherapy administration [assessments 1 and 4]; about one week following the administration of chemotherapy



[assessments 2 and 5]; and about two weeks after the administration of chemotherapy [assessments 3 and 6]). All the other measures were completed at enrollment (i.e., before the patients' second or third cycle of chemotherapy).

#### Data Analysis

Latent profile analysis (LPA) identified subgroups (i.e., latent classes) with distinct morning and evening fatigue profiles over six assessments. Separate LPAs were done for morning and evening fatigue. LPA was

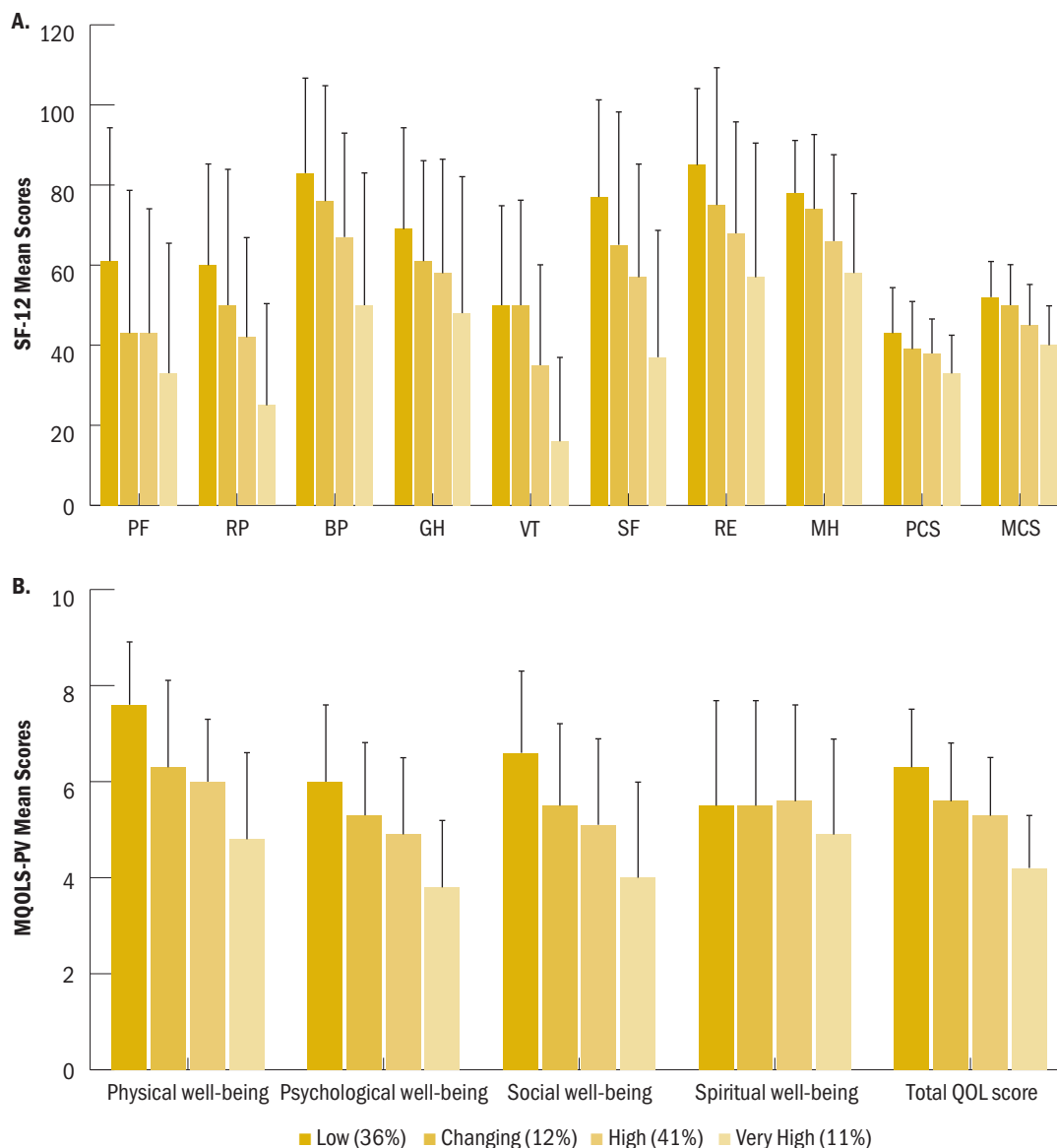
**TABLE 3. Differences in Symptom Severity Scores Among the Morning Fatigue Classes at Enrollment**

Symptom <sup>a</sup>	Low (0) (N = 84, 36%)		Changing (1) (N = 28, 12%)		High (2) (N = 95, 41%)		Very High (3) (N = 26, 11%)		Statistics
	$\bar{X}$	SD	$\bar{X}$	SD	$\bar{X}$	SD	$\bar{X}$	SD	
Evening fatigue ( $\geq 5.6$ )	4.5	1.8	5.4	1.9	5.8	1.7	7.2	1.8	F = 17.13, p < 0.001 0 < 2 and 3; 1 and 2 < 3
Morning energy ( $\leq 6.2$ )	4.7	2.4	4.5	2.4	4	1.6	3.8	2.6	F = 2.23, p = 0.086
Evening energy ( $\leq 3.5$ )	3.7	2	3.5	1.8	3.6	2	2.2	1.1	F = 4.72, p = 0.003 0 and 2 > 3
Trait anxiety ( $\geq 31.8$ )	30.8	7.8	34.9	8.3	38.8	11.3	41	9.3	F = 12.8, p < 0.001 0 < 2 and 3
State anxiety ( $\geq 32.2$ )	28.3	8.2	33.5	9.2	36.3	12.9	43.2	12.8	F = 14.7, p < 0.001 0 < 2 and 3; 1 and 2 < 3
Depression ( $\geq 16$ )	8.3	6.3	12.6	8.3	15.9	9.3	21.9	10.3	F = 21.31, p < 0.001 0 < 2 and 3; 1 and 2 < 3
Sleep disturbance ( $\geq 43$ )	42.9	18	50.3	18	59.8	16.8	71.9	16.1	F = 24.41, p < 0.001 0 < 2 and 3; 1 and 2 < 3
Attentional function (< 5 = low, 5–7.5 = moderate, > 7.5 = high)	7.1	1.5	6.6	1.7	5.6	1.5	4.6	1.4	F = 26.07, p < 0.001 0 and 1 > 2 and 3; 2 > 3
Symptom	n	%	n	%	n	%	n	%	Statistics
Type of pain									$\chi^2 = 35.72$ , p < 0.001
No pain	27	32	5	18	14	15	3	12	0 > 2
Only noncancer pain	17	20	–	–	11	12	–	–	NS
Only cancer pain	22	26	14	50	27	29	6	23	NS
Both cancer and noncancer pain	18	21	9	32	40	44	17	65	0 < 2 and 3
Symptom	$\bar{X}$	SD	$\bar{X}$	SD	$\bar{X}$	SD	$\bar{X}$	SD	Statistics
For patients with pain									
Worst pain intensity score	4.9	2.4	6.7	2.5	5.8	2.5	7.5	2	F = 6.27, p < 0.001 0 < 1 and 3; 2 < 3
Mean pain interference score	2	1.9	2.8	2.5	3.5	2.4	4.8	2.8	F = 8.74, p < 0.001 0 < 2 and 3; 1 < 3

<sup>a</sup> Clinically meaningful cutoff scores are in parentheses after the symptom.  
NS—not significant  
**Note.** Because of rounding, percentages may not total 100.



**FIGURE 2. Differences in SF-12® Scores (A) and MQOLS-PV Scores (B) Among the Morning Fatigue Latent Classes**



BP—bodily pain; GH—general health; MCS—mental component summary; MH—mental health; MQOLS-PV—Multidimensional Quality of Life Scale—Patient Version; PCS—physical component summary; PF—physical functioning; QOL—quality of life; RE—role emotional; RP—role physical; SF—social functioning; VT—vitality

**Note.** Figure 2A shows differences in SF-12 PF, RP, BP, GH, VT, SF, RE, MH, PCS, and MCS scores among the morning fatigue classes. All values are plotted as means and SDs. For the SF-12, compared to the Low class, patients in the High and Very High classes had significantly lower PF, RP, BP, VT, SF, RE, and MH scores. Compared to the Changing and High classes, patients in the Very High class had significantly lower RP, BP, VT, and MCS scores. Compared to the Low class, patients in the Changing and High classes had significantly lower PCS scores (all  $p < 0.05$ ).

**Note.** Figure 2B shows differences in MQOLS-PV scores for the physical, psychological, social, and spiritual well-being domains as well as total QOL among the morning fatigue latent classes. All values are plotted as means and SDs. For the MQOLS-PV, compared to the Low class, patients in the other 3 classes had significantly lower physical well-being and total QOL scores. Compared to the Changing and High classes, patients in the Very High class had significantly lower physical well-being, psychological well-being, social well-being, and total QOL scores (all  $p < 0.05$ ).

**TABLE 4. Differences in Demographic and Clinical Characteristics Between the Evening Fatigue Classes at Enrollment**

Characteristic	Low (N = 65, 28%)		High (N = 167, 72%)		Statistics
	$\bar{X}$	SD	$\bar{X}$	SD	
Age (years)	63.6	11.9	58	12.7	t = 3.07, p = 0.002
Education (years)	16.2	3	15.9	2.8	t = 0.62, p = 0.535
Body mass index (kg/m <sup>2</sup> )	25.7	5.3	28.1	6.9	t = -2.83, p = 0.005
Alcohol Use Disorders Identification Test score	2.4	1.2	2.9	2.3	t = -1.42, p = 0.157
Karnofsky Performance Status Scale score	82.4	12.9	77	11.8	t = 3, p = 0.003
Number of comorbidities (of 13)	2.2	1.1	2.5	1.5	t = -1.59, p = 0.113
Self-Administered Comorbidity Questionnaire score	4.6	2.2	5.7	3.6	t = -2.82, p = 0.005
Time since cancer diagnosis (years)	2.8	4.8	1.7	2.8	U, p = 0.021
Number of prior cancer treatments	1.9	1.1	1.8	1.1	t = 0.95, p = 0.342
Number of metastatic sites including lymph nodes	1.4	1.2	1.5	1.4	t = -0.73, p = 0.4673
Number of non-lymph metastatic sites	0.9	1	1.1	1.2	t = -1, p = 0.319
MAX2 score	0.14	0.06	0.15	0.06	t = -1.37, p = 0.171
Characteristic	n	%	n	%	Statistics
<b>Self-reported race and ethnicity</b>					$\chi^2 = 6.51$ , p = 0.089
Asian or Pacific Islander	6	9	14	9	
Black	5	8	3	2	
Hispanic, mixed, or other	9	14	15	9	
White	44	69	131	80	
<b>Married or partnered</b>					FE, p = 0.881
Yes	35	57	89	55	
<b>Lives alone</b>					FE, p = 0.211
Yes	17	27	60	37	
<b>Currently employed</b>					FE, p = 0.754
Yes	19	29	52	32	
<b>Annual household income (\$)</b>					U, p = 0.619
< 30,000	12	21	26	17	
30,000 to < 70,000	17	29	40	27	
70,000–100,000	7	12	28	19	
> 100,000	22	38	57	38	
<b>Childcare responsibilities</b>					FE, p = 0.14
Yes	3	5	20	12	

*Continued on the next page*

**TABLE 4. Differences in Demographic and Clinical Characteristics Between the Evening Fatigue Classes at Enrollment (Continued)**

Characteristic	Low (N = 65, 28%)		High (N = 167, 72%)		Statistics
	n	%	n	%	
<b>Eldercare responsibilities</b>					FE, p = 0.785
Yes	4	7	14	9	
<b>Current or past history of smoking</b>					FE, p = 0.162
Yes	17	27	61	37	
<b>Exercise on a regular basis</b>					FE, p = 0.872
Yes	47	72	114	70	
<b>Specific comorbidities</b>					
Heart disease	6	9	7	4	FE, p = 0.199
High blood pressure	21	32	56	34	FE, p = 1
Lung disease	3	5	4	2	FE, p = 0.403
Diabetes	3	5	9	5	FE, p = 1
Ulcer or stomach disease	1	2	12	7	FE, p = 0.118
Kidney disease	1	2	6	4	FE, p = 0.676
Liver disease	1	2	4	2	FE, p = 1
Anemia or blood disease	7	11	30	18	FE, p = 0.232
Depression	11	17	41	25	FE, p = 0.226
Osteoarthritis	8	12	31	19	FE, p = 0.329
Back pain	12	19	47	28	FE, p = 0.135
Rheumatoid arthritis	1	2	5	3	FE, p = 1
<b>Type of gynecologic cancer</b>					$\chi^2 = 1.69$ , p = 0.431
Ovarian	34	53	96	59	
Uterine	23	36	45	27	
Other	7	11	23	14	
<b>Type of prior cancer treatment</b>					$\chi^2 = 1.63$ , p = 0.653
No prior treatment	2	3	6	4	
Only surgery, CTX, or RT	33	51	90	55	
Surgery and CTX, or surgery and RT, or CTX and RT	26	40	52	32	
Surgery and CTX and RT	4	6	15	9	
<b>Cycle length (days)</b>					U, p = 0.425
14	2	3	10	6	
21	53	82	135	81	
28	10	15	22	13	
<b>Emetogenicity of the CTX regimen</b>					U, p = 0.588
Minimal/low	9	14	34	20	
Moderate	53	82	120	72	
High	3	5	13	8	
<b>Antiemetic regimen</b>					$\chi^2 = 6.98$ , p = 0.073
None	9	14	15	9	
Steroid alone or serotonin antagonist alone	21	33	39	24	

*Continued on the next page*

**TABLE 4. Differences in Demographic and Clinical Characteristics Between the Evening Fatigue Classes at Enrollment (Continued)**

Characteristic	Low (N = 65, 28%)		High (N = 167, 72%)		Statistics
	n	%	n	%	
Antiemetic regimen (continued)					$\chi^2 = 6.98, p = 0.073$
Serotonin antagonist and steroid	29	46	77	48	
NK-1 receptor antagonist and 2 other antiemetics	4	6	30	19	

CTX—chemotherapy; FE—Fisher’s exact test; NK-1—neurokinin-1; RT—radiation therapy; U—Mann–Whitney U test

**Note.** Median time since diagnosis was 0.61 years for Low and 0.48 years for High.

**Note.** Because of rounding, percentages may not total 100.

performed using Mplus, version 8.4. Estimation was carried out with full information maximum likelihood with standard error and a chi-square test that were robust to non-normality and non-independence of observations (“estimator=MLR”). Model fit was evaluated to identify the solution that best characterized the unobserved latent class structure with the Bayesian information criterion, Vuong–Lo–Mendell–Rubin likelihood ratio test, entropy, and latent class percentages that were large enough to be reliable (Muthén & Muthén, 2015). Missing data were accommodated using the expectation–maximization algorithm (Muthén & Shedden, 1999).

Data were analyzed using IBM SPSS Statistics, version 29.0. For each of the profiles (i.e., morning fatigue and evening fatigue), differences in demographic, clinical, and symptom characteristics, and QOL outcomes were evaluated using parametric and nonparametric tests. A p value of less than 0.05 was considered statistically significant. Post hoc contrasts were calculated using the Bonferroni procedure.

## Results

### Latent Classes for Morning Fatigue

Fit indices and details regarding selection of the four-class solution for morning fatigue are shown in Table 1. Trajectories for morning fatigue differed among the latent classes (see Figure 1A). For the Low (36%) and High (41%) classes, scores increased slightly at assessment 2, decreased slightly at assessment 3, and remained relatively stable at assessments 4 through 6. For the Changing class (12%), severity scores increased at assessment 2, followed by decreases at assessments 3 and 4, and had a sharp increase at assessment 5, followed by a large decrease at assessment 6. For the Very High class (11%), severity scores increased at assessment 2, decreased at assessment 3, increased at assessment 4, and remained very high at assessments 4 through 6.

### Differences in Demographic and Clinical Characteristics Among Morning Fatigue Classes

Compared to the Low class, the High and Very High classes had a higher comorbidity burden and were more likely to self-report a diagnosis of depression (see Table 2). Compared to the Low class, the Very High class was significantly younger, had a higher BMI, and was more likely to self-report a diagnosis of back pain. Compared to Low and High classes, the Changing class had higher MAX2 scores. Compared to the Low class, the other three classes had lower KPS scores.

### Differences in Symptom Scores Among Morning Fatigue Classes

Compared to the Low class, patients in the High and Very High classes had significantly higher levels of evening fatigue, trait anxiety, state anxiety, depressive symptoms, and sleep disturbance (see Table 3). Compared to the Low and Changing classes, patients in the other two classes had lower levels of attentional function. Compared to the Changing and High classes, patients in the Very High class had significantly higher levels of evening fatigue, state anxiety, depressive symptoms, and sleep disturbance. Compared to the Low class, a higher percentage of patients in the High and Very High classes reported the occurrence of cancer and noncancer pain and higher pain interference scores. Compared to the Low class, patients in the Changing and High classes had higher worst pain scores.

### Differences in QOL Scores Among Morning Fatigue Classes

For SF-12, compared to the Low class, the High and Very High classes had significantly lower physical functioning, role physical, bodily pain, vitality, social functioning, role emotional, and mental health scores (see Figure 2A). Compared to Changing and High classes, patients

in the Very High class had significantly lower role physical, bodily pain, vitality, and MCS scores. Compared to the Low class, patients in the Changing and High classes had significantly lower PCS scores.

For the MQOLS-PV, compared to the Low class, patients in the other three classes had significantly lower physical well-being and total QOL scores (see Figure 2B). Compared to the Changing and High classes, patients in the Very High class had significantly lower physical well-being, psychological well-being, social well-being, and total QOL scores.

#### Latent Classes for Evening Fatigue

Fit indices and details regarding selection of the two-class model for evening fatigue are shown in Table 1. Trajectories for evening fatigue differed between the latent classes (see Figure 1B). High class (72%)

severity scores remained relatively constant across the six assessments. Low class (28%) severity scores changed over the two cycles of chemotherapy, with slightly higher scores reported at assessments 2 and 5 (i.e., week following administration of chemotherapy).

#### Differences in Demographic and Clinical Characteristics Between Evening Fatigue Classes

Compared to the Low class, patients in the High class were younger and had a higher BMI, lower functional status, a higher comorbidity burden, and fewer years since their cancer diagnosis (see Table 4).

#### Differences in Symptom Scores Between Evening Fatigue Classes

Compared to the Low class, the High class had higher morning fatigue, trait anxiety, depression, and sleep

**TABLE 5. Differences in Common Symptom Severity Scores Between the Evening Fatigue Classes at Enrollment**

Symptom <sup>a</sup>	Low (N = 65, 28%)		High (N = 167, 72%)		Statistics
	$\bar{X}$	SD	$\bar{X}$	SD	
Morning fatigue ( $\geq 3.2$ )	2.1	2	3.6	2.1	$t = -4.72, p < 0.001$
Morning energy ( $\leq 6.2$ )	4.4	2.5	4.2	2	$t = 0.68, p = 0.5$
Evening energy ( $\leq 3.5$ )	4	1.7	3.3	2	$t = 2.74, p = 0.007$
Trait anxiety ( $\geq 31.8$ )	33.2	8.7	36.7	10.8	$t = -2.27, p = 0.024$
State anxiety ( $\geq 32.2$ )	31.4	10.6	34.9	12.4	$t = -1.97, p = 0.05$
Depression ( $\geq 16$ )	9.8	7.1	14.9	9.9	$t = -4.35, p < 0.001$
Sleep disturbance ( $\geq 43$ )	43.5	16.6	58.2	19.4	$t = -5.36, p < 0.001$
Attentional function ( $< 5 = \text{low}, 5-7.5 = \text{moderate}, > 7.5 = \text{high}$ )	6.8	1.7	5.9	1.7	$t = 3.53, p < 0.001$
Symptom	n	%	n	%	Statistics
Types of pain					$\chi^2 = 6.62, p = 0.085$
No pain	19	29	30	18	
Only noncancer pain	11	17	17	10	
Only cancer pain	17	26	51	31	
Both noncancer and cancer pain	18	28	66	40	
Symptom	$\bar{X}$	SD	$\bar{X}$	SD	Statistics
For patients with pain					
Worst pain intensity score	4.9	2.4	6.2	2.5	$t = -2.71, p = 0.008$
Mean pain interference score	2.2	1.9	3.4	2.5	$t = -3.27, p = 0.002$

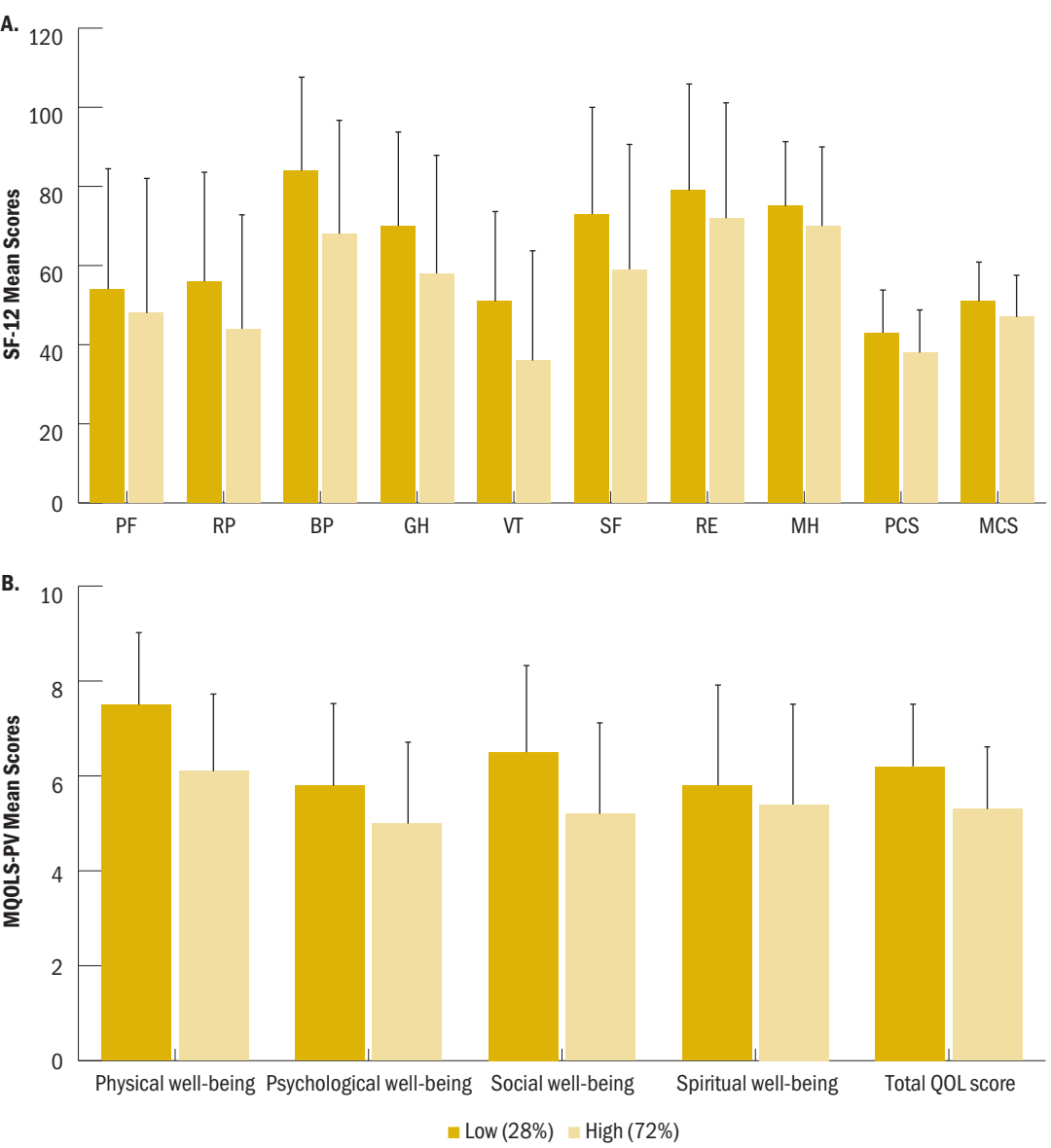
<sup>a</sup> Clinically meaningful cutoff scores are in parentheses after the symptom.

**Note.** Because of rounding, percentages may not total 100.

disturbance scores. They also reported lower evening energy and attentional function scores (see Table 5).

For patients who had pain, the High class had higher worst pain intensity and pain interference scores.

**FIGURE 3. Differences in SF-12® Scores (A) and MQOLS-PV Scores (B) Between the Evening Fatigue Latent Classes**



BP—bodily pain; GH—general health; MCS—mental component summary; MH—mental health; MQOLS-PV—Multidimensional Quality of Life Scale—Patient Version; PCS—physical component summary; PF—physical functioning; QOL—quality of life; RE—role emotional; RP—role physical; SF—social functioning; VT—vitality

**Note.** Figure 3A shows differences in SF-12 PF, RP, BP, GH, VT, SF, RE, MH, PCS, and MCS scores between the evening fatigue classes. All values are plotted as means and SDs. For the SF-12, compared to the Low class, patients in the High class had lower RP, BP, GH, VT, SF, PCS, and MCS scores (all  $p < 0.05$ ).

**Note.** Figure 3B shows differences in MQOLS-PV scores for the physical, psychological, social, and spiritual well-being domains as well as total QOL between the evening fatigue classes. All values are plotted as means and SDs. For the MQOLS-PV, compared to the Low class, patients in the High class had lower physical well-being, psychological well-being, social well-being, and total QOL scores (all  $p < 0.05$ ).

**TABLE 6. Overlap of Morning and Evening Fatigue Class Memberships**

Membership Class	Low Morning Fatigue (N = 83)		Changing Morning Fatigue (N = 28)		High Morning Fatigue (N = 95)		Very High Morning Fatigue (N = 26)	
	n	%	n	%	n	%	n	%
Low evening fatigue	44	53	9	32	10	11	2	8
High evening fatigue	39	47	19	68	85	90	24	92
<b>Note.</b> Overlap: % of n								
<b>Note.</b> Because of rounding, percentages may not total 100.								

### Differences in QOL Scores Between Evening Fatigue Classes

For the SF-12, compared to the Low class, patients in the High class had lower role physical, bodily pain, general health, vitality, social functioning, PCS, and MCS scores (see Figure 3A). For the MQOLS-PV, compared to the Low class, patients in the High class had lower physical well-being, psychological well-being, social well-being, and total QOL scores (see Figure 3B).

### Overlap of Morning and Evening Fatigue Class Membership

As shown in Table 6, 53% of the patients who were classified in the Low morning fatigue class were classified in the Low evening fatigue class. Of the patients who were classified in the Changing morning fatigue class, 68% were classified in the High evening fatigue class. Of the patients who were classified in the High and Very High morning fatigue classes, 90% and 92%, respectively, were classified in the High evening fatigue class.

## Discussion

### Characteristics of Latent Classes

This study is the first to use LPA to identify subgroups of patients with gynecologic cancers with distinct morning and evening fatigue profiles and associated risk factors. Given the paucity of research on fatigue in patients with gynecologic cancers, occurrence rates for and severity of morning and evening fatigue will be compared to the current authors' previous LPAs for morning (Wright et al., 2019) and evening (Wright et al., 2017) fatigue in the entire sample and patients with gastrointestinal cancer (Lin et al., 2023). These comparisons can be made because, across these studies, the classes were named based on the clinically meaningful cut points for the LFS.

Although four distinct morning fatigue profiles were identified for the total sample (i.e., Very Low,

Low, High, and Very High) (Wright et al., 2019), in the patients with gynecologic cancers, instead of a Very Low class, a Changing class was identified. Of note, more than 50% of the patients in both samples had High or Very High levels of morning fatigue that ranged from about 4 to 6.5. Although in the patients with gastrointestinal cancer (Lin et al., 2023) only two classes were identified (i.e., Low [64%] and Very High [36%]), morning fatigue scores reported by patients in the Very High class were comparable (about 5.2). These findings suggest that regardless of type of cancer, more than 50% of patients receiving chemotherapy experience clinically meaningful levels of morning fatigue.

The number of distinct evening fatigue profiles varied across the three samples. In the total sample (Wright et al., 2017), four profiles were identified (i.e., Low [14%], Moderate [17.2%], High [36%], and Very High [32.8%]). In the patients with gastrointestinal cancer (Lin et al., 2023), three profiles were identified (i.e., Low [24.9%], Moderate [44.7%], and Very High [30.4%]). Although these profiles differ from the Low (28%) and High (72%) profiles for the patients with gynecologic cancers, about 70% reported moderate to very high levels of evening fatigue. Any number of factors can influence the number of profiles identified using latent variable modeling, including sample size and number of assessments (Tein et al., 2013). Equally important, various demographic (e.g., employment status, childcare responsibilities) and clinical (e.g., variations in the toxicity of the chemotherapy regimens, comorbidity burden) characteristics can influence the trajectories of the symptom profiles. Additional research is warranted to determine whether occurrence rates and severity scores for morning and evening fatigue differ within and among patients with specific types of cancer and/or cancer treatments, as well as across the continuum of cancer care (e.g., active treatment, palliative care, survivorship).



**TABLE 7. Characteristics Associated With Membership in the Changing, High, and Very High Morning Fatigue Classes and the High Evening Fatigue Class Compared to the Low Classes for Morning and Evening Fatigue**

Characteristic <sup>a</sup>	Morning Fatigue			Evening Fatigue
	Changing	High	Very High	High
Demographic characteristics				
Younger age			♦	♦
Clinical characteristics				
Higher body mass index			♦	♦
Lower Karnofsky Performance Status Scale score	♦	♦	♦	♦
Higher SCQ score		♦	♦	♦
Higher MAX2 score	♦			
More likely to self-report depression		♦	♦	
More likely to report back pain			♦	
Higher emetogenicity of the chemotherapy regimen	♦			
Less time since cancer diagnosis (years)				♦
Symptom characteristics				
Higher depressive symptoms		♦	♦	♦
Higher sleep disturbance		♦	♦	♦
Higher trait anxiety		♦	♦	♦
Higher state anxiety		♦	♦	
Lower attentional function		♦	♦	♦
Higher morning fatigue				♦
Higher evening fatigue		♦	♦	
Lower evening energy			♦	♦
More likely to have both cancer and noncancer pain		♦	♦	
Higher worst pain intensity score	♦		♦	♦
Higher mean pain interference		♦	♦	♦
SF-12 <sup>®</sup>				
Lower physical function		♦	♦	
Lower role function		♦	♦	♦
Lower bodily pain		♦	♦	♦
Lower general health			♦	♦
Lower vitality		♦	♦	♦
Continued on next page				

**TABLE 7. Characteristics Associated With Membership in the Changing, High, and Very High Morning Fatigue Classes and the High Evening Fatigue Class Compared to the Low Classes for Morning and Evening Fatigue (Continued)**

Characteristic <sup>a</sup>	Morning Fatigue			Evening Fatigue
	Changing	High	Very High	High
<b>SF-12® (continued)</b>				
Lower social function		♦	♦	♦
Lower role emotional		♦	♦	
Lower mental health		♦	♦	
Lower physical component summary score	♦	♦		♦
Lower mental component summary score	♦	♦		♦
<b>Multidimensional Quality of Life Scale–Patient Version</b>				
Lower physical well-being	♦	♦	♦	♦
Lower psychological well-being		♦	♦	♦
Lower social well-being		♦	♦	♦
Lower total quality-of-life score	♦	♦	♦	♦
<sup>a</sup> Comparisons were done with the Low class for morning and evening fatigue. ♦—indicates the presence of the risk factor compared to the Low class for morning fatigue and the Low class for evening fatigue; SCQ—Self-Administered Comorbidity Questionnaire				

One of the goals of this study was to determine whether morning fatigue and evening fatigue were distinct symptoms in patients with gynecologic cancers. One line of evidence that supports this assertion is the differences in the number of profiles for morning and evening fatigue. In addition, if the two symptoms were not distinct, one would hypothesize that all the patients with low levels of morning fatigue would have low levels of evening fatigue. However, as shown in Table 6, of patients classified in the Low morning fatigue profile, only 53% were in the Low evening fatigue profile. In addition, of the patients who were classified in the Changing, High, and Very High morning fatigue classes, 68%, 90%, and 92%, respectively, were in the High evening fatigue class. Of note, the overall percent agreement between the morning and evening fatigue classifications was only 74%. This finding is lower than the 90% reported in the current authors' previous study of patients with cancer (Kober, Cooper, et al., 2016). For both studies, the percent agreement was best between the highest severity classes for morning and evening fatigue. Therefore, one can conclude that patients who wake

with very high morning fatigue are expected to have very high levels of evening fatigue.

Given that another goal of the current study was to identify common and distinct risk factors for morning and evening fatigue in patients with gynecologic cancers, the remainder of the Discussion focuses on comparing the current study's findings to the extant literature. The common and distinct risk factors associated with morning and evening fatigue in patients with gynecologic cancers are summarized in Table 7.

#### Demographic and Clinical Risk Factors

The common risk factors for both symptoms were younger age, higher BMI, lower functional status, and higher comorbidity burden. Consistent with the current authors' previous LPA studies (Lin et al., 2023; Wright et al., 2017, 2019), younger age was associated with the worst profiles for both symptoms. Age-related differences in inflammatory responses (Olivieri et al., 2023), perceptions of the symptom experience (Schwartz & Sprangers, 1999), and/or age-related decreases in chemotherapy doses (Cai et al., 2024) may explain this association.

Although in the current authors' previous study (Wright et al., 2019) a higher BMI was associated with only morning fatigue, in the current study it was associated with the worst profiles for both symptoms. This inconsistent finding may be partially explained by the slightly higher BMIs of the patients with gynecologic cancers (range = 28.1–29.9) compared to the current authors' previous study of patients with heterogeneous types of cancer (range = 25.6–27.6) (Wright et al., 2019). The association between a higher BMI (Khanna et al., 2022; Thrastardottir et al., 2023) and increases in fatigue severity in patients with cancer (Bower, 2014) may be related to increases in inflammatory responses.

Consistent with the current authors' previous studies, a higher comorbidity burden (Kober, Cooper, et al., 2016; Lin et al., 2023; Wright et al., 2015b, 2017, 2019) and lower functional status (Dhruva et al., 2013; Kober, Cooper, et al., 2016; Lin et al., 2023; Wright et al., 2015a, 2015b, 2017, 2019) were associated with higher levels of both morning and evening fatigue. This finding is not surprising, given that a higher comorbidity burden contributes to decrements in functional status (George et al., 2021). Of note, across the High and Very High classes for both symptoms, the KPS scores of between 71 and 77 indicate that although these patients care for themselves, they are not able to carry on normal activities or do active work. This level of disability warrants clinical evaluation before the initiation of chemotherapy and ongoing follow-up. These patients may benefit from prehabilitation if time permits and these services are available (Giles & Cummins, 2019).

In terms of the specific comorbidities, although the current findings are consistent with previous reports (Lin et al., 2023; Wright et al., 2019), it is not entirely clear why self-reported diagnoses of depression and back pain were risk factors only for morning fatigue. However, both depression (Côté et al., 2024) and back pain (Li et al., 2023) are associated with significant decrements in functional status, supporting the overall findings regarding multimorbidity.

### Common Symptoms

In terms of symptom burden, patients with gynecologic cancers report an average of 14 co-occurring symptoms (Pozzar et al., 2022). Therefore, and consistent with the current authors' previous studies (Dhruva et al., 2010, 2013; Lin et al., 2023; Miaskowski et al., 2008; Wright et al., 2017, 2019), women with the worst morning and evening fatigue profiles reported higher severity scores for most of the symptoms

listed in Table 7. Equally important, the symptom severity scores for these patients were above the clinically meaningful cut points for the various measures. For example, more than 50% of these women had Center for Epidemiological Studies Depression Scale scores that suggest a clinical evaluation for depression is warranted. Given that the prevalence rates for the co-occurrence of anxiety and depression (i.e., “mixed” anxiety and depression) range from 12% (Brintzenhofe-Szoc et al., 2009) to 45% (Gold et al., 2016) in patients with cancer, the high anxiety and depression scores reported by more than 50% of the patients with gynecologic cancers warrant investigation using a diagnostic interview.

Given the high levels of both morning and evening fatigue that persisted for about two months, it is unsurprising that the severity scores for sleep disturbance and decrements in both morning and evening energy exceeded these measures' clinically meaningful cut points. The sleep disturbance scores for these patients with gynecologic cancers are comparable to or higher than GSDS scores reported by mothers of newborn infants (i.e., 38–53) (Goyal et al., 2007) and shift workers (i.e., 45–60) (Lee, 1992). Given that obesity is a significant risk factor for obstructive sleep apnea (OSA) (Mohit et al., 2021) and the occurrence of OSA in patients with endometrial cancer was 32.4% (Madut et al., 2021), future studies need to determine the types of sleep disturbance these patients are experiencing (e.g., problems with sleep initiation and/or maintenance).

Although fatigue and energy are distinct but related symptoms (Kober, Smoot, et al., 2016), the current study is the first to evaluate for associations between fatigue and decrements in energy in patients with gynecologic cancers. Although it is reasonable to hypothesize that the high levels of sleep disturbance in the worst fatigue classes contributed to the decrements in energy, it should be noted that, across all the fatigue classes, the mean scores for both morning and evening energy were below the clinically meaningful cut points. The specific risk factors and mechanisms that underlie decrements in energy in patients with gynecologic cancers warrant additional investigation.

Consistent with the current authors' previous studies (Lin et al., 2023; Wright et al., 2017, 2019), patients in the worst morning and evening fatigue classes reported clinically meaningful decrements in cognitive function. This negative association between fatigue and cognitive function may be related to several shared pathophysiologic mechanisms, including

increases in inflammatory responses (Tan et al., 2023) and the deleterious effects of cancer and its treatment on DNA repair mechanisms and neurotransmission (Jaiswara & Shukla, 2023).

Findings regarding pain intensity and interference are inconsistent, with two studies showing no association (Wright et al., 2017, 2019) and one study (Lin et al., 2023) finding that higher scores were associated with the worst morning and evening fatigue profiles. Consistent with the current authors' systematic review that found a pain prevalence rate of 49% in patients with gynecologic cancers (Asakitogum et al., 2024), the co-occurrence of both cancer and non-cancer pain in the current sample ranged from 43% to 65%. In addition, pain scores were in the moderate to severe range. Additional research is warranted to determine the specific causes and characteristics of pain in these patients.

The findings reported in Tables 3 and 5 demonstrate that patients with gynecologic cancers experience a significant symptom burden associated with clinically meaningful levels of morning and evening fatigue. Previous research in patients with cancer demonstrates that pain, fatigue, sleep disturbance, and depression commonly co-occur as a "psychoneurological" symptom cluster (George et al., 2020). The initiation of inflammatory processes, as well as dysregulation of the hypothalamic-pituitary-adrenal axis and disruptions in circadian rhythms and the serotonergic system that occur following the administration of chemotherapy, are the most common mechanisms that underlie the occurrence of these symptoms (Kim et al., 2012). Additional research is needed to determine the common and distinct mechanisms for the co-occurrence of these symptoms and diurnal variations in fatigue severity.

### Changing Morning Fatigue Class

Although not found in any of the current authors' previous studies of morning or evening fatigue (Dhruva et al., 2010, 2013; Kober, Cooper, et al., 2016; Lerdal et al., 2016; Lin et al., 2023; Miaskowski et al., 2008; Wright et al., 2015a, 2015b, 2017, 2019), a Changing morning fatigue profile was identified in patients with gynecologic cancers. As shown in Figure 1A, 12% of the patients were in this class, and large increases in fatigue severity occurred in the weeks following the administration of chemotherapy (i.e., assessments 2 and 5). As shown in Table 7, a higher MAX2 score and the receipt of a highly emetogenic chemotherapy regimen were the unique risk factors associated with this profile. Given that a higher MAX2 score indicates

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### KNOWLEDGE TRANSLATION

- Patients with gynecologic cancers experience significant interindividual variability in the severity of morning and evening fatigue that requires ongoing assessments.
  - Risk factors for having the worst morning and evening fatigue profiles included being younger, having a higher body mass index, having a higher comorbidity burden, and having a poorer functional status.
  - Patients with the worst morning and evening fatigue profiles reported higher levels of trait anxiety, depression, sleep disturbance, and pain, as well as poorer levels of cognitive function and quality of life.
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the receipt of chemotherapy regimens with a higher toxicity profile, including those with a worse emetogenic potential (Extermann et al., 2004), one can hypothesize that patients in this class had higher levels of nausea and emesis that may have resulted in disruptions in sleep and associated increases in morning fatigue. This hypothesis warrants confirmation in future studies.

### QOL Outcomes

As noted in the current authors' systematic review (Asakitogum et al., 2024), research on associations between symptom burden and QOL outcomes in patients with gynecologic cancers is limited. This study is the first to report on worse morning and evening fatigue profiles associated with decrements in both generic and cancer-specific measures of QOL. As clearly illustrated in Figures 2 and 3, the worst morning and evening fatigue profiles were associated with clinically meaningful decrements in the various domains of QOL (e.g., compared to the scores for the Low morning fatigue class, the following effect sizes were found for the PCS [ $d = 0.99$ ], MCS [ $d = 1.2$ ], and total MQOLS-PV [ $d = 1.5$ ] scores for the Very High class) (Guyatt et al., 2002). Equally important, the MCS scores of the highest morning and evening fatigue profiles were less than 50, which is the normative score for the general population of the United States (Ware et al., 1996). An equally important finding is that regardless of morning or evening fatigue class membership, all the PCS scores for these patients with gynecologic cancers were below the normative score of 50. This finding is consistent with the low KPS scores reported by these patients and indicates clinically meaningful decrements in physical function.

## Limitations

Several limitations warrant consideration. Because patients were not assessed before the initiation of chemotherapy and followed to the completion of treatment, additional longitudinal studies are warranted to confirm these profiles. Given that most patients were White and well educated, the current findings may not generalize to more diverse samples. In addition, given the wide variations in treatment protocols for the various types of gynecologic cancer, future studies need to confirm these findings within and among patients with different types of gynecologic cancer and various types of treatments.

## Implications for Clinical Practice

The findings from this study have important implications for clinical practice. Given the high prevalence rates of clinically meaningful levels of both morning and evening fatigue, these two symptoms and associated risk factors warrant ongoing assessment in patients with gynecologic cancers. Clinicians can use a simple question (e.g., How tired are you in the morning versus the evening?) to evaluate for diurnal variations in fatigue severity. Depending on the patient's response, interventions can be tailored to reduce morning and/or evening fatigue (e.g., high levels of morning fatigue coupled with high levels of sleep disturbance could target sleep management interventions; high levels of evening fatigue with lack of regular exercise could target exercise interventions). In addition, the extremely high symptom burden in these patients warrants the prescription of individualized symptom management interventions. For example, some patients may warrant referrals to psychological services to manage depression and anxiety. Patients need education on sleep management principles to improve the quality and duration of their sleep (PDQ Supportive and Palliative Care Editorial Board, 2024). The significant decrements in physical function identified in the current study suggest that the majority of these patients warrant referrals to physical therapy during and following chemotherapy.

## Conclusion

Despite its limitations, this study is the first to identify subgroups of patients with gynecologic cancers with distinct morning and evening fatigue profiles and demonstrate that these symptoms are distinct. Based on the high occurrence rates for and severity of both morning and evening fatigue, clinicians need to assess for common risk factors, as well as other symptoms, and initiate personalized symptom management

interventions and referrals to physical therapy, as well as psychological and social services.

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This study was funded, in part, by a grant from the National Cancer Institute (CA134900). Miaskowski is an American Cancer Society Clinical Research Professor.

Asakitogum, Nutor, Pozzar, Conley, and Miaskowski contributed to the conceptualization and design. Hammer and Miaskowski completed the data collection. Cooper, Paul, and Miaskowski provided statistical support. Asakitogum, Cooper, and Miaskowski provided the analysis. Asakitogum, Nutor, Hammer, Pozzar, Conley, Levine, and Miaskowski contributed to the manuscript preparation.

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