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Distinct Co-occurring Morning and Evening Fatigue Profiles in Patients with Gastrointestinal Cancers Receiving Chemotherapy

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Abstract

Background: Patients with gastrointestinal cancers experience diurnal variations in fatigue severity during chemotherapy that decrease their functional status and quality of life.

Objectives: Study purposes were to identify subgroups of patients with distinct co-occurring morning and evening fatigue profiles and evaluate for differences among these subgroups in demographic, clinical, stress, and symptom characteristics.

Methods: Patients with gastrointestinal cancers (n=405) completed questionnaires six times over two cycles of chemotherapy. Lee Fatigue Scale was used to evaluate diurnal variations in fatigue severity. Latent profile analysis was used to identify subgroups of patients with distinct co-occurring morning AND evening fatigue profiles. Differences among the subgroups in demographic, clinical, stress, and symptom characteristics at enrollment were evaluated using parametric and non-parametric analyses.

Results: Two classes were identified; namely: low morning and moderate evening fatigue (i.e., Low-Moderate, 60.0%) and high morning and high evening fatigue (i.e., Both High,

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40.0%). Compared to the Low-Moderate class, the Both High class was significantly younger, female, unmarried, unemployed, and lacked regular exercise. In addition, they had childcare responsibilities, lower annual income, lower functional status, higher comorbidity burden, and self-reported anemia and depression. Patients in the Both High class reported higher levels of anxiety, depressive symptoms, sleep disturbance, pain, and stress, and lower levels of energy and cognitive function.

Conclusions: Findings provide new insights into risk factors for higher levels of co-occurring morning and evening fatigue in patients with gastrointestinal cancers.

Implications for Practice: Clinicians can use this information to identify high risk patients and develop personalized symptom management interventions.

Introduction

Fatigue is one of the most common and distressing symptoms in patients with gastrointestinal cancers undergoing chemotherapy that decrease their functional status and quality of life.[1, 2] Diurnal variability is used to describe the variations in fatigue severity that occur throughout the day and is an emerging area of fatigue-related research.[3, 4] Prior studies demonstrated that morning and evening fatigue are distinct symptoms in terms of both risk factors and trajectories.[5–7] In a study that evaluated inter-individual variability in the trajectories of morning and evening fatigue severity in patients undergoing chemotherapy,[5] a lower functional status, and higher sleep disturbance and depressive symptom scores were associated with higher levels of both morning and evening fatigue. However, higher body mass index, lack of exercise, and higher state anxiety were associated with only higher levels of morning fatigue. In contrast, being white, having more years of education and childcare responsibilities, and a lower functional status were associated with only higher levels of evening fatigue.[7]

In another study that explored associations between variations in genes involved in inflammatory processes and morning and evening fatigue,[8] polymorphisms in six genes from the inflammasome, Janus kinase/signal transducers and activators of transcription, and nuclear factor-kappa beta (NFkB) pathways were associated with only morning fatigue. Polymorphisms in three different genes from the inflammasome and the NFkB pathways were associated with only evening fatigue.[8] The mechanisms that underlie diurnal variability in fatigue may be partially explained by some of these genetic differences.[9] Taken together, these findings suggest that morning and evening fatigue are distinct but related symptoms. While these studies were conducted in patients with heterogenous types of cancers, additional research is warranted on diurnal variations in fatigue in specific types of cancer, like gastrointestinal cancer.

In our previous study,[10] separate latent profile analysis (LPA) were used to identify subgroups of patients with gastrointestinal cancers with distinct morning and evening fatigue severity profiles. Two distinct morning (i.e., low and very high) and three distinct evening (i.e., low, moderate, and very high) fatigue classes were identified. Common risk factors associated with membership in the very high classes for both morning and evening fatigue included: younger age, a lower functional status, a higher comorbidity burden, and a self-

reported diagnosis of depression. The unique risk factors for being in the very high morning fatigue class were: being unmarried, living alone, being unemployed, having a lower annual household income, lack of regular exercise, and a self-reported diagnosis of anemia. Of note, being female, white, and having childcare responsibilities were the unique risk factors associated with membership in the very high evening fatigue class. These findings support the hypothesis that morning fatigue and evening fatigue are distinct but related symptoms in patients with gastrointestinal cancers. While previous research demonstrated that morning and evening fatigue can co-occur during chemotherapy,[11] little is known about risk factors for the co-occurrence of both symptoms. Information on how these two symptoms co-occur and associated risk factors for a worse profile will help clinicians to target patients with the highest fatigue burden.

Stress is associated with higher levels of fatigue in patients with cancer.[12, 13] Repeated stressful events or cumulative exposure (e.g., cancer treatments, a variety of stressful life events) may increase allostatic load on the hypothalamic-pituitary-adrenal (HPA) axis that results in increased fatigue severity.[14] As noted in our previous longitudinal study,[15] oncology patients in both the very high morning and evening fatigue classes reported the highest global stress scores. While findings from previous studies suggest that higher levels of perceived stress are associated with greater fatigue severity, the majority of them were cross-sectional,[16] and evaluated patients with breast cancer[17] or heterogenous types of cancer.[15] Additional research is warranted on the association between diurnal variability in fatigue and stress in patients with gastrointestinal cancers.

In addition, both morning and evening fatigue are associated with higher levels of common symptoms (e.g., sleep disturbance, depressive symptoms, anxiety, and pain) in oncology patients.[10, 15] Understanding the relationships between the co-occurrence of morning and evening fatigue and other common symptoms may be the key to successful tiered or multi-modal symptom management interventions. Given the paucity of research on diurnal variations in fatigue severity in patients with gastrointestinal cancers, the purposes of this study were to identify subgroups of these patients with distinct co-occurring morning AND evening fatigue severity profiles and evaluate for differences among these subgroups in demographic, clinical, stress, and symptom characteristics.

Methods

Patients and settings

Details regarding this prospective, longitudinal study of the symptom experience of oncology outpatients receiving chemotherapy were published previously.[18, 19] The overall study was guided by the Theory of Symptom Management.[20] In brief, eligible patients were ≥18 years of age; had a diagnosis of breast, gastrointestinal, gynecological, or lung cancer; had received chemotherapy within the preceding four weeks; were scheduled to receive at least two additional cycles of chemotherapy; were able to read, write, and understand English; and provided written informed consent. Patients were recruited from two Comprehensive Cancer Centers, one Veteran's Affairs hospital, and four community-based oncology programs. A total of 2234 patients were approached and 1343 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 and evening fatigue were included (n=405).

Instruments

Patients completed a demographic questionnaire, the Karnofsky Performance Status (KPS) scale,[21] and the Self-administered Comorbidity Questionnaire (SCQ).[22] Patients' medical records were reviewed for disease and treatment information.

Morning and Evening Fatigue Measures—The 18-item Lee Fatigue Scale (LFS) was designed to assess physical fatigue and energy.[23] 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 established 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).[24] 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.

Stress and Resilience Measures—The 14-item Perceived Stress Scale (PSS) was used as a measure of global perceived stress according to the degree that life circumstances are appraised as stressful over the course of the previous week.[25] In this study, its Cronbach's alpha was 0.85.

The 22-item Impact of Event Scale-Revised (IES-R) was used to measure cancer-related distress.[26] Patients rated each item based on how distressing each potential difficulty was for them during the past week "with respect to their cancer and its treatment". Three subscales evaluate levels of intrusion, avoidance, and hyperarousal perceived by the patient. Sum scores of ≥24 indicate clinically meaningful post traumatic symptomatology and scores of ≥33 indicate probable posttraumatic stress disorder (PTSD).[27] In this study, the Cronbach's alpha for the IES-R total score was 0.92.

The 30-item Life Stressor Checklist-Revised (LSC-R) is an index of lifetime trauma exposure (e.g., being mugged, the death of a loved one, a sexual assault).[28] The total LSC–R score is obtained by summing the total number of events endorsed. If patients endorsed an event, they were asked to indicate how much that stressor affected their life in the past year. These responses were averaged to yield a mean "Affected" score. In addition, a PTSD sum score was created based on the number of positively endorsed items (out of 21) that reflect the DSM-IV PTSD Criteria A for having experienced a traumatic event.

The 10-item Connor-Davidson Resilience Scale (CDRS) evaluates a patient's personal ability to handle adversity (e.g., "I am able to adapt when changes occur"; "I tend to bounce back after illness, injury, or other hardships").[29] Total scores range from 0 to 40, with higher scores indicative of higher self-perceived resilience. The normative adult mean score in the United States is 31.8 (±5.4).[30] In this study, its Cronbach's alpha was 0.90.

Symptoms Measures—All the instruments that were used to assess six of the most common co-occurring symptoms associated with cancer and its treatment were valid and reliable. The symptoms that were assessed included: state and trait anxiety (Spielberger State-Trait Anxiety Inventories (STAI-S and STAI-T[31]); depressive symptoms (Center for Epidemiological Studies-Depression scale (CES-D)[32]); sleep disturbance (General Sleep Disturbance Scale (GSDS)[33, 34]); cognitive dysfunction (Attentional Function Index (AFI)[35]); and pain (Brief Pain Inventory (BPI)[36]).

Study procedures

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. 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 cycle, 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

LPA was used to identify subgroups of patients with distinct co-occurring morning and evening fatigue profiles. Using Mplus version 8.4,[37] this LPA was performed with the combined set of variables over time (i.e., using the morning and evening LFS scores obtained during the six assessments in a single LPA). This approach provides a profile description of these two symptoms with two profiles over time.

In order to incorporate expected correlations among the repeated measures of the same variable and cross-correlations of the series of the two variables (i.e., morning and evening LFS scores), we included covariance parameters among measures at the same occasion and those that were one or two occasions apart. Covariances of each variable with the other at the same assessments were included in the model and autoregressive covariances were estimated with a lag of two with the same measures and with a lag of one for each variable's series with the other variable. We limited the covariance structure to a lag of two to accommodate the expected reduction in the correlations that would be introduced by two chemotherapy cycles within each set of three measurement occasions and to reduce model complexity.[38] Statistical fit indices were used to determine the number of classes that best captured variability, while maintaining conceptual clarity.[39]

Data were analyzed using SPSS version 27 (IBM Corporation, Armonk, NY). Differences among the co-occurring morning and evening fatigue classes in demographic, clinical, stress, and symptom characteristics were evaluated using parametric and nonparametric tests. A p-value of $<.05$ was considered statistically significant.

Results

Results of the LPA

The fit indices and details regarding the selection of the two-class model for the co-occurring morning and evening fatigue profiles are shown in Table 1. The trajectories for morning and evening fatigue differed between the latent classes (Figure). For the Low morning and Moderate evening fatigue class (i.e., Low-Moderate, 60.0%), while the severity of morning fatigue increased at assessment 2 and decreased at assessment 4, the evening fatigue scores remained relatively constant over the six assessments. For the High morning and High evening fatigue class (i.e., Both High, 40.0%), while the severity of morning fatigue increased at assessments 2 and 5 (i.e., one week following the administration of chemotherapy), the evening fatigue scores remained relatively constant over the six assessments.

Differences in Demographic and Clinical Characteristics

Compared to the Low-Moderate class, the Both High class was significantly younger, more likely to be female, less likely to be married or partnered, more likely to have childcare responsibilities, less likely to be employed, reported a lower annual household income, and were less likely to exercise on a regular basis (Table 2). In addition, the Both High class had a lower KPS score, a higher number of comorbidities, a higher SCQ score, had received a higher number of prior cancer treatments, and were more likely to self-report anemia and depression.

Differences in Stress and Resilience

For all of the subscale and total scores on the stress measures, compared to the Low-Moderate class, the Both High class reported higher scores (Table 3). In addition, the Both High class reported lower resilience scores.

Differences in Common Co-occurring Symptoms

Compared to the Low-Moderate class, the Both High class had higher levels of trait anxiety, state anxiety, depressive symptoms, and sleep disturbance and lower levels of morning energy, evening energy, and attentional function (Table 3). In addition, a higher percentage of patients in the Both High class reported the occurrence of non-cancer pain and both cancer and non-cancer pain. For the patients who had pain, those in the Both High class had higher worst pain intensity and pain interference scores.

Discussion

This study is the first to identify subgroups of patients with gastrointestinal cancers with distinct co-occurring morning and evening fatigue severity profiles. While our previous study of patients with gastrointestinal cancers identified two classes for morning fatigue and three classes for evening fatigue,[10] when the symptoms were combined, two classes (i.e., Low-Moderate, Both High) were found and 40% of our patients with gastrointestinal cancer had high levels of both morning and evening fatigue. While prevalence rates for average fatigue in patients receiving chemotherapy range from 62%[40] to 83%,[1] our findings suggest

that a large percentage of patients wake up with high levels of fatigue that persist throughout the day.

Given the paucity of research on diurnal variations in fatigue severity in patients with gastrointestinal cancer, the focus of this discussion will be on a comparison of the common and distinct risk factors for membership in the highest fatigue classes identified in the LPAs for the single symptoms of morning (i.e., Very High) and evening (i.e., Very High) fatigue in our previous study[10] compared to the joint LPA (i.e., Both High) in the present study. As shown in Table 4, seven common risk factors were identified across these three analyses, namely: younger age, female gender, having childcare responsibilities, a lower performance status, a higher comorbidity burden, a higher number of prior cancer treatments, and a self-reported diagnosis of depression.

Findings regarding gender differences in morning and evening fatigue are inconsistent.[5, 41] This inconsistency may be related to differences in the gender distribution of patients within various studies (e.g., a higher number of women with breast cancer in a study of fatigue in patients with heterogeneous types of cancer). However, given that gastrointestinal cancer effects men and women equally and 54.3% of our sample was men, our finding supports previous work that suggests that women receiving chemotherapy have higher levels of both morning and evening fatigue. This finding on gender differences is supported by the higher percentage of patients with child care responsibilities being in the three highest fatigue classes given that women have primary responsibility for child care.

In terms of clinical characteristics, receipt of a higher number of cancer treatments as well as a higher comorbidity burden, and lower functional status were associated with the three highest fatigue profiles. A plausible explanation for these relationships is that the cumulative effects of different cancer treatments may contribute to this extremely high fatigue burden.[1] Clinicians can use these common risk factors to identify patients who are at increased risk for clinically meaningful levels of fatigue. In addition, they can make referrals to programs that provide assistance with childcare responsibilities. Equally important, oncology clinicians need to work with the patients' primary care providers to manage their comorbidities and improve their functional status.

Several unique risk factors were associated with both the Very High morning fatigue and the Both High Morning and Evening fatigue classes, namely: not being married/partnered, being unemployed, having a lower annual household income, lack of regular exercise, and a self-reported diagnosis of anemia or blood disease. Employment status and annual income are well established risk factors for increased stress and the associated financial challenges may lead to inadequate resources and/or support to enable patients to manage their fatigue.[42, 43] Findings regarding lack of regular exercise and a self-reported diagnosis of anemia may be related given that a large population study found that lack of exercise was associated with increased risk for anemia.[44] In addition, lower levels of hemoglobin were associated with increases in fatigue severity.[45] Given that exercise is the only evidenced-based intervention for fatigue,[46] clinicians need to refer patients to physical therapy to develop an individualized exercise regimen.

While in our previous LPAs of the single symptoms,[10] stress measures were not evaluated, in the joint morning and evening fatigue LPA, compared to the Low-Moderate class, the subscale and total scores for all of the stress measures were significantly higher in the Both High class. These differences represent clinically meaningful increases in global, cancer-specific, and cumulative life stress (effect size, d = 0.3 to 1.0).[47] In addition, these patients reported clinically meaningful decrements in resilience (d = 0.5). Taken together, patients with less stress and higher levels of resilience may have more resources (both financial and social support) to cope with their symptoms.[48] Our findings are consistent with previous research that found that higher levels of global stress (i.e., PSS scores) were associated with higher levels of fatigue in patients with a number of chronic conditions (e.g., rheumatoid arthritis, inflammatory bowel disease).[49] Given that inflammatory processes are associated with cancer and other chronic conditions,[50] as well as with cancer-related fatigue[51] and chronic fatigue syndrome[52], these findings suggest shared underlying mechanisms for both symptoms. Additional research is warranted to confirm the associations between stress and diurnal variations in fatigue across cancer types and other chronic conditions, as well as common and distinct underlying mechanisms.

As shown in Table 4, except for morning energy, the highest classes in the single symptom LPAs, as well as the joint LPA for morning and evening fatigue reported higher scores for state and trait anxiety, depressive symptoms, sleep disturbance, and pain, and lower levels of evening energy and cognitive function. In addition, all of the symptom severity scores reported by the Both High class in the current study were above the clinically meaningful cutoff. Of note, the CES-D scores in these patients suggest the need for a clinical evaluation, In addition, the sleep disturbance scores are comparable to those of parents of newborn infants.[53] The co-occurrence of these common symptoms may be explained by increases in proinflammatory responses, dysregulation of the hypothalamic-pituitary-adrenal axis, and/or alterations in various neurotransmitters.[54–56] However, the specific mechanisms underlying diurnal variations in fatigue severity and the associations with other common symptoms warrant additional investigation.

Limitations

Several limitations warrant consideration. Because patients were not recruited prior to the initiation of chemotherapy, risk profiles for co-occurring morning and evening fatigue from its initiation through completion were not evaluated. In addition, because most of the patients were White and well educated, our findings may not generalize to more diverse samples. Given the heterogeneity in gastrointestinal cancers in this study, similar evaluations are warranted in patients with specific gastrointestinal cancers (e.g., pancreatic, gastric).

Implications for Practice

This study is the first to identify subgroups of patients with gastrointestinal cancers with distinct co-occurring morning AND evening fatigue profiles and identify common and distinct risk factors associated with the worst profiles from the single and joint symptom analyses. Additional research is warranted to explore underlying molecular mechanisms that contribute to the co-occurrence of morning AND evening fatigue, as well as the associations between other common symptoms and stress. Clinicians need to assess for these common

risk factors to identify patients who are at increased risk for the co-occurrence of morning and evening fatigue and initiate personalized symptom management interventions that target the modifiable risk factors.

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References

1. Tantoy IY, Dhruva A, Cataldo J, et al. Differences in symptom occurrence, severity, and distress ratings between patients with gastrointestinal cancers who received chemotherapy alone or chemotherapy with targeted therapy. J Gastrointest Oncol. 2017;8(1):109–126. [PubMed: 28280616]
2. Tantoy IY, Cooper BA, Dhruva A, et al. Quality of life of patients with gastrointestinal cancers undergoing chemotherapy. Qual Life Res. 2018;27(7):1865–1876. [PubMed: 29679368]
3. Lerdal A, Gay CL, Aouizerat BE, Portillo CJ, Lee KA. Patterns of morning and evening fatigue among adults with HIV/AIDS. J Clin Nurs. 2011;20(15–16):2204–2216. [PubMed: 21752119]
4. Lerdal A, Kottorp A, Gay C, Aouizerat BE, Lee KA, Miaskowski C. A Rasch analysis of assessments of morning and evening fatigue in oncology patients using the Lee Fatigue Scale. J Pain Symptom Manage. 2016;51(6):1002–1012. [PubMed: 26975624]
5. Wright F, D'Eramo Melkus G, Hammer M, et al. Predictors and trajectories of morning fatigue are distinct from evening fatigue. J Pain Symptom Manage. Aug 2015;50(2):176–189.
6. Dhruva A, Aouizerat BE, Cooper B, et al. Differences in morning and evening fatigue in oncology patients and their family caregivers. Eur J Oncol Nurs. 2013;17(6):841–848. [PubMed: 24012189]
7. Wright F, D'Eramo Melkus G, Hammer M, et al. Trajectories of evening fatigue in oncology outpatients receiving chemotherapy. J Pain Symptom Manage. 2015;50(2):163–175. [PubMed: 25828560]
8. Wright F, Hammer M, Paul SM, et al. Inflammatory pathway genes associated with inter-individual variability in the trajectories of morning and evening fatigue in patients receiving chemotherapy. Cytokine. 2017;91:187–210. [PubMed: 28110208]
9. Dhruva A, Aouizerat BE, Cooper B, et al. Cytokine gene associations with self-report ratings of morning and evening fatigue in oncology patients and their family caregivers. Biol Res Nurs. 2015;17(2):175–184. [PubMed: 24872120]
10. Lin Y, Bailey DE, Docherty SL, et al. Distinct morning and evening fatigue profiles in gastrointestinal cancer during chemotherapy. BMJ Support Palliat Care. May 28 2021.
11. Kober KM, Cooper BA, Paul SM, et al. Subgroups of chemotherapy patients with distinct morning and evening fatigue trajectories. Support Care Cancer. 2016;24(4):1473–1485. [PubMed: 26361758]
12. Weber D, O'Brien K. Cancer and cancer-related fatigue and the interrelationships with depression, stress, and inflammation. J Evid Based Complementary Altern Med. 2017;22(3):502–512. [PubMed: 30208733]
13. Lai S Cancer related fatigue and cancer cachexia are the consequence of endocrine failure caused by persistent stress. Med Hypotheses. 2019;123:60–62. [PubMed: 30696594]
14. Shields GS, Slavich GM. Lifetime stress exposure and health: A review of contemporary assessment methods and biological mechanisms. Soc Personal Psychol Compass. 2017;11(8).
15. Wright F, Kober KM, Cooper BA, et al. Higher levels of stress and different coping strategies are associated with greater morning and evening fatigue severity in oncology patients receiving chemotherapy. Support Care Cancer. 2020;28(10):4697–4706. [PubMed: 31956947]
16. Johnson A, Rice M, Turner-Henson A, Haase JE, Azuero A. Perceived stress and the fatigue symptom cluster in childhood brain tumor survivors. Oncol Nurs Forum. 2018;45(6):775–785. [PubMed: 30339150]

17. Gosain R, Gage-Bouchard E, Ambrosone C, Repasky E, Gandhi S. Stress reduction strategies in breast cancer: review of pharmacologic and non-pharmacologic based strategies. Semin Immunopathol. 2020;42(6):719–734. [PubMed: 32948909]
18. Wright F, Cooper BA, Conley YP, et al. Distinct evening fatigue profiles in oncology outpatients receiving chemotherapy. Fatigue. 2017;5(3):131–144. [PubMed: 29725554]
19. Wright F, Dunn LB, Paul SM, et al. Morning fatigue severity profiles in oncology outpatients receiving chemotherapy. Cancer Nurs. 2019;42(5):355–364. [PubMed: 30024437]
20. Humphreys J, Janson S, Donesky D, et al. A middle range theory of symptom management. In: Smith MJ, Liehr PR, eds. Middle Range Theory in Nursing. 3rd ed. New York: Springer Publishing Company; 2014:141–164.
21. Karnofsky D Performance scale. New York: Plenum Press; 1977.
22. Cieza A, Geyh S, Chatterji S, Kostanjsek N, Ustun BT, Stucki G. Identification of candidate categories of the International Classification of Functioning Disability and Health (ICF) for a Generic ICF Core Set based on regression modelling. BMC Med Res Methodol. 2006;6:36. [PubMed: 16872536]
23. Lee KA, Hicks G, Nino-Murcia G. Validity and reliability of a scale to assess fatigue. Psychiatry Res. 1991;36(3):291–298. [PubMed: 2062970]
24. Fletcher BS, Paul SM, Dodd MJ, et al. Prevalence, severity, and impact of symptoms on female family caregivers of patients at the initiation of radiation therapy for prostate cancer. J Clin Oncol. 2008;26(4):599–605. [PubMed: 18235118]
25. Cohen S, Kamarck T, Mermelstein R. A global measure of perceived stress. J Health Soc Behav. 1983;24(4):385–396. [PubMed: 6668417]
26. Horowitz M, Wilner N, Alvarez W. Impact of Event Scale: a measure of subjective stress. Psychosom Med. 1979;41(3):209–218. [PubMed: 472086]
27. Creamer M, Bell R, Failla S. Psychometric properties of the Impact of Event Scale - Revised. Behav Res Ther. 2003;41(12):1489–1496. [PubMed: 14705607]
28. Wolfe J, Kimmerling R. Gender issues in the assessment of posttraumatic stress disorder. New York: Guilford; 1997.
29. Campbell-Sills L, Stein MB. Psychometric analysis and refinement of the Connor-davidson Resilience Scale (CD-RISC): Validation of a 10-item measure of resilience. J Trauma Stress. 2007;20(6):1019–1028. [PubMed: 18157881]
30. Campbell-Sills L, Forde DR, Stein MB. Demographic and childhood environmental predictors of resilience in a community sample. J Psych Res. 2009;43(12):1007–1012.
31. Spielberger CG, Gorsuch RL, Suchene R, Vagg PR, Jacobs GA. Manual for the State-Anxiety (Form Y): Self Evaluation Questionnaire. Palo Alto, CA: Consulting Psychologists Press; 1983.
32. Radloff LS. The CES-D Scale: A self-report depression scale for research in the general population. Applied Psychological Measurement. 1977;1(3):385–401.
33. Lee KA. Self-reported sleep disturbances in employed women. Sleep. 1992;15(6):493–498. [PubMed: 1475563]
34. Lee KA, DeJoseph JF. Sleep disturbances, vitality, and fatigue among a select group of employed childbearing women. Birth. 1992;19(4):208–213. [PubMed: 1472269]
35. Cimprich B, Visovatti M, Ronis DL. The Attentional Function Index--a self-report cognitive measure. Psychooncology. 2011;20(2):194–202. [PubMed: 20213858]
36. Daut RL, Cleeland CS, Flanery RC. Development of the Wisconsin Brief Pain Questionnaire to assess pain in cancer and other diseases. Pain. 1983;17(2):197–210. [PubMed: 6646795]
37. Muthen LK, Muthen BO. Mplus User's Guide (8th ed.). 8th ed. Los Angeles, CA: Muthen & Muthen; 1998–2020.
38. Jung T, Wickrama KAS. An introduction to latent class growth analysis and growth mixture modeling. Soc Personal Psychol Compass. 2008;2(1):302–317.
39. Nylund KL, Asparouhov T, Muthén BO. Deciding on the number of classes in latent class analysis and growth mixture modeling: A Monte Carlo simulation study. Structural Equation Modeling: A Multidisciplinary Journal. 2007;14(4):535–569.

40. Pettersson G, Berterö C, Unosson M, Börjeson S. Symptom prevalence, frequency, severity, and distress during chemotherapy for patients with colorectal cancer. Support Care Cancer. 2014;22(5):1171–1179. [PubMed: 24337684]
41. Al Maqbali M, Al Sinani M, Al Naamani Z, Al Badi K, Tanash MI. Prevalence of fatigue in patients with cancer: A systematic review and meta-analysis. J Pain Symptom Manage. 2021;61(1):167–189 e114. [PubMed: 32768552]
42. de Moor JS, Partridge AH, Winer EP, Ligibel J, Emmons KM. The role of socioeconomic status in adjustment after ductal carcinoma in situ. Cancer. 2010;116(5):1218–1225. [PubMed: 20143325]
43. Stump TK, Eghan N, Egleston BL, et al. Cost concerns of patients with cancer. J Oncol Pract. 2013;9(5):251–257. [PubMed: 23943901]
44. Zamani M, Poustchi H, Shayanrad A, et al. Prevalence and determinants of anemia among Iranian population aged ≥35 years: A PERSIAN cohort-based cross-sectional study. PLoS One. 2022;17(2):e0263795. [PubMed: 35139138]
45. Ahlberg K, Ekman T, Gaston-Johansson F. Levels of fatigue compared to levels of cytokines and hemoglobin during pelvic radiotherapy: a pilot study. Biol Res Nurs. 2004;5(3):203–210. [PubMed: 14737921]
46. Song J, Wang T, Wang Y, et al. Evaluation of evidence for exercise intervention in patients with cancer-related fatigue during chemoradiotherapy. J Clin Nurs. 2021;30(13–14):1854–1862. [PubMed: 33555639]
47. Cohen J Statistical power analysis for the behavioral sciences. 2 nd ed. Hillsdale NJ: Lawrence Erlbaum Associates; 1988.
48. Langford DJ, Cooper B, Paul S, et al. Distinct stress profiles among oncology patients undergoing chemotherapy. J Pain Symptom Manage. 2020;59(3):646–657. [PubMed: 31711968]
49. Hirsch JK, Sirois FM. Hope and fatigue in chronic illness: The role of perceived stress. J Health Psychol. 2016;21(4):451–456. [PubMed: 24677432]
50. Greten FR, Grivennikov SI. Inflammation and cancer: Triggers, mechanisms, and consequences. Immunity. 2019;51(1):27–41. [PubMed: 31315034]
51. Bower JE. The role of neuro-immune interactions in cancer-related fatigue: Biobehavioral risk factors and mechanisms. Cancer. 2019;125(3):353–364. [PubMed: 30602059]
52. Rusin A, Seymour C, Cocchetto A, Mothersill C. Commonalities in the features of cancer and Chronic Fatigue Syndrome (CFS): Evidence for stress-induced phenotype instability? Int J Mol Sci. 2022;23(2).
53. Gay CL, Lee KA, Lee SY. Sleep patterns and fatigue in new mothers and fathers. Biol Res Nurs. 2004;5(4):311–318. [PubMed: 15068660]
54. Illi J, Miaskowski C, Cooper B, et al. Association between pro- and anti-inflammatory cytokine genes and a symptom cluster of pain, fatigue, sleep disturbance, and depression. Cytokine. 2012;58(3):437–447. [PubMed: 22450224]
55. Kim HJ, Barsevick AM, Fang CY, Miaskowski C. Common biological pathways underlying the psychoneurological symptom cluster in cancer patients. Cancer Nurs. 2012;35(6):E1–E20.
56. Miaskowski C, Aouizerat BE. Is there a biological basis for the clustering of symptoms? Semin Oncol Nurs. 2007;23(2):99–105. [PubMed: 17512436]

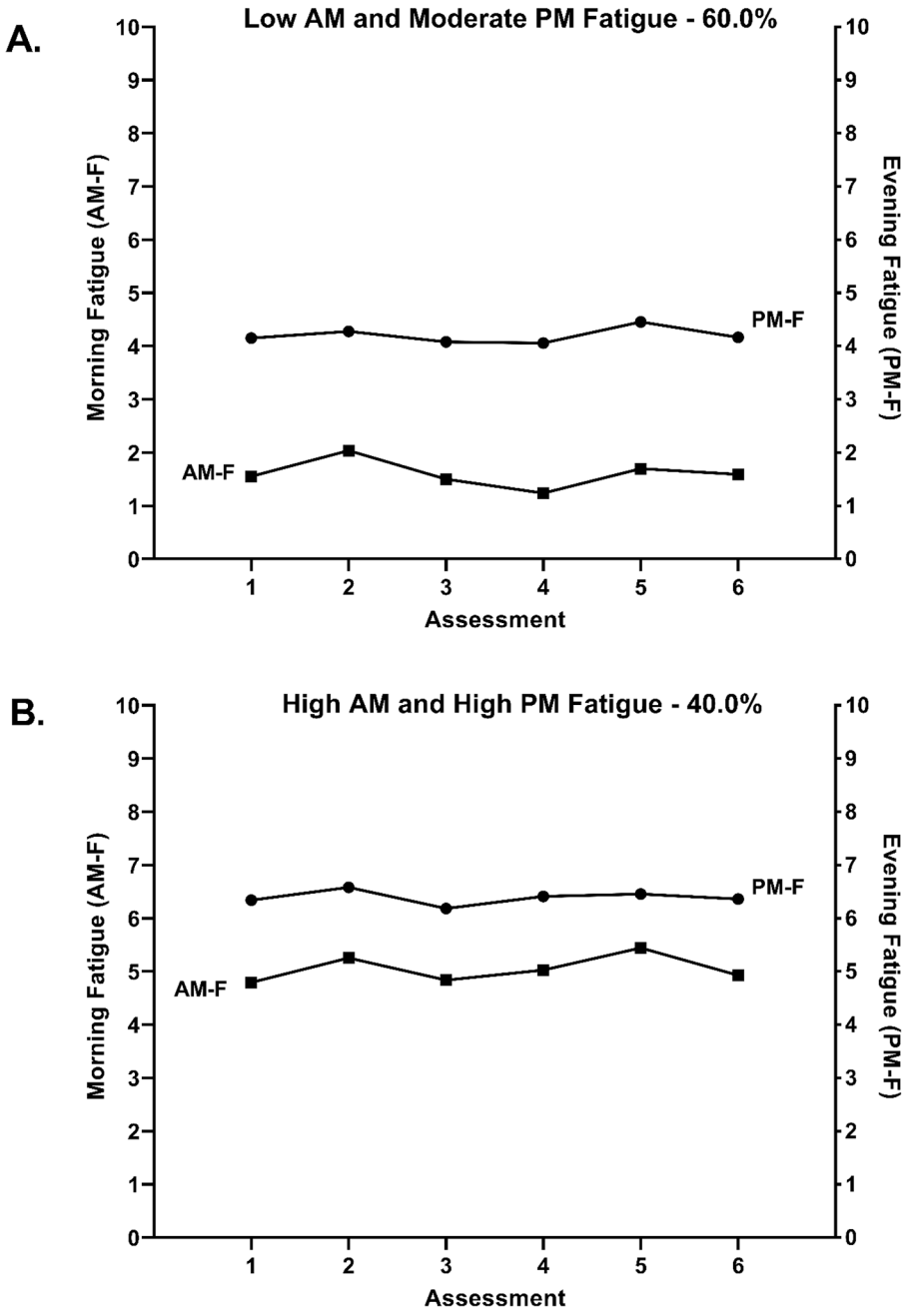

Figure.

Trajectories of morning fatigue (AM-F) and evening fatigue (PM-F) for the two latent classes. The numbers on the x-axis indicated the assessments of morning and evening fatigue (i.e., using the Lee Fatigue Scale) that were done prior to the administration of chemotherapy (i.e., assessments 1 and 4), in the week following the administration of chemotherapy (i.e., assessments 2 and 5), and two weeks after the administration of chemotherapy (i.e., assessments 3 and 6).

Table 1.

Morning and Evening Fatigue Latent Profile Solutions and Fit Indices for One through Three Classes for Patients with Gastrointestinal Cancers

Model	LL	AIC	BIC	Entropy	VLMR
1 Class	−7777.57	15671.13	15903.36	n/a	n/a
2 Class[a]	−7507.40	15156.79	15441.07	0.86	540.34[+]
3 Class	−7386.30	14940.60	15276.93	0.82	242.19[ns]

Baseline entropy and VLMR are not applicable for the one-class solution

[*] p <.05;

[+] p = .0001

[a] The two-class solution was selected because the BIC for that solution was lower than the BIC for the 1-class (baseline) solution. In addition, the VLMR was significant for the 2-class solution, indicating that two classes fit the data better than one class. Although 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.

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

Table 2.

Differences in Demographic and Clinical Characteristics at Enrollment Between the Combined Morning and Evening Fatigue Classes

Characteristic	Low AM Fatigue and Moderate PM Fatigue 60% (n=243)	High AM Fatigue and High PM Fatigue 40% (n=162)	Statistics
	Mean (SD)	Mean (SD)	
Age (years)	59.9 (11.1)	55.0 (12.1)	t=4.19, p<.001
Education (years)	16.2 (3.1)	15.9 (3.0)	t=0.87, p=.384
Body mass index (kg/m^2)	25.5 (4.7)	26.0 (5.8)	t=−0.84 p=.404
Karnofsky Performance Status score	85.0 (10.5)	74.1 (12.0)	t=9.31, p<.001
Number of comorbidities	2.2 (1.3)	2.5 (1.4)	t=−2.34, p=.020
Self-administered Comorbidity Questionnaire score	4.8 (2.6)	6.1 (3.2)	t=−4.20, p<.001
Time since cancer diagnosis (years)	1.3 (2.9)	1.6 (2.8)	U, p=.064
Time since diagnosis (median; years)	0.40	0.46	
Number of prior cancer treatments	1.3 (1.3)	1.7 (1.4)	t=−2.96, p=.003
Number of metastatic sites including lymph node involvement	1.4 (1.1)	1.5 (1.2)	t=−0.81, p=.420
Number of metastatic sites excluding lymph node involvement	0.9 (0.9)	1.0 (1.0)	t=−0.55, p=.584
AUDIT score	3.4 (2.7)	3.3 (3.3)	t=0.11, p=.912
Hemoglobin (gm/dl)	12.0 (1.5)	11.8 (1.6)	t=0.92, p=.360
Hematocrit (%)	36.0 (4.0)	35.4 (4.4)	t=1.21, p=.226
MAX-2 score	0.14 (0.06)	0.14 (0.06)	t=0.89, p=.372
	% (n)	% (n)	
Gender (% female)	38.7 (94)	56.2 (91)	FE, p=.001
Ethnicity			X^2=6.77, p=.080
White	68.8 (163)	65.4 (106)	
Asian or Pacific Islander	12.2 (29)	12.3 (20)	
Black	11.0 (26)	6.8 (11)	
Hispanic Mixed or Other	8.0 (19)	15.4 (25)	
Married or partnered (% yes)	71.7 (172)	61.1 (99)	FE, p=.030
Lives alone (% yes)	16.3 (39)	22.4 (36)	FE, p=.150
Child care responsibilities (% yes)	16.0 (38)	27.8 (44)	FE, p=.005
Adult care responsibilities (% yes)	5.4 (12)	10.1 (15)	FE, p=.103
Currently employed (% yes)	38.4 (91)	28.0 (45)	FE, p=.032
Income			U, p=.012
< $30,000	14.6 (31)	27.3 (41)	
$30,000 to < $70,000	20.3 (43)	18.7 (28)	
$70,000 to < $100,000	17.9 (38)	16.0 (24)	
> $100,000	47.2 (100)	38.0 (57)	

Specific comorbidities (% yes)			
Heart disease	6.2 (15)	3.1 (5)	FE, p=.241
High blood pressure	36.2 (88)	29.0 (47)	FE, p=.162
Lung disease	4.9 (12)	7.4 (12)	FE, p=.391
Diabetes	11.1 (27)	16.0 (26)	FE, p=.176
Ulcer or stomach disease	5.8 (14)	5.6 (9)	FE, p=1.000
Kidney disease	1.2 (3)	1.9 (3)	FE, p=.687
Liver disease	11.9 (29)	12.3 (20)	FE, p=1.000
Anemia or blood disease	5.8 (14)	14.8 (24)	FE, p=.003
Depression	7.0 (17)	25.3 (41)	FE, p<.001
Osteoarthritis	8.2 (20)	9.9 (16)	FE, p=.596
Back pain	20.2 (49)	24.1 (39)	FE, p=.390
Rheumatoid arthritis	1.6 (4)	2.5 (4)	FE, p=.719
Exercise on a regular basis (% yes)	74.1 (180)	55.7 (88)	FE, p<.001
Current or history of smoking (% yes)	31.8 (76)	31.0 (48)	FE, p=.912
Type of prior cancer treatment			
No prior treatment	33.3 (78)	22.8 (36)	
Only surgery, CTX, or RT	37.6 (88)	37.3 (59)	X^2=6.91, p=.075
Surgery & CTX, or Surgery & RT, or CTX & RT	19.2 (45)	26.6 (42)	
Surgery & CTX & RT	9.8 (23)	13.3 (21)	
Colon and rectal cancer (% yes)	59.2 (142)	68.3 (110)	FE, p=.073
Chemotherapy regimen			
FOLFIRI	11.5 (27)	18.0 (29)	
FOLFOX	42.1 (99)	44.7 (72)	X^2=5.09, p=.165
FOLFIRINOX	12.3 (29)	8.7 (14)	
Other	34.0 (80)	28.6 (46)	
CTX cycle length			
14 day	81.3 (196)	85.1 (137)	U, p=.296
21 day	15.4 (37)	13.7 (22)	
28 day	3.3 (8)	1.2 (2)	
Emetogenicity of CTX			
Minimal/low	16.1 (39)	12.4 (20)	U, p=.439
Moderate	80.2 (194)	84.5 (136)	
High	3.7 (9)	3.1 (5)	
Antiemetic regimen			
None	4.2 (10)	7.0 (11)	
Steroid alone or serotonin antagonist alone	11.4 (27)	10.8 (17)	X^2=3.43, p=.329
Serotonin receptor antagonist and steroid	65.0 (154)	57.6 (91)	
NK-1 receptor antagonist and two other antiemetics	19.4 (46)	24.7 (39)	

Abbreviations: AM = morning, AUDIT = Alcohol Use Disorders Identification Test, dl = deciliter; FOLFIRI = leucovorin/5-fluorouracil/irinotecan, FOLFIRINOX = leucovorin/5-fluorouracil/irinotecan/oxaliplatin, FOLFOX = leucovorin/5-fluorouracil/oxaliplatin, gm = grams, kg = kilograms,

m^2 = meter squared, NK-1 = neurokinin-1, NS = not significant, PM = evening, RT = radiation therapy, SD = standard deviation, U = Mann Whitney U test

Table 3.

Differences in Stress and Symptom Scores at Enrollment Between the Combined Morning and Evening Fatigue Classes

Stress and Symptom measures[a]	**Low AM Fatigue and Moderate PM Fatigue 60% (n=243)**	**High AM Fatigue and High PM Fatigue 40% (n=162)**	**Statistics**
	Mean (SD)	**Mean (SD)**	
Stress scores			
Perceived Stress Scale total score	15.0 (6.8)	21.9 (7.3)	t=−9.42, p<.001
Impact of Event Scale-Revised total score (≥24)	15.0 (10.3)	25.7 (15.1)	t=−7.69, p<.001
LSCR – total score	5.4 (3.6)	6.6 (4.1)	t=−2.83, p=.005
LSCR – affected sum score	9.2 (8.0)	13.9 (11.9)	t=−3.89, p<.001
LSCR – PTSD sum score	2.7 (2.8)	3.5 (2.2)	t=−2.23, p=.027
Connor Davidson Resilience total score	31.6 (6.2)	28.6 (6.3)	t=4.63, p<.001
Symptom scores			
Trait anxiety (≥31.8)	30.2 (7.5)	39.5 (10.5)	t=−9.62, p<.001
State anxiety (≥32.2)	29.4 (9.6)	39.1 (12.4)	t=−8.28, p<.001
Depressive symptoms (≥16.0)	8.3 (6.3)	17.3 (9.3)	t=−10.72, p<001
Sleep disturbance (≥43.0)	41.1 (16.6)	63.9 (17.7)	t=−12.93, p<.001
Attentional function (≤7.5)	7.3 (1.5)	5.4 (1.6)	t=12.10, p<.001
Morning fatigue (≥3.2)	1.5 (1.4)	4.8 (2.0)	t=−18.03, p<.001
Evening fatigue (≥5.6)	4.1 (2.2)	6.3 (1.7)	t=−11.09, p<.001
Morning energy (≤6.2)	4.9 (2.5)	3.8 (2.0)	t=4.60, p<.001
Evening energy (≤3.5)	3.8 (2.1)	3.0 (1.8)	t=4.38, p<.001
	% (n)	**% (n)**	
Pain type			X^2=19.05, p<.001
No pain	38.5 (92)	21.3 (34)	0 > 1
Only non-cancer pain	21.3 (51)	32.5 (52)	0 < 1
Only cancer pain	17.2 (41)	12.5 (20)	NS
Both cancer and non-cancer pain	23.0 (55)	33.8 (54)	0 < 1
For patients with pain	**Mean (SD)**	**Mean (SD)**	
Worst pain intensity score	5.4 (2.4)	6.4 (2.7)	t=−2.82, p=.005
Pain interference score	2.2 (2.0)	4.1 (2.6)	t=−6.35, p<.001

Abbreviations: AM = morning, LSCR = Life Stressor Checklist-Revised, NS = not significant, PM = evening, SD = standard deviation

[a]Numbers in parentheses represent clinically meaningful cutoff scores

Table 4.

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

Characteristics (All comparisons done to the Low class)	Both High AM + PM Fatigue (Joint LPA analysis)	Very High AM Fatigue* (LPA analysis)	Very High PM Fatigue* (LPA analysis)
Demographic Characteristics			
Younger age	♦	♦	♦
Being female	♦	♦	♦
Being White			♦
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	♦	♦	♦
Having a diagnosis of anemia or blood disease	♦	♦	
Having a diagnosis of depression	♦	♦	♦
Symptom Characteristics			
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, LPA = latent profile analysis, PM = evening, SCQ = Self-administered Comorbidity Questionnaire

*Lin, Y., Bailey, D. E., Docherty, S. L., Porter, L. S., Cooper, B., Paul, S., Kober, K., Hammer, M. J., Wright, F., Conley, Y., Levine, J., & Miaskowski, C. (2021). Distinct morning and evening fatigue profiles in gastrointestinal cancer during chemotherapy. *BMJ Support Palliat Care*. https://doi.org/10.1136/bmjspcare-2021-002914