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Distinct Morning and Evening Fatigue Profiles in Gastrointestinal Cancer During Chemotherapy

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Abstract

Background: Purposes were to identify subgroups of patients with gastrointestinal cancers with distinct morning and evening fatigue severity profiles and evaluate for differences among these subgroups in demographic and clinical characteristics, co-occurring symptoms, and quality of life (QOL) outcomes.

Methods: Patients with gastrointestinal cancers (n=405) completed questionnaires six times over two cycles of chemotherapy. Latent profile analysis was used to identify distinct morning and evening fatigue profiles. Differences in demographic and clinical characteristics, co-occurring symptoms, and QOL outcomes among the subgroups were evaluated using parametric and non-parametric tests.

Results: Two distinct morning (i.e., Low, Very High) and three distinct evening (i.e., Low, Moderate, Very High) fatigue classes were identified. Common risk factors for both morning and evening fatigue included: younger age, lower performance status, higher comorbidity burden, and self-reported depression. Higher levels of morning fatigue were associated with being unmarried, living alone, being unemployed, having a lower income, lack of regular exercise, and a self-reported diagnosis of anemia. Higher levels of evening fatigue were associated with being female, White, and having childcare responsibilities. Patients in the Very High morning and evening

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fatigue classes reported higher levels of anxiety, depressive symptoms, sleep disturbance, and pain, and lower levels of attentional function and poorer QOL.

Conclusion: Findings provide new insights into risk factors for and deleterious effects of morning and evening fatigue in patients with gastrointestinal cancers. Clinicians can use this information to identify high risk patients and develop individualized interventions for morning and evening fatigue and other co-occurring symptoms.

Keywords

morning fatigue; evening fatigue; depression; anxiety; pain; sleep disturbance; chemotherapy; gastrointestinal cancer; quality of life

INTRODUCTION

While fatigue is the most common symptom reported by oncology patients during chemotherapy,[1] less is known about its occurrence, severity, and impact in patients with gastrointestinal cancers. Findings suggest that in patients with gastrointestinal cancers, fatigue occurrence rates range from 62.0%[2] to 83.3%[3] and that severity scores are approximately 2.0[3,4] using the 1 to 4 scale on the Memorial Symptom Assessment Scale (MSAS). In a longitudinal study of 21 patients with colorectal cancer,[5] mean fatigue severity scores were in the mild range prior to and increased to moderate levels over the course of three cycles of chemotherapy. These findings suggest that a significant number of patients with gastrointestinal cancers report mild to moderate levels of fatigue during chemotherapy.

In two studies of patients with gastrointestinal cancers,[3,6] younger age, a longer time from cancer diagnosis, receipt of a higher number of cancer treatments, and receipt of FOLFIRINOX (i.e., leucovorin/5-fluorouracil/irinotecan/oxaliplatin) were associated with higher fatigue occurrence rates. For patients with colorectal cancer, younger age, female gender, and receipt of surgery contributed to a higher occurrence of fatigue.[7] In terms of co-occurring symptoms, cognitive dysfunction,[8] depressive symptoms,[8–10] sleep disturbance,[9,10] and pain[11] were associated with higher fatigue occurrence rates. Fatigue has a negative impact on patients' quality of life (QOL)[8,12] and decreases their ability to tolerate chemotherapy.[13,14] While these studies provided important information on fatigue in patients with gastrointestinal cancers, several limitations warrant consideration. First, only two studies evaluated for changes over time in fatigue severity in these patients during chemotherapy.[6,15] Second, only three studies identified risk factors for higher levels of fatigue.[3,6,7] In addition, none of these studies used a person-centered analytic approach to evaluate for distinct fatigue severity profiles in patients with gastrointestinal cancers.

Because fatigue severity varies markedly over the course of a day,[16] an emerging area of research is an evaluation of diurnal variability in fatigue.[17,18] Work by our team demonstrated that morning and evening fatigue are distinct symptoms both in terms of risk factors and trajectories.[19,20] For example, in one study of patients undergoing chemotherapy,[10] risk factors associated with higher levels of morning fatigue included: younger age, higher body mass index (BMI), and lack of regular exercise. To date, no studies have evaluated for diurnal variations in fatigue severity in patients with

gastrointestinal cancers. Therefore, the purposes of this study were to identify subgroups of patients with gastrointestinal cancers with distinct morning and evening fatigue severity profiles and evaluate for differences among these subgroups in demographic and clinical characteristics, co-occurring symptoms, and QOL outcomes.

METHODS

Patients and settings

Details regarding this prospective longitudinal study of symptom clusters in oncology outpatients receiving chemotherapy were published previously.[21,22] In brief, eligible patients for the parent study: were ≥18 years of age; had a diagnosis of breast, gastrointestinal, gynecological, or lung cancer; had received chemotherapy within the preceding four weeks; were scheduled to receive at least two additional cycles of chemotherapy; and were able to read, write, and understand English. Patients were recruited from two Comprehensive Cancer Centers, one Veteran's Affairs hospital, and four community-based oncology programs. Of the 2,234 patients approached, 1,343 consented to participate (60.1% response rate). The major reason for refusal was being overwhelmed with their cancer treatment. For this study, only patients with gastrointestinal cancers who had complete data for morning (n=404) and evening (n=405) fatigue were included.

Instruments

Patients completed a demographic questionnaire, the Karnofsky Performance Status (KPS) scale,[23] and the Self-administered Comorbidity Questionnaire (SCQ).[24] Patients medical records were reviewed for disease and treatment information.

Assessment of Morning and Evening Fatigue—The 18-item Lee Fatigue Scale (LFS)[25] assesses physical fatigue and energy. Each item was rated on a 0 to 10 numeric rating scale (NRS). Fatigue and energy scores were calculated as the mean of the 13 fatigue and 5 energy items. Higher scores indicate greater fatigue severity and higher levels of energy. Patients were asked to rate each item based on how they felt within 30 minutes of awakening (i.e., morning fatigue, morning energy) and prior to going to bed (i.e., evening fatigue, evening energy). The LFS has cut-off scores for clinically meaningful levels of fatigue (i.e., ≥3.2 for morning fatigue, ≥5.6 for evening fatigue) and energy (i.e., ≤6.2 for morning energy, ≤3.5 for evening energy).[26] In our study, the Cronbach's alphas were 0.96 for morning and 0.93 for evening fatigue and 0.95 for morning and 0.93 for evening energy.

Assessment of Common Co-occurring Symptoms—All of the instruments that were used to assess six of the most common co-occurring symptoms associated with cancer and its treatment are valid and reliable. The symptoms that were assessed included: state and trait anxiety (Spielberger State-Trait Anxiety Inventories (STAI-T and STAI-S)[27]); depressive symptoms (Center for Epidemiological Studies-Depression scale (CES-D)[28]); sleep disturbance (General Sleep Disturbance Scale (GSDS)[29]); cognitive dysfunction (Attentional Function Index (AFI)[30]); and pain (Brief Pain Inventory (BPI)[31]).

Assessment of QOL—Quality of life 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)) measures. The 41-item QOL-PV evaluated four dimensions of QOL (i.e., physical, psychological, social, and spiritual well-being) in oncology patients, as well as a total QOL score.[32] The SF-12 was scored into two components (i.e., physical component summary (PCS) and mental component summary (MCS) scores). Higher PCS and MCS scores indicate a better QOL.[33]

Ethics statement

The parent study was approved by the Committee on Human Research at the University of California, San Francisco, by the Institutional Review Board (IRB) at each of the study sites, and by the IRB of Duke University. Written informed consent was obtained from all patients.

Study procedures

Patients were approached by a research staff member in the infusion unit, during their first or second cycle of chemotherapy, to discuss participation in the study. Depending on the length of their chemotherapy cycles, patients completed paper questionnaires in their home a total of six times over two cycles of chemotherapy. Assessments 1 and 4 evaluated symptoms during the week prior to the next cycle of chemotherapy (i.e. recovery from previous cycle. Assessments 2 and 5 evaluated symptoms during the week following the administration of chemotherapy (i.e., acute symptoms). Assessments 3 and 6 evaluated symptoms during the week following assessments 2 and 5 (i.e., potential nadir).

Data analysis

Latent profile analysis (LPA) was used to identify subgroups of patients with distinct morning and evening fatigue severity profiles over the six assessments. Separate LPAs were done for morning and evening fatigue. Estimation was carried out with full information maximum likelihood with standard errors and a Chi-square test that are robust to non-normality and non-independence of observations. To determine the best fitting model, multiple information criteria were used. Lower values for the Akaike Information Criteria (AIC) and Bayesian Information Criterion (BIC) represent better fitting models. Entropy values classify the quality of the model, in which values close to 1 indicate good classification. When using the Vuong-Lo-Mendell-Rubin likelihood ratio test (VLMR) to compare the models, a significant p-value suggests that one estimated model fits the data better than another model with one fewer group.[34,35] Estimation of model fit was conducted with Mplus Version 8 with 1,000 to 2,400 random starts.

Using SPSS, version 27 (IBM Corporation, Armonk, NY), differences in demographic and clinical characteristics, co-occurring symptoms, and QOL outcomes, among the subgroups, were evaluated using parametric and non-parametric tests. Post hoc contrasts were calculated using the Bonferroni procedure. A p-value of <0.05 was considered statistically significant.

RESULTS

Latent Classes for Morning Fatigue

The fit indices and details regarding selection of the two class model for morning fatigue are shown in Table 1. The trajectories for morning fatigue differed between the latent classes (Figure 1). For the Very High class (35.6%), severity scores remained relatively constant across the six assessments. In contrast, for the Low class (64.4%), severity scores changed over the two cycles of chemotherapy, with slightly higher scores reported at assessments 2 and 5 (i.e., week following the administration of chemotherapy).

Differences in Demographic and Clinical Characteristics Between Morning Fatigue Classes

Compared to the Low class, patients in the Very High class were significantly younger (59.7 (±10.9) vs 54.9 (±12.6) years), more likely to be female (40.0% vs 55.6%), less likely to be married or partnered (73.2% vs 56.9%), more likely to live alone (15.6% vs 24.5%), more likely to have childcare responsibilities (16.9% vs 27.1%), less likely to be employed (38.6% vs 25.9%), reported a lower annual household income, and were less likely to exercise on a regular basis (73.7% vs 54.6%; Supplemental Table 1). In addition, compared to the Low class, patients in the Very High class had a lower KPS score (84.4 (±10.8) vs 73.9 (±12.2)), a higher number of comorbidities (2.2 (±1.3) vs 2.5 (±1.4)), a higher SCQ score (4.9 (±2.6) vs 6.1 (±3.6)), and a higher number of prior cancer treatments (1.3 (±1.2) vs 1.7 (±1.4)), and were more likely to self-report anemia (6.5% vs 13.9%) and depression (8.1% vs 25.7%).

Differences in Symptom Scores and QOL Between Morning Fatigue Classes

Compared to the Low class, patients in the Very High class had higher trait anxiety, state anxiety, depression, sleep disturbance, morning fatigue, and evening fatigue scores, and had lower morning energy, evening energy, and attentional function scores at enrollment (Table 2). Compared to the Low class, a higher percentage of patients in the Very High class reported pain. For the patients who had pain, compared to the Low class, patients in the Very High class had higher worst pain intensity and pain interference scores.

For the QOL-PV, compared to the Low class, patients in the Very High morning fatigue class had lower subscale (except for the spiritual well-being subscale) and total QOL scores. For the PCS and MCS scores of the SF-12, compared to the Low class, patients in the Very High morning fatigue class had significantly lower scores.

Latent Classes for Evening Fatigue

The fit indices and details regarding selection of the three class model for evening fatigue are shown in Table 1. The trajectories for evening fatigue differed among the latent classes (Figure 2). For the Moderate class (44.7%), their scores remained relatively constant across the six assessments. In contrast, for the Low class (24.9%), severity scores decreased from assessment 1 to assessment 4. For the Very High class (30.4%), severity scores increased as assessment 2, decreased at assessment 3, and increased slightly over assessments 4, 5, and 6.

Differences in Demographic and Clinical Characteristics Among Evening Fatigue Classes

Compared to the Low class, patients in the Moderate and Very High classes were significantly younger (60.6 (±11.5) vs 58.4 (±11.7) and 55.1 (± 11.6) years), more likely to be White (56.6% vs 71.9% and 69.7%), and reported a higher SCQ score (4.7 (±2.7) vs 5.2 (±2.6) and 6.1 (±3.4)); Supplemental Table 2). Compared to the Low and Moderate classes, patients in the Very High class were more likely to be female (42.6% and 38.1% vs 59.3%) and reported having childcare responsibilities (12.9% and 16.6% vs 33.3%). In addition, significant differences were found among the three classes for their KPS scores (i.e., Low > Moderate > Very High) and the occurrence of depression (i.e., Low < Moderate < Very High). Compared to the Low class, patients in the Very High class had a higher number of prior cancer treatments (1.1 (±1.2) vs 1.6 (±1.4)).

Differences in Symptom Scores and QOL Outcomes Among Evening Fatigue Classes

Significant differences were found among the three classes for trait anxiety, state anxiety, depression, sleep disturbance, morning fatigue, and evening fatigue scores (i.e., Low < Moderate < Very High; Table 3). For attentional function, the pattern was as expected (i.e., Low > Moderate > Very High). For morning energy, compared to the Moderate class, patients in the Very High class had lower scores. For evening energy, compared to the other two classes, patients in the Very High class had lower scores. In terms of the occurrence of pain, compared to the Low class, a higher percentage of patients in the Very High class reported non-cancer pain. For patients who had pain, compared to the Low class, patients in the Moderate and Very High classes had higher worst pain intensity and pain interference scores.

Except for the spiritual well-being subscale, significant differences were found among the three classes for the QOL-PV subscales and total scores (i.e., Low > Moderate > Very High). For the PCS scores of the SF-12, compared to the other two classes, patients in the Very High evening fatigue class had significantly lower scores. Significant differences were found among the three evening fatigue classes for the MCS scores (i.e., Low > Moderate > Very High).

DISCUSSION

This study is the first to identify subgroups of patients with gastrointestinal cancers with distinct morning and evening fatigue severity profiles. Given the paucity of research on diurnal variations in fatigue severity in these patients, one focus of this discussion will be on a comparison of our findings with average fatigue severity scores in patients with these types of cancer. In addition, to evaluate for common and distinct risk factors associated with a more severe morning or evening fatigue profile, as well as for consistency across cancer types, comparisons of these characteristics are made between the patients with gastrointestinal cancers (i.e., current sample) and our previous reports of the total sample of patients with heterogenous cancer diagnoses (Table 4).[21,22]

While four distinct morning and evening fatigue classes were identified in the total sample,[21,22] for both the current and total sample, two common classes were identified

for both morning and evening fatigue (i.e., Low, Very High). The severity scores for the Low morning fatigue classes (range=1.5–2.8) were comparable across the two samples. However, for the patients with gastrointestinal cancers, the fatigue severity scores for the Very High morning fatigue class were ~1.5 points lower across the six assessments. For evening fatigue, the severity scores for the Low (range=1.9 to 2.8) and Very High (range=6.9 to 7.6) classes were comparable across both samples. These findings suggest that while evening fatigue severity is similar across cancer types, patients with gastrointestinal cancers may be at decreased risk for higher levels of morning fatigue. One potential explanation for this finding is that the MAX2 score (a measure of chemotherapy-induced toxicity) was lower (0.14) in the current sample compared to the total sample (0.17). In addition, given that previous studies found that women reported more severe symptoms during chemotherapy,[36] the lower morning fatigue scores may be related to the lower percentage of women (45.5%) in the current sample compared to the total sample (77.9%). In addition, our findings are consistent with a previous report that found that patients with gastrointestinal cancers experienced less severe fatigue than patients with breast and lung cancers.[37]

Given that most of the studies of oncology patients did not evaluate for diurnal variations in fatigue severity, associations with various risk factors will be described in relationship to previously reported mean fatigue severity scores. As shown in Table 4, across our two samples, four common risk factors for higher levels of morning and evening fatigue were identified, namely: younger age, a higher comorbidity burden, a lower performance status, and a self-reported diagnosis of depression. Age-related differences in inflammatory responses, perceptions of the symptom experience, and dose adjustments in chemotherapy regimens may explain the relationships between younger age and higher levels of fatigue.[38,39] Previous studies have found that a higher level of comorbidity (e.g., back pain) is associated with increases in fatigue severity.[40] Given that a higher number of comorbidities contribute to decrements in functional status,[41] it is not surprising that a common risk factor for higher levels of morning and evening fatigue was a lower KPS score. Of note, for both samples, the differences in KPS scores between the patients in the Very High classes compared to the Low classes, represent not only statistically significant but clinically meaningful differences (i.e., d=0.9). Equally important, our associations between more severe morning and evening fatigue and a clinical diagnosis of depression may all be related to a shared biological pathway (i.e., activation of the immune-inflammatory pathways and concurrent release of pro-inflammatory cytokines).[1] Clinicians can use these four common characteristics to identify patients who are at increased risk for severe levels of both morning and evening fatigue. Clinician can refer patients for psychological care or physical therapy depending on their risk profile.

For both samples, the common risk factors for higher levels of evening fatigue were: being female, being White, and having childcare responsibilities (Table 4). Our findings suggest that the additional burden of childcare responsibilities, primarily for women, contributes to higher levels of evening fatigue. Given that 25.8% of the women in the current sample reported having childcare responsibilities compared to 16.4% of the men (p=.025), future studies need to evaluate the linkages between these two risk factors. Findings regarding ethnic differences in the severity of evening fatigue in oncology patients are inconsistent. While gender and race are not modifiable risk factors, clinicians can identify

support services for female patients and those patients with childcare responsibilities. While the number of prior cancer treatments was comparable across the two samples, this characteristic was the only risk factor associated with higher levels of morning and evening fatigue in the patients with gastrointestinal cancers. This association may be partially explained by the cumulative effects of various cancer treatments or differences in the sequence of these treatments.[11]

For both samples, the common risk factors for higher levels of morning fatigue included: being unmarried, living alone, being unemployed, having a lower annual household income, lack of regular exercise, and a self-reported diagnosis of anemia or blood disease (Table 4). Lower incomes and lack of social support may exacerbate the financial burden of cancer treatment and increase psychological distress.[22] These worries may disrupt sleep and result in higher levels of morning fatigue. While these characteristics are not easily modifiable, particularly in patients who are socioeconomically disadvantaged, referrals to social workers or social services may be warranted. Lack of regular exercise was the only modifiable risk factor for higher levels of morning fatigue. While the effects of exercise on diurnal variations in fatigue severity have not been investigated, regular exercise results in decreases in average fatigue severity.[42] Therefore, clinicians need to encourage patients to exercise during and following chemotherapy. While a self-reported diagnosis of anemia was associated with higher morning fatigue severity, for both the current and total sample, no between group differences in hemoglobin and hematocrit levels were found. While previous studies found associations between average fatigue severity and anemia,[43] additional research is warranted to confirm or refute this association.

A growing body of evidence suggests that patients with gastrointestinal cancers experience multiple co-occurring symptoms.[2,36,44] In fact, the patients with gastrointestinal cancers in the current study reported an average of 13 symptoms prior to their second or third cycle of chemotherapy.[6] Except for morning energy, across both samples, patients in the Very High morning and evening fatigue classes reported higher symptom severity scores for trait and state anxiety, depressive symptoms, sleep disturbance, and pain as well as lower levels of attentional function and evening energy. In both samples, all of the symptom severity scores reported by the Very High morning and evening fatigue classes were above the clinically meaningful cutoff scores for the various instruments. In addition, for both samples, the differences between the Low and Very High fatigue classes represent not only statistically significant but clinically meaningful differences in symptom severity scores (i.e., effect sizes ranged from 0.4 [morning and evening energy] to 1.1 [sleep disturbance, depressive symptoms, and attentional function]).

Psychoneurological symptoms including fatigue, anxiety, depression, sleep disturbance, cognitive dysfunction, and pain are known to co-occur as a symptom cluster.[45] The initiation of a series of inflammatory processes, as well as dysregulation of the hypothalamic-pituitary-adrenal axis, circadian rhythms, and the serotonin system that occur following the administration of chemotherapy, are the commonly hypothesized mechanisms for these co-occurring psychoneurological symptoms.[46] Future research needs to determine the common and distinct mechanisms for the co-occurrence of these symptoms and diurnal variations in fatigue severity. For example, in one study,[47] while higher levels of average fatigue were

associated with increased evening cortisol levels and increased overall cortisol secretion, they were not associated with morning cortisol levels.

In the current sample, but not in the total sample, lower levels of morning energy were associated with higher levels of morning and evening fatigue. Energy is defined as a person's potential to perform physical and mental activities[21] and decrements in energy is a distinct symptom from fatigue.[48] Because diurnal variations in levels of energy are not routinely evaluated in oncology patients, future studies need to evaluate for the common and distinct molecular mechanisms associated with the co-occurrence of morning and evening fatigue, morning and evening energy, and sleep disturbance.

In terms of QOL outcomes, except for the spiritual well-being subscale of the disease specific QOL measure and the PCS score of the generic QOL measure, statistically and clinically meaningful decrements in QOL outcomes were found among the distinct morning and evening fatigue profiles (d = 0.2 to 148.3). Of note, across all of the morning and evening fatigue classes, patients in the current sample reported PCS scores of <50 which is lower than the normative score for the general population.[32]

Limitations

Several limitations warrant consideration. Because patients were not recruited prior to the initiation of chemotherapy, risk profiles for fatigue from its initiation through completion were not evaluated. Given that the majority of the patients were White and well educated, our findings may not generalize to more diverse and socioeconomically disadvantaged patients. In addition, given the heterogeneity in gastrointestinal cancers in this study, futures studies need to perform similar evaluations of patients with specific gastrointestinal cancers (e.g., pancreatic).

CONCLUSIONS

Despite these limitations, this study is the first to identify subgroups of patients with GI cancers with distinct morning and evening fatigue profiles and identify risk factors associated with higher levels of morning and evening fatigue. Based on the high occurrence and severity of both morning and evening fatigue, clinicians need to assess for the four common risk factors, as well as associated co-occurring symptoms and initiate personalized symptom management interventions and referrals to physical therapy, psychological counseling, and social services.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Key Message Box

What was already known?

- Fatigue is common in oncology patients

What are the new findings?

- Diurnal variations in fatigue are common in patients with gastrointestinal cancer
- Risk factors for severe fatigue – younger age, higher comorbidity, lower level of function, and depression

What is their significance?

- Physical therapy and psychological counseling referrals are need

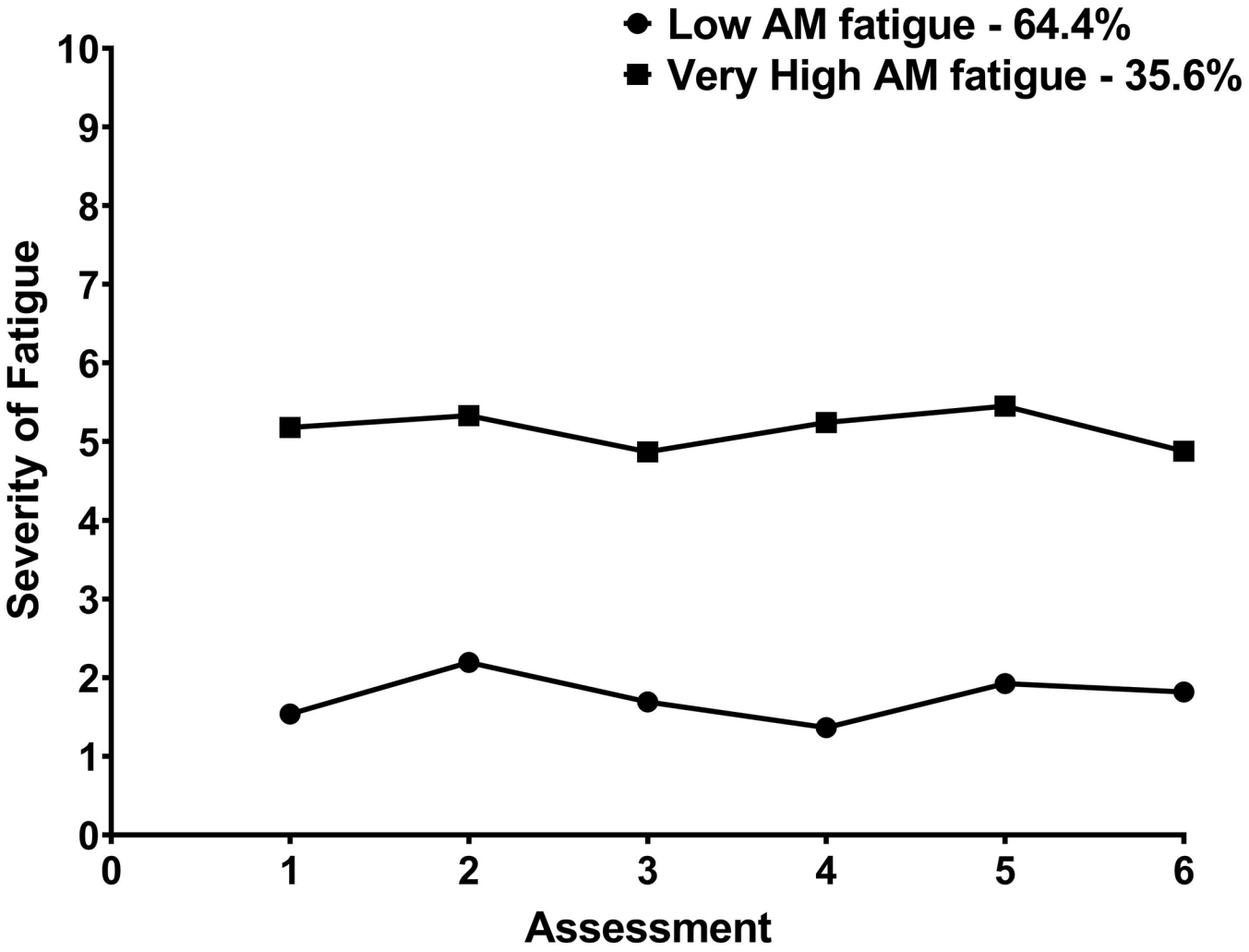

Figure 1 –.
Trajectories of morning fatigue for the two latent classes.

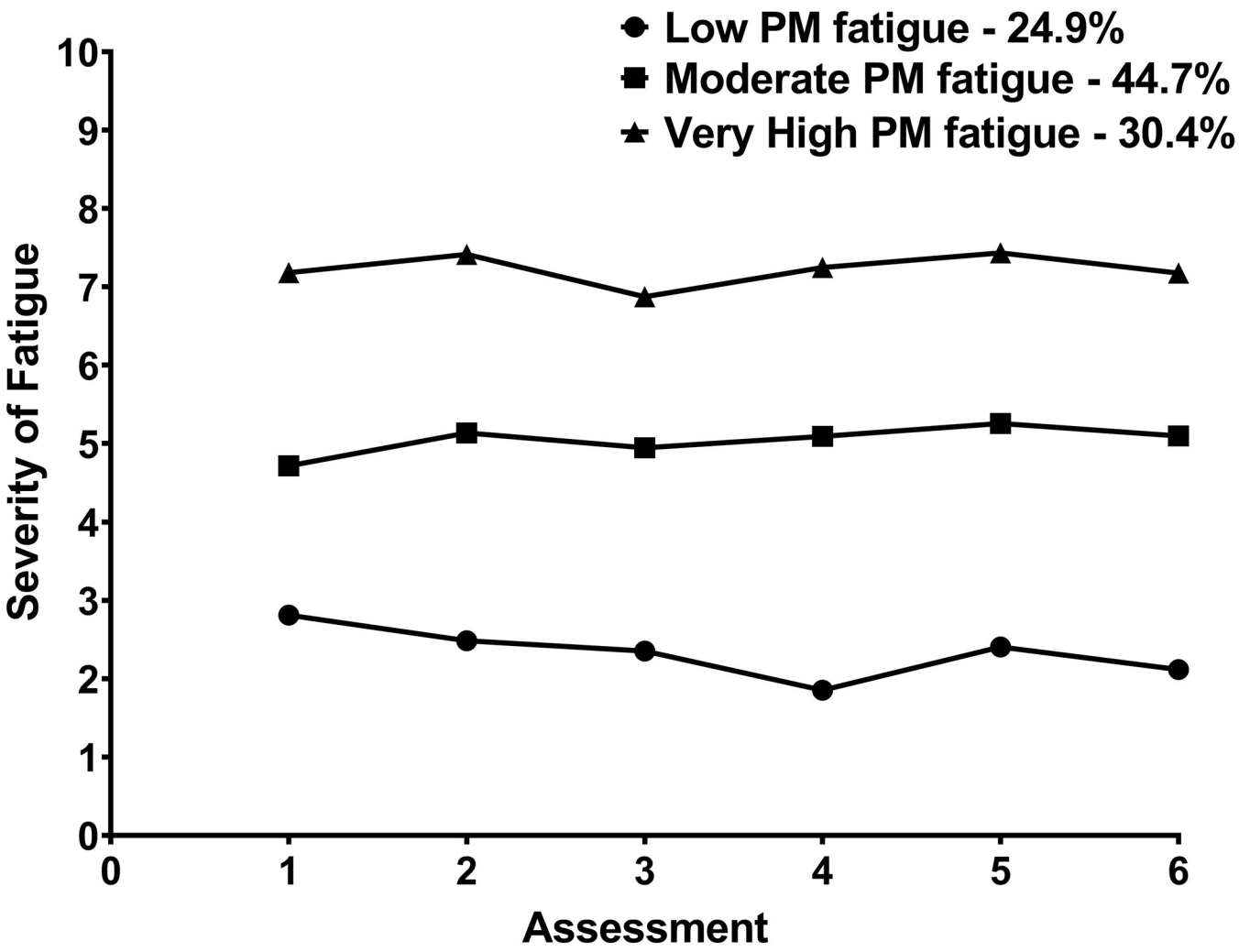

Figure 2 –.
Trajectories of evening fatigue for the three latent classes.

Table 1.

Morning and Evening Fatigue Latent Profile Solutions and Fit Indices Over Six Assessments

Model	LL	AIC	BIC	Entropy	VLMR
Morning fatigue					
1 Class	−4031.95	8105.90	8189.93	n/a	n/a
2 Class[a]	−3855.19	7766.37	7878.41	0.86	353.53 +
3 Class	−3787.73	7645.45	7785.50	0.86	134.92 ns
Evening fatigue					
1 Class	−3951.43	7944.86	8028.95	n/a	n/a
2 Class	−3829.55	7715.11	7827.21	0.77	243.76 +
3 Class[b]	−3769.68	7609.35	7749.49	0.77	119.76 *
4 Class	−3739.63	7563.25	7731.42	0.82	60.10 ns

Abbreviations: AIC = Akaike's 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 vs. K-1 model

* p <.05

+ p <.01

Entropy and VLMR are not applicable for the one-class solution

[a] For morning fatigue, the two-class solution was selected because the BIC for that solution was lower than the BIC for the 1-class solution. In addition, the VLMR was significant for the 2-class solution, indicating that two classes fit the data better than one class. While the BIC was smaller for the 3-class than for the 2-class solution, the VLMR was not significant for the 3-class solution, indicating that too many classes were extracted. In addition, the 3-class solution included a small predicted class (only 42 predicted cases; approximately 10% of the sample), raising the concern that the solution may not generalize to other samples.

[b] For evening fatigue, The three-class solution was selected because the BIC for that solution was lower than the BIC for the 2-class solution. In addition, the VLMR was significant for the 3-class solution, indicating that three classes fit the data better than two classes. However, the VLMR was not significant for the 4-class solution, indicating that too many classes were extracted. While the BIC for the 4-class solution was smaller than the BIC for the 3-class solution, one predicted class in the 4-class solution was very small (only eight predicted cases; less than 2% of the sample), raising the concern that the solution would not generalize to other samples.

Table 2.

Differences in Symptom Scores and QOL Outcomes Between the Morning Fatigue Classes

	Low AM Fatigue 64.4% (n=260)	Very High AM Fatigue 35.6% (n=144)	Statistics
	Mean (SD)	Mean (SD)	
Symptom scores			
Trait anxiety (≥31.8)	30.4 (7.7)	40.2 (10.4)	
State anxiety (≥32.2)	29.5 (9.5)	40.3 (12.3)	t=−9.02, p<.001
Depressive symptoms (≥16.0)	8.5 (6.3)	18.0 (9.4)	t=−10.84, p<001
Sleep disturbance (≥43.0)	41.9 (16.8)	65.1 (17.4)	t=−12.82, p<.001
Attentional function (≤7.5)	7.3 (1.5)	5.3 (1.6)	t=11.99 p<.001
Morning fatigue (≥3.2)	1.5 (1.2)	5.2 (1.8)	t=−21.62, p<.001
Evening fatigue (≥5.6)	4.2 (2.2)	6.4 (1.7)	t=−11.00, p<.001
Morning energy (≤6.2)	4.8 (2.5)	3.9 (2.1)	t=3.51. p=.001
Evening energy (≤3.5)	3.8 (2.1)	3.0 (1.8)	t=3.58, p<.001
	% (n)	% (n)	
Pain type No pain Only non-cancer pain Only cancer pain Both cancer and non-cancer pain	 37.9 (97) 23.0 (59) 16.0 (41) 23.0 (59)	 20.4 (29) 31.0 (44) 14.1 (20) 34.5 (49)	X^2 =15.67, p=.001 0 > 1 NS NS NS
For patients with pain	Mean (SD)	Mean (SD)	
Worst pain intensity score	5.3 (2.4)	6.5 (2.8)	t=−3.48, p=.001
Pain interference score	2.2 (2.0)	4.1 (2.6)	t=−6.21, p<.001
Multidimensional Quality of Life Scale- Patient Version			
Physical well-being	7.5 (1.5)	5.4 (1.6)	t=12.95, p<.001
Psychological well-being	6.4 (1.6)	4.7 (1.6)	t=10.29, p<.001
Social well-being	6.4 (1.8)	4.6 (1.8)	t=9.57, p<.001
Spiritual well-being	5.3 (2.1)	5.2 (2.1)	t=0.65, p=.516
Total QOL score	6.5 (1.2)	4.9 (1.2)	t=11.75, p<.001
Medical Outcomes Study- Short Form 12			
Physical Component Summary score	43.7 (9.9)	37.4 (10.3)	t=5.78, p<.001
Mental Component Summary score	52.9 (7.5)	43.4 (10.6)	t=9.10, p<.001

Abbreviations: NS = not significant, QOL = quality of life, SD = standard deviation

Table 3.

Differences in Symptoms Scores and QOL Outcomes Among the Evening Fatigue Classes

	Low PM Fatigue (0) 24.9% (n=101)	**Moderate PM Fatigue (1) 44.7% (n=181)**	**Very High PM Fatigue (2) 30.4% (n=123)**	**Statistics**
	Mean (SD)	**Mean (SD)**	**Mean (SD)**	
Symptoms scores				
Trait anxiety (≥31.8)	28.8 (7.8)	33.2 (8.7)	39.1 (10.8)	F=33.71, p<.001 0 < 1 < 2
State anxiety (≥32.2)	27.5 (9.2)	32.8 (10.1)	38.9 (13.5)	F=29.17, p<.001 0 < 1 < 2
Depressive symptoms (≥16)	7.2 (6.5)	10.8 (7.0)	17.3 (10.2)	F=45.59, p<.001 0 < 1 < 2
Sleep disturbance (≥43)	37.0 (16.9)	49.7 (17.5)	61.8 (20.3)	F=48.63, p<.001 0 < 1 < 2
Attentional function (≤7.5)	7.5 (1.6)	6.7 (1.6)	5.6 (1.9)	F=36.17, p<.001 0 > 1 > 2
Morning fatigue (≥3.2)	1.5 (1.7)	2.5 (1.8)	4.3 (2.5)	F=54.00, p<.001 0 < 1 < 2
Evening fatigue (≥5.6)	2.7 (1.8)	4.7 (1.4)	7.3 (1.4)	F=250.45, p<.001 0 < 1 < 2
Morning energy (≤6.2)	4.6 (2.7)	4.8 (2.2)	3.9 (2.3)	F=5.83, p=.003 1 > 2
Evening energy (≤3.5)	4.1 (2.4)	4.0 (1.7)	2.3 (1.8)	F=32.09, p<.001 0 and 1 > 2
	% (n)	% (n)	% (n)	
Pain type No pain Only non-cancer pain Only cancer pain Both cancer and non-cancer pain	 39.4 (39) 19.2 (19) 19.2 (19) 22.2 (22)	 34.3 (61) 23.6 (42) 15.7 (28) 26.4 (47)	 21.3 (26) 34.3 (42) 11.5 (14) 32.8 (40)	X^2 =16.42, p=.012 0 and 1 > 2 0 < 2 NS NS
For patients with pain	Mean (SD)	Mean (SD)	Mean (SD)	
Worst pain intensity score	5.2 (2.8)	5.5 (2.5)	6.6 (2.5)	F=5.85, p=.003 0 < 1 and 2
Pain interference score	1.9 (2.1)	2.8 (2.2)	4.0 (2.7)	F=13.70, p<.001 0 < 1 and 2
Multidimensional Quality of Life Scale- Patient Version				
Physical well-being	7.9 (1.5)	6.7 (1.6)	5.8 (1.8)	F=45.67, p<.001 0 > 1 > 2

	Low PM Fatigue (0) 24.9% (n=101)	Moderate PM Fatigue (1) 44.7% (n=181)	Very High PM Fatigue (2) 30.4% (n=123)	Statistics
	Mean (SD)	Mean (SD)	Mean (SD)	
Psychological well-being	7.0 (1.7)	5.8 (1.5)	4.9 (1.7)	F=46.18, p<.001 0 > 1 > 2
Social well-being	7.0 (1.8)	5.7 (1.8)	4.9 (1.8)	F=37.24, p<.001 0 > 1 > 2
Spiritual well-being	5.6 (2.2)	5.2 (2.1)	5.0 (2.1)	F=2.25, p=.107
Total QOL score	7.0 (1.3)	5.8 (1.2)	5.1 (1.3)	F=58.26, p<.001 0 > 1 > 2
Medical Outcomes Study- Short Form 12				
Physical Component Summary score	44.5 (9.7)	42.5 (10.0)	37.5 (10.7)	F=13.39, p<.001 0 and 1 > 2
Mental Component Summary score	54.4 (7.7)	50.2 (8.4)	44.7 (11.0)	F=29.41, p<.001 0 > 1 > 2

Abbreviations: LFS = Lee Fatigue Scale, NS = not significant, QOL = quality of life, SD = standard deviation

Table 4.

Comparisons of Demographic, Clinical, and Symptom Characteristics Associated with Membership in the Higher Morning and Evening Fatigue Latent Classes

Characteristics (All comparisons done to the Low class)	Very High AM Fatigue GI Sample	Very High AM Fatigue Total Sample[1]	Very High PM Fatigue GI Sample	Very High PM Fatigue Total Sample[2]
Demographic Characteristics				
Younger age	♦	♦	♦	♦
Being female	♦		♦	♦
Being White			♦	♦
Higher BMI		♦		
Not being married or partnered	♦	♦		
Living alone	♦	♦		
Having childcare responsibilities	♦		♦	♦
Not being employed	♦	♦		
Lower income	♦	♦		
Not exercising on a regular basis	♦	♦		
Clinical Characteristics				
Lower KPS score	♦	♦	♦	♦
Higher number of comorbidities	♦	♦		
Higher SCQ score	♦		♦	♦
Higher number of prior cancer treatments	♦		♦	
Not having high blood pressure				♦
Having a diagnosis of anemia or blood disease	♦	♦		
Having a diagnosis of depression	♦	♦	♦	♦
Having back pain		♦		
Symptoms				
Higher trait anxiety	♦	♦	♦	♦
Higher state anxiety	♦	♦	♦	♦
Higher depressive symptoms	♦	♦	♦	♦
Higher sleep disturbance	♦	♦	♦	♦
Lower attentional function	♦	♦	♦	♦
Higher morning fatigue	♦	♦	♦	♦
Higher evening fatigue	♦	♦	♦	♦
Lower morning energy	♦	♦		
Lower evening energy	♦	♦	♦	♦
Having pain	♦	♦	♦	♦

Abbreviations: AM = morning, BMI = body mass index, KPS = Karnofsky Performance Status, PM = evening, SCQ = Self-administered Comorbidity Questionnaire

[1]Wright F, Dunn LB, Paul SM, et al. Morning Fatigue Severity Profiles in Oncology Outpatients Receiving Chemotherapy. *Cancer Nurs* 2019;42(5):355–64. doi: 10.1097/NCC.0000000000000626 [published Online First: 2018/07/20]

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