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ORIGINAL ARTICLE

Subgroups of patients undergoing chemotherapy with distinct cognitive fatigue and evening physical fatigue profiles

Lisa Morse[1] · Kord M. Kober[1] · Carol Viele[1] · Bruce A. Cooper[1] · Steven M. Paul[1] · Yvette P. Conley[2] · Marilyn Hammer[3] · Jon D. Levine[4] · Christine Miaskowski[1]

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Abstract

Purpose The purpose was to model cognitive fatigue and evening physical fatigue together to determine subgroups of patients with distinct cognitive fatigue AND evening physical fatigue profiles. Once these profiles were identified, differences among the subgroups in demographic and clinical characteristics, co-occurring symptoms, and quality of life outcomes were evaluated.

Methods Oncology patients (n = 1332) completed self-report measures of cognitive fatigue and evening physical fatigue, six times over two cycles of chemotherapy. Latent profile analysis, which combined the two symptom scores, was done to identify subgroups of patients with distinct cognitive fatigue AND evening physical fatigue profiles.

Results Three distinct profiles (i.e., Low [20.5%], Moderate [39.6%], and High [39.6%]) were identified. Compared to the Low class, patients in the High class were younger, female, and more likely to live alone and had a higher comorbidity burden and a lower functional status. In addition, these patients had a higher symptom burden and a poorer quality of life.

Conclusion Based on clinically meaningful cutoff scores, 80% of the patients in this study had moderate to high levels of both cognitive fatigue and evening physical fatigue. In addition, these patients experienced high levels of other common symptoms (e.g., anxiety, depression, sleep disturbance, and pain). These co-occurring symptoms and other modifiable characteristics associated with membership in the Moderate and High classes may be potential targets for individualized symptom management interventions.

Keywords Physical fatigue · Cognitive fatigue · Chemotherapy · Cancer · Latent profile analysis

Introduction

Fatigue occurs in approximately 80% of oncology patients [6]. This symptom decreases patients' adherence with treatments [28] and impairs their quality of life (QOL) [21]. Cancer-related fatigue is defined as "a distressing, persistent, subjective sense of physical, emotional, and/or cognitive tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity and interferes with usual functioning" [6]. This definition emphasizes the multidimensional nature of fatigue.

As noted in one review [15], consensus does not exist on the number of dimensions of fatigue that warrant evaluation. For example, the Fatigue Questionnaire evaluates two dimensions (i.e., physical and mental). In contrast, both the Multidimensional Fatigue Inventory (MFI; i.e., general fatigue, physical fatigue, mental fatigue, reduced motivation, and reduced activity) [55] and the Multidimensional Fatigue Symptom Inventory (i.e., global, somatic, affective, cognitive, and behavioral) [57] evaluate five dimensions. The authors of this review commented that one expert panel endorsed the existence of at least physical and cognitive or mental fatigue in oncology patients [48].

Given the large amount of inter-individual variability in fatigue occurrence [17] and severity [64–68], one needs to

✉ Christine Miaskowski
chris.miaskowski@ucsf.edu

[1] Department of Physiological Nursing, University of California, 2 Koret Way – N631Y, San Francisco, CA 94143-0610, USA

[2] School of Nursing, University of Pittsburgh, Pittsburg, PA, USA

[3] Dana Farber Cancer Institute, Boston, MA, USA

[4] School of Medicine, University of California, San Francisco, CA, USA

consider how to characterize the multiple dimensions of fatigue in oncology patients. As noted by deRaaf and colleagues [15], three possible conceptualizations of fatigue exist (i.e., unidimensional, multidimensional, and multiple symptoms). Based on the results of their systematic review that focused on an evaluation of the "behavior of physical fatigue and mental fatigue in cancer patients" [15], they concluded that physical fatigue and mental fatigue may be separate phenomena.

Two of the studies cited in the review [15] evaluated for changes over time in physical [12] and cognitive [13] fatigue in breast cancer patients receiving adjuvant chemotherapy. Fatigue was assessed at the first, third, and fifth cycles, and at 4 and 12 weeks after the last cycle of chemotherapy using the MF [55]. While physical fatigue increased over the course of chemotherapy and declined following the completion of treatment, cognitive fatigue remained relatively stable over time. While changes over time were evaluated, in the same sample of patients, each dimension of the fatigue experience was analyzed separately.

In a cross-sectional study of long-term survivors of colorectal cancer [58], latent class analysis was used to identify subgroups of survivors with distinct fatigue profiles using the five dimensions of the MFI. Three distinct profiles were identified (i.e., no fatigue and distress [56%], low fatigue and moderate distress [22%], and high fatigue and moderate distress [22%]). Compared to the no fatigue and distress class, the high fatigue and moderate distress class were more likely to be female and overweight, had co-occurring diabetes, and had received radiation therapy. In addition, survivors in the two higher classes were more likely to have comorbid heart disease and higher levels of anxiety and sleep disturbance. Across the three classes, cognitive fatigue scores were low. While this study provides insights into fatigue subtypes, it was cross-sectional and focused on only cancer survivors.

Recent work from our group evaluated for inter-individual differences in and risk factors for physical fatigue, using the Lee Fatigue Scale (LFS) [37], in a sample of patients with heterogeneous types of cancer undergoing chemotherapy [64–68]. Using latent profile analysis (LPA), four subgroups of patients with distinct morning (i.e., Very Low, Low, High, and Very High) [67] and four subgroups with distinct evening (i.e., Low, Moderate, High, and Very High) [64] fatigue profiles were identified. Given that the severity and trajectories of fatigue differed between the morning and evening fatigue, latent classes and different demographic and clinical characteristics were associated with membership in the higher morning and evening fatigue classes, we concluded that diurnal variations in physical fatigue occurred over two cycles of chemotherapy and that morning and evening fatigue were distinct but related symptoms. In terms of cognitive fatigue [4], in the same sample, we used LPA to evaluate for distinct cognitive fatigue profiles using the Attentional Function Index (AFI) [10]. Three subgroups of patients with distinct cognitive fatigue profiles were identified (i.e., Low, Moderate, and High). Patients with moderate and high levels of cognitive fatigue were younger, more likely to be female, and were less likely to be employed.

Given the paucity of research on the relationships among multiple dimensions of the fatigue experience and on the identification of subgroups of patients with distinct cognitive fatigue AND evening physical fatigue profiles, in this study, we modeled cognitive fatigue and evening physical fatigue together to determine subgroups of patients with distinct cognitive fatigue AND evening physical fatigue profiles. Once these profiles were identified, we evaluated for differences among the subgroups in demographic and clinical characteristics, co-occurring symptoms, and QOL outcomes.

Methods

Patients and settings

This longitudinal study is described in detail elsewhere [40, 41]. 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 gave 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.

Instruments

Demographic and clinical characteristics

Patients completed a demographic questionnaire, Karnofsky Performance Status (KPS) scale [31], Alcohol Use Disorders Identification Test (AUDIT) [5], and Self-Administered Comorbidity Questionnaire (SCQ). The SCQ evaluates the occurrence, treatments for, and impact of 13 common medical conditions [51]. A MAX-2 score was calculated for each patient's chemotherapy regimen. This score is a valid and reliable indicator of the toxicity of various chemotherapy regimens [19].

Cognitive fatigue and evening physical fatigue measures

Attentional Function Index assesses an individual's perceived effectiveness in performing daily activities that are supported by attention and working memory [10]. Total scores can be grouped into categories of attentional function (i.e., < 5.0 low function, 5.0 to 7.5 moderate function, and > 7.5 high function) [9].

Lee Fatigue Scale was designed to assess physical fatigue and energy [37]. Total fatigue and energy scores were calculated as the mean of the 13 fatigue items and the 5 energy items, respectively. Higher scores indicate greater fatigue severity and higher levels of energy. Using separate questionnaires, patients rated each item based on how they felt within 30 min of awakening (i.e., morning fatigue and morning energy) and prior to going to bed (i.e., evening fatigue and evening energy). The LFS has established cut-off scores for clinically meaningful levels of fatigue (i.e., ≥ 3.2 for morning fatigue and ≥ 5.6 for evening fatigue) [20] and energy (i.e., ≤ 6.2 for morning energy and ≤ 3.5 for evening energy) [20].

Symptom measures

To assess the severity of common symptoms associated with cancer and its treatment, patients completed Center for Epidemiological Studies-Depression scale (CES-D) [49], Spielberger State-Trait Anxiety Inventories (STAI-S, STAI-T) [56], General Sleep Disturbance Scale (GSDS) [36], and Brief Pain Inventory [11].

QOL measures

QOL was evaluated using generic (i.e., Medical Outcomes Study-Short Form-12 [SF-12] [60]) and disease-specific (i.e., QOL-Patient Version [QOL-PV] [45]) measures. The individual items on the SF-12 were evaluated and the instrument was scored into two components (i.e., physical component summary [PCS] and mental component summary [MCS] scores). QOL-PV measures four dimensions of QOL (i.e., physical, psychological, social, and spiritual well-being), as well as a total QOL score. For both measures, higher scores indicate a better QOL.

Study procedures

The study was approved by the Committee on Human Research at the University of California, San Francisco, and by the Institutional Review Board at each of the study sites. Written informed consent was obtained from all patients. Patients completed questionnaires in their homes, a total of six times over two cycles of chemotherapy. Medical records were reviewed for disease and treatment information.

Data analysis

LPA was used to identify subgroups of patients with distinct cognitive fatigue AND evening physical fatigue profiles. Using Mplus version 8.4 [43], this LPA was done with the combined set of variables over time (i.e., using the AFI AND evening LFS scores obtained during the six assessments in a single LPA). This approach provides a profile description of these two symptoms with parallel 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., evening LFS and AFI 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 [30].

Data were analyzed using SPSS version 27 (IBM Corporation, Armonk, NY). Differences among the cognitive fatigue AND evening physical fatigue classes in demographic, clinical, and symptom characteristics, and QOL were evaluated using parametric and nonparametric tests. Bonferroni corrected p-value of < 0.017 was considered statistically significant for the pairwise contrasts.

Results

Latent class solution

Three-class solution was selected because the Bayesian Information Criterion (BIC) for that solution was lower than the BIC for the 2-class solution. In addition, the Vuong-Lo-Mendell-Rubin likelihood ratio test was significant for the three-class solution, indicating that three classes fit the data better than two classes (Table 1). This approach allowed for the identification of three groups of patients with distinct evening physical fatigue AND cognitive fatigue profiles.

Cognitive fatigue AND evening physical fatigue classes were labeled as Low cognitive fatigue and Low evening physical fatigue (i.e., Low), Moderate cognitive fatigue and Moderate evening physical fatigue (i.e., Moderate), and High cognitive fatigue and high evening physical fatigue (i.e., High) based on clinically meaningful cut-off scores for cognitive fatigue and for evening

Table 1 Evening physical fatigue and cognitive fatigue over six assessments — latent profile solutions and fit indices for one through four class solutions

Model	LL	AIC	BIC	Entropy	VLMR
1 Class	−24,456.76	49,029.52	49,330.80	n/a	n/a
2 Class	−23,838.86	47,819.73	48,188.53	.78	1235.80+
3 Class[a]	−23,559.85	47,287.71	47,724.04	.77	558.02+
4 Class	−23,389.03	46,972.06	47,457.92	.76	341.65 [ns]

Baseline LL is not applicable for the one class solution

+p < .00005

[a]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. While the BIC was lower for the 4-class solution, the VLMR was not significant for the 4-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

physical fatigue. As shown in Fig. 1, the trajectories for the two symptoms that were modeled together were relatively similar across the three latent classes. For the Low (20.5%), Moderate (39.6%), and High (39.9%) classes, cognitive fatigue and evening physical fatigue scores increased slightly at the second and fifth assessments (i.e., assessments following the administration of chemotherapy).

Demographic and clinical characteristics

Significant differences were found among the latent classes for many of the demographic and clinical characteristics (Table 2). Compared to the Low class, the other two classes were significantly younger, more likely to be female, more likely to be White, less likely to be Black, less likely to exercise on a regular basis, more likely to be diagnosed with breast cancer, less likely to be diagnosed with gastrointestinal cancer, more likely to self-report a diagnosis of depression, and more likely to have received previous cancer treatments.

Compared to the other two classes, the High class was less likely to be married/partnered, less likely to be employed, and more likely to self-report a diagnosis of back pain and had a higher number of comorbidities. Compared to the Low class, the High class was more likely to live alone, more likely to have child care responsibilities, and more likely to report a past or current history of smoking; had received a higher number of previous cancer treatments; and had a higher MAX-2 score.

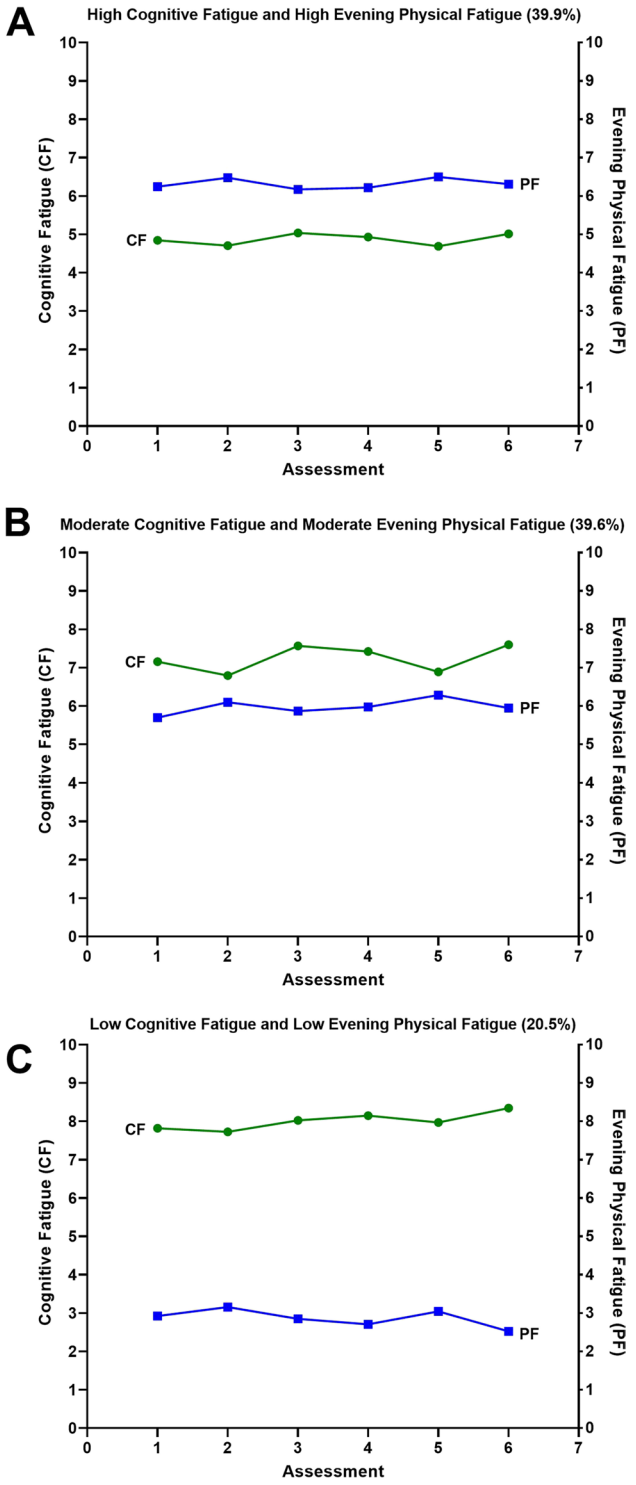

Fig. 1 Changes in cognitive fatigue (CF, left y-axis; lower scores indicate higher levels of cognitive fatigue) and evening physical fatigue (PF, right y-axis; higher scores indicate higher levels of physical fatigue) scores over two cycles of chemotherapy for subgroups of oncology patients with High Cognitive Fatigue and High Evening Physical Fatigue (panel **A**), Moderate Cognitive Fatigue and Moderate Evening Physical Fatigue (panel **B**) and Low Cognitive Fatigue and Low Evening Physical Fatigue (panel **C**)

Table 2 Differences in demographic and clinical characteristics among the cognitive fatigue and evening physical fatigue subgroups at enrollment

Characteristic	Low cognitive fatigue and low evening physical fatigue (0) 20.5% (n = 273)	Moderate cognitive fatigue and moderate evening physical fatigue (1) 39.6% (n = 528)	High cognitive fatigue and high evening physical fatigue (2) 39.9% (n = 531)	Statistics
	Mean (SD)	Mean (SD)	Mean (SD)	
Age (years)	60.3 (11.7)	56.5 (11.8)	56.1 (12.9)	$F = 11.47$, $p < 0.001$ 0 > 1 and 2
Education (years)	15.9 (3.1)	16.6 (3.1)	16.0 (2.9)	$F = 6.31$, $p = 0.002$ 1 > 0 and 2
Body mass index (kg/m^2)	26.1 (5.4)	26.2 (5.5)	26.2 (5.9)	$F = 0.03$, $p = 0.969$
Karnofsky Performance Status score	86.2 (11.1)	82.0 (11.4)	74.8 (12.2)	$F = 95.23$, $p < 0.001$ 0 > 1 > 2
Number of comorbidities out of 13	2.2 (1.4)	2.2 (1.3)	2.7 (1.5)	$F = 16.11$, $p < 0.001$ 0 and 1 < 2
SCQ score out of 13 conditions	4.6 (2.8)	5.1 (2.9)	6.3 (3.5)	$F = 32.03$, $p < 0.001$ 0 < 1 and 2
AUDIT score	2.9 (2.5)	2.9 (2.2)	3.1 (2.8)	$F = 0.89$, $p = 0.412$
Hemoglobin	11.6 (1.5)	11.6 (1.5)	11.5 (1.4)	$F = 1.86$, $p = 0.156$
Hematocrit	34.9 (4.1)	34.7 (4.2)	34.2 (4.0)	$F = 3.23$, $p = 0.040$ no significant pairwise contrasts
Time since cancer diagnosis (years)	1.7 (3.2)	2.1 (4.1)	2.0 (4.0)	KW, $p = 0.347$
Median time since diagnosis (years)	0.43	0.40	0.45	
Number of prior cancer treatments	1.4 (1.4)	1.6 (1.5)	1.7 (1.6)	$F = 3.54$, $p = 0.029$ 0 < 2
Number of metastatic sites including lymph node involvement	1.3 (1.2)	1.2 (1.2)	1.3 (1.3)	$F = 0.48$, $p = 0.620$
Number of metastatic sites excluding lymph node involvement	0.8 (1.1)	0.8 (1.0)	0.8 (1	$F = 0.30$, $p = 0.738$
MAX-2 score	0.16 (0.08)	0.18 (0.08)	0.18 (0.08)	$F = 3.81$, $p = 0.022$ 0 < 2
	% (n)	% (n)	% (n)	
Female	68.9 (188)	77.1 (407)	83.4 (442)	$\chi^2 = 22.46$, $p < 0.001$ 0 < 1 and 2, 1 < 2
Ethnicity				$\chi^2 = 24.39$, $p < 0.001$
White	58.9 (159)	74.2 (386)	70.3 (369)	0 < 1 and 2
Asian or Pacific Islander	16.3 (44)	11.5 (60)	11.6 (61)	NS
Black	11.9 (32)	5.8 (30)	6.3 (33)	0 > 1 and 2
Hispanic, Mixed, or Other	13.0 (35)	8.5 (44)	11.8 (62)	NS
Married or partnered (% yes)	69.3 (187)	69.0 (359)	57.6 (301)	$\chi^2 = 18.38$, $p < 0.001$ 0 and 1 > 2
Lives alone (% yes)	16.3 (44)	19.8 (103)	25.9 (136)	$\chi^2 = 11.19$, $p = 0.004$ 0 < 2
Child care responsibilities (% yes)	15.9 (43)	23.1 (118)	24.5 (128)	$\chi^2 = 8.02$, $p = 0.018$ 0 < 2
Care of adult responsibilities (% yes)	7.5 (19)	6.5 (31)	9.6 (46)	$\chi^2 = 3.22$, $p = 0.200$
Currently employed (% yes)	38.7 (104)	42.5 (222)	26.0 (137)	$\chi^2 = 33.30$, $p < 0.001$ 0 and 1 > 2

Table 2 (continued)

Characteristic	Low cognitive fatigue and low evening physical fatigue (0) 20.5% (n = 273)	Moderate cognitive fatigue and moderate evening physical fatigue (1) 39.6% (n = 528)	High cognitive fatigue and high evening physical fatigue (2) 39.9% (n = 531)	Statistics
	Mean (SD)	Mean (SD)	Mean (SD)	
Annual household income				
< $30,000 +	17.4 (40)	11.1 (53)	26.0 (126)	KW, $p < 0.001$
$30,000 to < $70,000	25.2 (58)	16.8 (80)	23.5 (114)	0 and 2 < 1
$70,000 to < $100,000	17.8 (41)	19.3 (92)	14.2 (69)	
> $100,000	39.6 (91)	52.8 (252)	36.3 (176)	
Specific comorbidities (% yes)				
Heart disease	7.3 (20)	3.0 (16)	7.3 (39)	$\chi^2 = 11.13$, $p = 0.004$ 0 and 2 > 1
High blood pressure	34.8 (95)	29.5 (156)	28.2 (150)	$\chi^2 = 3.81$, $p = 0.149$
Lung disease	10.6 (29)	9.7 (51)	13.4 (71)	$\chi^2 = 3.80$, $p = 0.149$
Diabetes	7.7 (21)	9.1 (48)	9.4 (50)	$\chi^2 = 0.69$, $p = 0.710$
Ulcer or stomach disease	4.4 (12)	3.8 (20)	6.2 (33)	$\chi^2 = 3.53$, $p = 0.171$
Kidney disease	1.8 (5)	1.1 (6)	1.5 (8)	$\chi^2 = 0.66$, $p = 0.719$
Liver disease	7.0 (19)	7.6 (40)	5.1 (27)	$\chi^2 = 2.86$, $p = 0.239$
Anemia or blood disease	9.5 (26)	11.6 (61)	14.5 (77)	$\chi^2 = 4.60$, $p = 0.100$
Depression	6.6 (18)	12.9 (68)	32.2 (171)	$\chi^2 = 99.06$, $p < 0.001$ 0 < 1 and 2, 1 < 2
Osteoarthritis	9.9 (27)	11.9 (63)	13.2 (70)	$\chi^2 = 1.86$, $p = 0.3960$
Back pain	20.9 (57)	19.9 (105)	34.1 (181)	$\chi^2 = 32.18$, $p < 0.001$ 0 and 1 < 2
Rheumatoid arthritis	2.6 (7)	2.7 (14)	3.8 (20)	$\chi^2 = 1.41$, $p = 0.495$
Exercise on a regular basis (% yes)	75.0 (201)	73.4 (383)	66.0 (338)	$\chi^2 = 9.63$, $p < 0.008$ 0 and 1 > 2
Smoking, current or history of (% yes)	29.7 (80)	34.2 (179)	39.2 (203)	$\chi^2 = 7.34$, $p = 0.025$ 0 < 2
Cancer diagnosis				$\chi^2 = 29.21$, $p < 0.001$
Breast	31.1 (85)	43.4 (229)	42.2 (224)	0 < 1 and 2
Gastrointestinal	43.2 (118)	28.2 (149)	26.0 (138)	0 > 1 and 2
Gynecological	14.7 (40)	16.9 (89)	19.4 (103)	NS
Lung	11.0 (30)	11.6 (61)	12.4 (66)	NS
Type of prior cancer treatment				$\chi^2 = 19.06$, $p = 0.004$
No prior treatment	32.8 (86)	23.2 (119)	22.8 (119)	0 > 1 and 2
Only surgery, CTX, or RT	34.7 (91)	45.5 (234)	42.0 (219)	0 < 1
Surgery & CTX, or Surgery & RT, or CTX & RT	22.1 (58)	19.5 (100)	19.2 (100)	NS
Surgery & CTX & RT	10.3 (27)	11.9 (61)	15.9 (83)	NS
Cycle length				
14 day cycle	47.6 (130)	41.7 (219)	39.1 (204)	$\chi^2 = 5.84$, $p = 0.212$
21 day cycle	45.8 (125)	50.5 (265)	53.8 (281)	
28 day cycle	6.6 (18)	7.8 (41)	7.1 (37)	
Emetogenicity of the CTX regimen				
Minimal/low	19.0 (52)	18.7 (98)	20.7 (108)	KW, $p = 0.758$
Moderate	64.5 (176)	61.9 (325)	58.3 (305)	
High	16.5 (45)	19.4 (102)	21.0 (110)	

Table 2 (continued)

Characteristic	Low cognitive fatigue and low evening physical fatigue (0) 20.5% (n = 273) Mean (SD)	Moderate cognitive fatigue and moderate evening physical fatigue (1) 39.6% (n = 528) Mean (SD)	High cognitive fatigue and high evening physical fatigue (2) 39.9% (n = 531) Mean (SD)	Statistics
Antiemetic regimen				
None	7.1 (19)	7.0 (36)	7.3 (37)	$\chi^2 = 3.25$, p = 0.777
Steroid alone or serotonin antagonist alone	21.4 (57)	20.4 (105)	20.2 (103)	
Serotonin antagonist and steroid	50.8 (135)	47.6 (245)	46.2 (235)	
NK-1 receptor antagonist and two other antiemetics	20.7 (55)	25.0 (129)	26.3 (134)	

Abbreviations: *AUDIT*, Alcohol Use Disorders Identification Test; *CF*, cognitive function; *CTX*, chemotherapy; *kg*, kilograms; *KW*, Kruskal Wallis; m^2, meter squared; *NK*, neurokinin; *PF*, physical function; *RT*, radiation therapy; *SCQ*, Self-Administered Comorbidity Questionnaire; *SD*, standard deviation

+Reference group

Compared to the other two classes, the Moderate class had more years of education and a higher annual household income. Among the three classes, KPS scores followed the expected pattern (Low > Moderate > High).

Symptom severity

For trait anxiety, state anxiety, depressive symptoms, morning fatigue, evening fatigue, and sleep disturbance, the scores followed the expected pattern (i.e., Low < Moderate < High). In terms of evening energy and cognitive fatigue, the scores followed the expected pattern (i.e., Low > Moderate > High; Table 3). Compared to the Low and Moderate classes, the High class had lower evening energy scores. In terms of types of pain, the proportion of patients who reported no pain was in the expected direction (i.e., Low > Moderate > High). Compared to the other two classes, a higher percentage of patients in the High class reported the occurrence of both cancer and non-cancer pain and higher worst pain intensity scores. Pain interference scores followed a similar pattern to other symptoms (i.e., Low < Moderate < High).

Differences in QOL

For the physical functioning, role functioning, bodily pain, vitality, social functioning, mental health, and for the PCS and MCS, SF-12 scores followed the expected pattern (i.e., Low > Moderate > High). For general health and role emotional subscales, compared to the other two classes, patients in the High class reported lower scores (Table 4). For the physical well-being, psychological well-being, social well-being subscales, and total QOL-PV scale, scores followed the expected pattern (i.e., Low > Moderate > High). For spiritual well-being, compared to the Low class, the High class reported lower scores.

Discussion

This study is the first to use LPA to identify subgroups of oncology patients with distinct cognitive fatigue AND evening physical fatigue profiles over two cycles of chemotherapy. While our previous LPAs found three distinct profiles for cognitive fatigue [4] and four distinct profiles for evening physical fatigue [64], when these two dimensions of fatigue were modeled together, three distinct profiles were identified. Consistent with previous reports [6, 7, 24], based on the clinically meaningful cutoff scores for these two symptoms, 80% of our patients were categorized in either the Moderate or High classes.

Comparison of the trajectories of the cognitive fatigue and evening physical fatigue scores among the latent classes suggests that when the two symptoms are modeled together, both scores fluctuate in a similar pattern regardless of class assignment. Consistent with previous reports of the individual symptoms from our group [4, 64] and others [12–14], both types of fatigue increase following the administration of chemotherapy and then decline prior to the next infusion.

In their systematic review [15], de Raaf and colleagues suggested that if cognitive fatigue and physical fatigue were different symptoms within the multiple symptom concept of fatigue (versus fatigue as a multidimensional concept

Table 3 Differences in symptom severity scores among the cognitive fatigue and evening physical fatigue subgroups at enrollment

Symptoms*	Low cognitive fatigue and low evening physical fatigue (0) 20.5% (n = 273)	Moderate cognitive fatigue and moderate evening physical fatigue (1) 39.6% (n = 528)	High cognitive fatigue and high evening physical fatigue (2) 39.9% (n = 531)	Statistics
	Mean (SD)	Mean (SD)	Mean (SD)	
Trait anxiety (≥ 31.8)	29.1 (7.7)	31.9 (8.0)	41.7 (10.5)	F = 223.89, p < 0.001 0 < 1 < 2
State anxiety (≥ 32.2)	27.7 (9.2)	30.7 (10.1)	40.3 (13.0)	F = 145.82, p < 0.001 0 < 1 < 2
Depressive symptoms (≥ 16)	7.1 (6.0)	9.8 (7.1)	19.0 (10.2)	F = 242.16, p < 0.001 0 < 1 < 2
Morning fatigue (≥ 3.2)	1.4 (1.5)	2.7 (1.9)	4.5 (2.1)	F = 256.40, p < 0.001 0 < 1 < 2
Evening fatigue (≥ 5.6)	2.8 (1.7)	5.7 (1.7)	6.2 (1.8)	F = 363.56, p < 0.001 0 < 1 < 2
Morning energy (≤ 6.2)	4.9 (2.7)	4.7 (2.2)	3.8 (1.9)	F = 33.19, p < 0.001 0 and 1 > 2
Evening energy (≤ 3.5)	4.2 (2.2)	3.6 (2.0)	3.2 (2.0)	F = 21.98, p < 0.001 0 > 1 > 2
Cognitive function (< 5 = low, 5 to 7.5 = moderate, > 7.5 = high)	7.9 (1.4)	7.2 (1.2)	4.8 (1.2)	F = 708.99, p < 0.001 0 > 1 > 2
Sleep disturbance (≥ 43)	38.2 (16.6)	49.5 (18.2)	63.0 (18.1)	F = 178.79, p < 0.001 0 < 1 < 2
	% (n)	% (n)	% (n)	
Pain type				$\chi^2 = 86.45$, p < 0.001
No pain	39.8 (107)	29.8 (155)	18.5 (96)	0 > 1 > 2
Only non-cancer pain	20.1 (54)	16.7 (87)	12.7 (66)	0 < 2
Only cancer pain	22.3 (60)	28.8 (150)	25.9 (134)	NS
Both cancer and non-cancer pain	17.8 (48)	24.6 (128)	42.9 (222)	0 and 1 < 2
For patients with pain	Mean (SD)	Mean (SD)	Mean (SD)	
Worst pain intensity score	5.4 (2.6)	5.8 (2.5)	6.5 (2.4)	F = 12.82, p < 0.001 0 and 1 < 2
Pain interference score	1.7 (1.8)	2.6 (2.2)	4.0 (2.6)	F = 63.79, p < 0.001 0 < 1 < 2

*Numbers in parentheses indicate clinically meaningful cutpoints for symptom severity

Abbreviations: *PM*, evening; *SD*, standard deviation

that is experienced in different ways), these two symptoms would differ in intensity in different types of cancer; differ in intensity across courses of treatment; have different characteristics associated with each symptom; and have different responses to interventions. Unfortunately, like the findings from the systematic review, no definitive conclusions can be made regarding this question. While we found three groups of patients with distinct cognitive fatigue and evening physical fatigue profiles, the severity of the pairs of symptoms and their changes over time remained relatively similar across the three groups. However, as shown in Table 5, some of the characteristics associated with the Moderate and High groups were different. One criterion that was not listed in this review was whether the mechanisms that underlie the single symptoms are similar or different. Information on the common and distinct aspects of cognitive and physical fatigue, including common and distinct underlying mechanisms, are essential in order to answer the multiple symptom versus multidimensional symptom question.

One of our study purposes was to identify demographic, clinical, and symptom characteristics that were associated with a higher symptom burden (Table 5). Compared to the Low class, some of characteristics associated with membership in the Moderate and High classes were common while others were distinct. For example, compared to the Low class, the other two classes shared the following characteristics: younger age, more likely to be female, more likely to be White, and less likely to be Black. While findings regarding age differences in cognitive and physical fatigue are inconsistent [3, 25], for both symptoms, potential explanations for

Table 4 Differences in quality of life outcomes among the cognitive fatigue and evening physical fatigue subgroups at enrollment

Characteristic	Low cognitive fatigue and low evening physical fatigue (0) 20.5% (n = 273) Mean (SD)	Moderate cognitive fatigue and moderate evening physical fatigue (1) 39.6% (n = 528) Mean (SD)	High cognitive fatigue and high evening physical fatigue (2) 39.9% (n = 531) Mean (SD)	Statistics
Medical Outcomes Study — Short Form-12				
Physical functioning	66.2 (33.7)	57.8 (33.7)	39.8 (31.3)	F = 66.50, p < 0.001 0 > 1 > 2
Role physical	69.7 (27.2)	59.4 (27.3)	36.0 (24.0)	F = 177.82, p < 0.001 0 > 1 > 2
Bodily pain	87.4 (20.8)	81.6 (24.0)	63.4 (31.4)	F = 92.84, p < 0.001 0 > 1 > 2
General health	70.8 (23.6)	66.6 (26.9)	54.1 (29.2)	F = 42.64, p < 0.001 0 and 1 > 2
Vitality	64.5 (22.0)	49.5 (24.5)	31.2 (23.9)	F = 185.28, p < 0.001 0 > 1 > 2
Social functioning	83.0 (23.7)	73.6 (27.4)	51.8 (30.4)	F = 132.60, p < 0.001 0 > 1 > 2
Role emotional	86.2 (21.2)	85.0 (21.9)	60.4 (28.3)	F = 160.14, p < 0.001 0 and 1 > 2
Mental health	82.2 (17.2)	77.3 (16.3)	60.9 (21.7)	F = 149.15, p < 0.001 0 > 1 > 2
Physical component summary score	45.9 (9.9)	42.8 (10.0)	37.3 (10.1)	F = 70.24, p < 0.001 0 > 1 > 2
Mental component summary score	54.6 (8.0)	52.2 (8.0)	42.8 (10.8)	F = 184.44, p < 0.001 0 > 1 > 2
Multidimensional Quality of Life Scale — Cancer				
Physical well-being	7.9 (1.5)	6.9 (1.6)	5.7 (1.7)	F = 195.89, p < 0.001 0 > 1 > 2
Psychological well-being	6.8 (1.7)	5.8 (1.6)	4.5 (1.6)	F = 196.06, p < 0.001 0 > 1 > 2
Social well-being	7.1 (1.8)	6.0 (1.8)	4.7 (1.8)	F = 162.30, p < 0.001 0 > 1 > 2
Spiritual well-being	5.8 (2.2)	5.4 (2.1)	5.3 (2.0)	F = 4.74, p = 0.009 0 > 2
Total quality of life score	6.9 (1.2)	6.0 (1.2)	4.9 (1.3)	F = 249.38, p < 0.001 0 > 1 > 2

Abbreviations: *CF*, cognitive function; *PF*, physical function; *SD*, standard deviation

the association with younger age include that older patients may be given lower doses of chemotherapy [61]; age-related changes in inflammatory responses [7]; and/or a "response shift" occurs in the symptom perceptions of older patients [22]. Another potential explanation is the emerging evidence that suggests that younger age is associated higher rates of social isolation [44]. In addition, recent evidence suggests that compensatory neural changes may occur in older adults that offset cognitive fatigue [16].

Findings regarding gender differences in cognitive fatigue and physical fatigue are inconclusive [3]. These inconsistencies may be related to the gender distribution of patients in previous studies. Future studies need to evaluate for gender differences in these two symptoms, in cancers with an equal gender distribution (e.g., lung). Given the paucity of research on the association between ethnicity and either symptom, direct comparisons with our findings cannot be made.

A larger number of unique characteristics were associated with membership in the High class (Table 5). Consistent with previous studies of physical fatigue [64, 66], patients who were not married or partnered, were living alone, had child care responsibilities, and did not exercise on a regular basis were in the High class. It is readily apparent why patients with the additional responsibilities of child care would be classified in the High class. A plausible explanation for the associations between marital status and living arrangements and membership in the High class is the recent findings that perceptions of lack of social support and loneliness are associated with higher

Table 5 Characteristics associated with membership in the moderate and high cognitive fatigue and evening physical fatigue groups

Characteristic[a]	Moderate cognitive fatigue and moderate evening physical fatigue	High cognitive fatigue and high evening physical fatigue
Demographic characteristics		
Younger age	■	■
Higher education	■	
More likely to be female	■	■
More likely to be White	■	■
Less likely to be Black	■	■
Less likely to be married/partnered		■
More likely to live alone		■
More likely to have child care responsibilities		■
Less likely to be employed		■
More likely to have a higher annual income	■	
Less likely to exercise on a regular basis		■
More likely to have a past or current history of smoking		■
Clinical characteristics		
Lower functional status	■	■
Higher number of comorbidities		■
Higher comorbidity burden	■	■
Higher number of cancer treatments		■
Higher MAX-2 score		■
Less likely to self-report heart disease	■	
More likely to self-report depression	■	■
More likely to self-report back pain		■
More likely to have breast cancer	■	■
Less likely to have gastrointestinal cancer	■	■
More likely to have had prior cancer treatments	■	■
Symptom characteristics		
Higher trait anxiety	■	■
Higher state anxiety	■	■
Higher depressive symptoms	■	■
Higher morning physical fatigue	■	■
Higher evening physical fatigue	■	■
Lower morning energy		■
Lower evening energy	■	■
Higher cognitive fatigue	■	■
Higher sleep disturbance	■	■
Lower occurrence rate of no pain	■	■
Higher occurrence rate of both cancer and noncancer pain		■
Higher worst pain intensity		■
Higher pain interference	■	■

[a]Comparisons done with the low cognitive fatigue and low evening physical fatigue group

levels of cancer-related fatigue [47, 53]. Finally, the findings regarding exercise are consistent with meta-analyses that demonstrated the beneficial effects of exercise in reducing cancer-related fatigue [8, 32]. Future studies should incorporate measures of loneliness, social isolation, and social support to evaluate these associations.

In terms of clinical characteristics, compared to the Low class, the other two classes had a higher comorbidity burden and a lower functional status, and were more likely to have breast cancer, were less likely to have gastrointestinal cancer, were more likely to have received prior cancer treatments, and were more likely to self-report depression. Previous studies of oncology patients found that both symptoms are

associated with a higher comorbidity burden [64] and poorer functional status [64]. As noted in one review [69], the prevalence of cancer-related fatigue increases as the number of comorbid conditions increases. A potential explanation for this finding is that the fatigue associated with various chronic conditions may share similar underlying mechanisms [39]. In addition, the occurrence of multiple chronic conditions may potentiate symptom severity in a synergistic manner [27].

In terms of differences in the occurrence of cognitive and physical fatigue among patients with different types of cancer, comparisons are difficult because of differences in the measures used and the timing of the measures. In one study that controlled for age and sex in their analysis [54], the highest prevalence rates for fatigue were found in patients with gall bladder cancer. Findings from a study, which used a multidimensional fatigue inventory to assess physical, cognitive, and emotional fatigue in patients with fifteen different types of cancer [52], suggest that all three types of fatigue were lowest in patients with breast cancer.

In terms of the unique clinical characteristics associated with membership in the High class, these patients reported a higher number of comorbidities and a higher number of previous cancer treatments, were receiving a more toxic chemotherapy regimen, and were more likely to have back pain. All of these characteristics may potentiate cognitive fatigue and physical fatigue in a synergistic manner [27].

This suggestion of synergistic interactions among co-occurring symptoms is supported by the differences in symptom severity scores among the three classes. For the majority of the symptoms, the severity scores increased in a stepwise fashion. Equally important, all of the symptom severity scores for the High class were above the clinically meaningful cutpoints. While some evidence suggests that pain, fatigue, sleep disturbance, cognitive dysfunction, and depression occur as a psychoneurological symptom cluster and have shared biological mechanisms [33], additional research is warranted to determine the common and unique mechanisms that contribute to a higher symptom burden.

Less is known about the relationship between anxiety and fatigue. Our findings are consistent with previous reports that found that higher rates of trait anxiety were associated with higher levels of fatigue in patients with breast cancer undergoing chemotherapy [62] and in cancer survivors [29, 47, 59]. One potential explanation is that higher levels of anxiety cause dysregulation of the hypothalamic–pituitary–adrenal axis, which may increase cytokine production and associated increases in both symptoms [7].

For the majority of the QOL outcomes, the scores decreased in a stepwise fashion. As noted in two reviews [1, 50], this association is well established. It stands to reason that patients who are not able to engage fully in their daily activities due to both cognitive and physical fatigue would experience decrements in QOL. These decreases were found in both the general and disease-specific measures of QOL. In fact, the PCS and MCS scores for the High class were below the normative scores for the US population.

Several limitations warrant consideration. While a total of six assessments were done over two cycles of chemotherapy, patients were not assessed prior to the initiation of chemotherapy. Second, our assessment of cognitive function was limited to a self-report measure that primarily evaluates attention and executive function. Third, the findings related to ethnicity need to be interpreted with caution given the relatively small sample sizes for the different ethnic groups. However, this large representative sample of oncology patients undergoing chemotherapy, the evaluation of both cognitive fatigue and evening physical fatigue across two cycles of chemotherapy, and the use of LPA to identify risk factors associated with cognitive fatigue AND evening physical fatigue are major strengths of this study.

The phenotypic characteristics associated with membership in the High class can be used to identify high-risk patients. The identification of nonmodifiable (e.g., age and gender) and modifiable (e.g., childcare responsibilities, depressive symptoms, sleep disturbance, and lack of regular exercise) risk factors allows clinicians to tailor interventions for specific patients. For example, a growing body of evidence suggests that exercise can decrease cognitive and physical fatigue [35, 42]. In addition, behavioral interventions to improve sleep may reduce both cognitive and physical fatigue. Equally important, programs that offer support to patients with childcare responsibilities and improve the perception of social connection may benefit patients with both types of fatigue.

Given that pre-treatment fatigue was found to predict post-treatment fatigue [38, 46], future studies should include measures of pre-treatment fatigue. In addition, given the diurnal variations in fatigue severity, future studies need to determine if the same profiles and risk factors are identified when morning physical fatigue and cognitive fatigue are modeled together in the same LPA. To determine whether cognitive fatigue and evening physical fatigue are multiple symptom or a multidimensional concept, future research should investigate whether the mechanisms that underlie the single symptoms are similar or different. In addition, studies are needed that use objective measures of cognitive and physical fatigue to determine if latent class membership differs depending on the assessment method used and the domains of cognitive and physical fatigue that are evaluated. Finally, given the compelling evidence that childhood adversity [23, 34, 63], coping styles [18, 26], and perceptions of social support [2] influence the severity of fatigue, future studies should include measures of psychosocial and behavioral risk factors for both cognitive and physical fatigue.

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Data availability Data will be provided to the publisher after they obtain a material transfer agreement from the University of California, San Francisco.

Declarations

Ethics approval This study was approved by the Committee on Human Research at the University of California.

Consent to participate This study was exempted from written informed consent.

Consent for publication All of the authors approved the final paper for publication.

Conflict of interest The authors declare no competing interests.

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