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Co-occurrence of Physical and Cognitive Impairments Are Associated With a Higher Symptom Burden in Oncology Patients

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Co-occurrence of Physical and Cognitive Impairments Are Associated With a Higher Symptom Burden in Oncology Patients

by

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Co-Occurrence of Physical and Cognitive Impairments Are Associated With a Higher Symptom Burden in Oncology Patients

Dianne Sorrera

ABSTRACT

Objectives: Physical and cognitive function are two of the most important patient-reported outcomes. In oncology patients receiving chemotherapy (n = 1331), purposes were to identify subgroups of patients with distinct joint physical and cognitive function profiles and evaluate for differences in demographic and clinical characteristics, severity of common symptoms, and quality of life outcomes.

Data sources: Measures of physical and cognitive functions were obtained six times over two cycles of chemotherapy. All of the other measures were done prior to the second or third cycle of chemotherapy. Latent profile analysis was done to identify the distinct joint physical and cognitive function profiles. Differences among the profiles were evaluated using parametric and non-parametric tests.

Results: Five distinct profiles were identified (i.e., Very Low Physical and Low Cognitive Function (18.4%; Both Low), Low Physical and High Cognitive Function (19.8%), Moderate Physical and Low Cognitive Function (26.7%), Changing Physical and Cognitive Function (5.4%), and Normal Physical and Cognitive Function (29.7%)). Patients in the Both Low class had the highest symptom burden and the poorest quality of life.

Conclusion: Over 70% of the sample had moderate to severe decrements in one or both of these extremely important patient outcomes. Clinicians need to assess for both physical and cognitive function using simple subjective and objective measures.

Key words: anxiety; cancer; cognitive function; cognitive impairment; depression; fatigue; pain, patient reported outcomes; physical function; sleep disturbance

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LIST OF ABBREVIATIONS

ADL: Activities of daily living

AFI: Attentional Function Index

AUDIT: Alcohol Use Disorders Identification Test

BIC: Bayesian Information Criterion

BPI: Brief Pain Inventory

CES-D: Center for Epidemiological Studies-Depression scale

CF: Cognitive function

CFS: Clinical Frailty Scale

CRCI: Cancer-related cognitive impairment

GSDS: General Sleep Disturbance Scale

IADL: Instrumental activities of daily living

KPS: Karnofsky Performance Status

LFS: Lee Fatigue Scale

LPA: Latent profile analysis

MCS: Mental component summary

MQOLS-PV: Multidimensional Quality of Life Scale Cancer-Patient Version

NRS: Numerical rating scale

PCS: Physical component summary

PF: Physical function

PRO: Patient reported outcomes

QOL: Quality of life

SCQ: Self-Administered Comorbidity Questionnaire

SF-12: Medical Outcomes Study-Short Form 12

STAI: Spielberger State-Trait Anxiety Inventories

VLMR: Vuong-Lo-Mendell-Rubin

INTRODUCTION

Two of the most important patient-reported outcomes (PROs) for patients undergoing cancer treatment are the maintenance of physical function (PF) and cognitive function (CF). In fact, in a study of older patients with cancer,[1] over 70% stated that they would not receive a treatment that resulted in functional impairment even if it improved survival. While a growing body of evidence suggests that the co-occurrence of declines in PF and CF are linked,[2-4] in most studies these two outcomes are evaluated independently. In addition, most of the evaluations of changes in PF and CF were done in older adults with[5-11] and without[12-15] a cancer diagnosis.

Functional status refers to an individual's ability to perform normal activities required to maintain adequate health and meet basic needs.[16] While the exact prevalence of functional decline is difficult to determine due to a lack of standardized assessments, in a meta-analysis of studies that evaluated impairments in activities of daily living (ADLs) in adults with cancer,[17] 36.7% and 54.6% of the patients reported impairments in basic and instrumental ADLs. The most frequently effected basic ADLs were personal hygiene, walking, and transfers. The most frequently effected instrumental ADLs were housework, shopping, and transportation. Studies summarized in this review included primarily older adults and both inpatients and outpatients receiving cancer treatment.

In terms of risk factors for functional decline in patients receiving cancer treatment, in a recent systematic review focused on older adults,[18] functional decline ranged from 6% to 90%. The most common characteristics associated with functional decline were older age, poorer performance status, progression of disease, as well as the presence of pain, anemia, and poor nutritional status. These findings suggest a large amount of inter-individual variability in PF in patients receiving cancer treatment. Additional studies are warranted because as noted in a recent review of functional decline in oncology patients,[19] ongoing evaluation of PF in oncology patients is extremely important given the fact that functional decline is associated with a higher

comorbidity burden; increases in caregiver needs, impairments in quality of life (QOL); and increased mortality.

In terms of changes in CF, most studies focused on an evaluation of cancer-related cognitive impairment (CRCI) that occurs in approximately 75% of patients undergoing cancer treatment.[20] This change in CF is characterized by decrements in memory, attention, processing speed, and executive function.[21] As noted in one review,[22] the risk factors for cognitive decline in oncology patients are likely to be multifactorial and may differ based on whether subjective or objective measures are used to assess for CRCI. Possible risk factors include genetic predisposition and age, as well as the co-occurrence of anxiety, depression, and/or fatigue. Similar to declines in PF, a large amount of inter-individual variability exists in declines in CF associated with cancer treatment. In addition given that declines in CF are associated with decrements in personal relationships,[23] ability to work,[24] ability to perform routine activities,[23] and overall QOL,[25] additional research on changes in CF are warranted.

As noted above, research on the inter-relationships between PF and CF has increased because of the growing body of evidence that suggests that physical activity improves CF.[12-15, 26-32] While the majority of these studies evaluated PF and CF separately, two studies evaluate for these two outcomes in the same sample of oncology patients.[7, 11] In the first study,[11] the co-occurrence of decrements in CF and PF were evaluated in older adults receiving chemotherapy. Using latent profile analysis (LPA), three subgroups of patients with distinct PF and CF profiles were identified (i.e., Very Low PF and Moderate CF, Low PF and Low CF (Both Low), Normal PF and Normal CF (Both Normal)). Compared to the Both Normal class, older adults in the two other classes were less likely to exercise on a regular basis and had a worse comorbidity profile. In addition, compared to the Both Normal class, older adults in the Both Low class were less likely to be married/partnered, more likely to live alone, less likely to be employed, and more likely to report depression and back pain.

In the second study that evaluated the bidirectional relationships between CF and physical activity,[7] older women with and without breast cancer were assessed prior to the initiation of treatment and yearly for 36 months. Both subjective and objective measures were used to assess CF and the International Physical Activity Questionnaire-Short Form was used to assess physical activity. While not seen in women without breast cancer, patients who reported higher activity had better cognition measured objectively at 12 months and better perceived cognition at 12 and 24 months after systemic therapy. The authors concluded that additional research is needed to examine the relationships between PF and CF in patients receiving cancer treatment. Given the large amount of inter-individual variability in both PF and CF in oncology patients and the paucity of research on the relationships between these two extremely important PROs, the purposes of this study, in a sample of oncology patients who were receiving chemotherapy (n = 1331), were to identify subgroups of patients with distinct joint PF and CF profiles and evaluate for differences in demographic and clinical characteristics among these subgroups. In addition, differences among the subgroups in the severity of common symptoms associated with cancer and its treatments and QOL outcomes were evaluated. Of these 1343 patients, 1331 provided complete data on the PF and CF measures.

PATIENTS AND METHODS

Patients and Settings

This study is part of a larger, longitudinal study that evaluated the symptom experience of oncology outpatients receiving chemotherapy. 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 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

A demographic questionnaire obtained information on age, gender, ethnicity, marital status, living arrangements, education, employment status, and income. In addition, patients completed the Karnofsky Performance Status (KPS) scale,[33] the Alcohol Use Disorders Identification Test,[34] and the Self-Administered Comorbidity Questionnaire (SCQ).[35]

Measures of PF and CF

Physical function was assessed using the physical component summary (PCS) score from the Medical Outcomes Study-Short Form 12 (SF-12).[36] The SF-12 consists of 12 questions about physical and mental health as well as overall health status. The SF-12 was scored into two components (i.e., physical component summary (PCS) score and mental component summary (MCS) score) that evaluate physical and psychological function, respectively. These scores can range from 0 to 100 with higher scores indicating better function.

Cognitive function was assessed using the 16-item Attentional Function Index (AFI) that evaluates an individual's perceived effectiveness in performing daily activities that are supported by attention and working memory.[37] A higher total mean score on a 0 to 10 numeric rating scale (NRS) indicates greater capacity to direct attention.[37] Total scores can be grouped into categories of attentional function (i.e., <5.0 low function, 5.0 to 7.5 moderate function, >7.5 high function).[38] Its Cronbach's alpha was 0.93.

Measures of Common Symptoms

To assess the severity of common symptoms associated with cancer and its treatment, patients completed: Center for Epidemiological Studies-Depression scale,[39] Spielberger State-Trait Anxiety Inventories,[40] Lee Fatigue Scale,[41] General Sleep Disturbance Scale,[42] and Brief Pain Inventory.[43]

QOL Measures

QOL was evaluated using general (i.e., SF-12) and disease specific (i.e., Multidimensional Quality of Life Scale Cancer-Patient Version (MQOLS-PV)) measures. The SF-12 consists of 12 questions about physical and mental health, as well as overall health status. The instrument is 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.[36]

The 41-item MQOLS-PV assesses four dimensions of QOL (i.e., physical, psychological, social, and spiritual well-being) in cancer patients, as well as a total QOL score. Each item was rated on a 0 to 10 NRS with higher scores indicating a better QOL.[44]

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. Eligible 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. Written informed consent was obtained from all patients. Patients completed SF-12 and AFI, a total of six times over two cycles of chemotherapy (i.e., prior to chemotherapy administration (Assessments 1 and 4), approximately 1 week after chemotherapy administration (Assessments 2 and 5), approximately 2 weeks after chemotherapy administration (Assessments 3 and 6)). The remaining questionnaires were completed at enrollment (i.e., prior to the administration of the second or third cycle of chemotherapy). Medical records were reviewed for disease and treatment information.

Data Analysis

Latent profile analysis (LPA) was used to identify subgroups of patients with distinct joint PF AND CF profiles. This LPA was done with the combined set of variables over time (i.e., using the PCS AND AFI scores obtained during the six assessments in a single LPA). This

approach provides a profile description of these two outcomes with parallel profiles over time. The LPA was done using Mplus version 8.4.[45]

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., PCS 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.[46]

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 ("estimator=MLR"). Model fit was evaluated to identify the solution that best characterized the observed latent class structure with the Bayesian Information Criterion (BIC), Vuong-Lo-Mendell-Rubin likelihood ratio test (VLMR), entropy, and latent class percentages that were large enough to be reliable.[47] Missing data were accommodated for with the use of the Expectation-Maximization algorithm.[48]

Descriptive statistics and frequency distributions were calculated for demographic and clinical characteristics using SPSS version 28 (IBM Corporation, Armonk, NY). Differences among the PF AND CF classes in demographic, clinical, and symptom characteristics and QOL outcomes were evaluated using parametric and nonparametric tests. A Bonferroni corrected p-value of <.005 (i.e., .05/10) was considered statistically significant for the pairwise contrasts.

RESULTS

Latent Class Solution for Physical and Cognitive Function

As shown in Table 1, a 5-class solution was selected because the BIC for that solution was lower than the BIC for the 4-class solution. In addition, the VLMR was significant for the 5-class solution, indicating that five classes fit the data better than four classes. Although the BIC was smaller for the 6-class than for the 5-class solution, the VLMR was not significant for the 6-class solution, indicating that too many classes were extracted.

As shown in Figure 1, the trajectories for the PCS and AFI scores differed among the latent classes. Using the normative score for the PCS (i.e., 50)[36] and the clinically meaningful cutoff scores for the AFI,[38] the five PF AND CF classes were named: Very Low PF and Low CF (18.4%; Both Low), Low PF and High CF (19.8%, Low PF+High CF), Moderate PF and Low CF (26.7%, Moderate PF+Low CF), Changing PF and CF (5.4%, Changing), and Normal PF and CF (29.7%; Both Normal). Except for the Changing class, for the other four classes, both the PF and CF trajectories remained relatively stable over the two cycles of chemotherapy. In the Changing class, PF and CF scores declined one week after receiving chemotherapy (assessments 2 and 5) and then recovered.

Demographic and Clinical Characteristics

As shown in Table 2, differences in demographic and clinical characteristics among the five latent classes were highly variable. In brief, compared to the Both Normal class, the Both Low, Low PF+High CF, and Moderate PF+Low CF classes were more likely to be unemployed, to have a lower annual income, as well as to have a poorer functional status, a higher number of comorbidities and comorbidity burden, and higher occurrence rates for back pain.

In addition, compared to the Both Normal class, the Both Low and Moderate PF+Low CF classes were more likely to be female and less likely to be married/partnered. Compared to the Both Normal class, the Both Low class reported a lower level of education; was more likely to live alone; had received a higher number of cancer treatments; had a higher number of

metastatic sites; and was more likely to report lung disease, diabetes, anemia or blood disease, osteoarthritis, or rheumatoid arthritis. Compared to the Both Normal class, the Changing class was younger; had a lower number of positive lymph nodes; had a higher MAX2 score; was less likely to have gastrointestinal cancer; was more likely to have received only surgery, radiation therapy, or chemotherapy; was more likely not to have metastatic disease; and was more likely to have received a more emetogenic chemotherapy regimen.

Symptom Severity Scores

As shown in Table 3, differences in symptom severity scores among the five latent classes were highly variable. In brief, compared to the Both Normal class, the Both Low, Low PF+High CF and Moderate PF+Low CF classes reported higher scores for depressive symptoms, decrements in evening energy, and pain interference. In addition, compared to the Both Normal class, the other four classes reported higher scores for morning fatigue, evening fatigue and sleep disturbance and decrements in morning energy and cognitive function, as well as higher occurrence rates for both cancer and non-cancer pain.

QOL Scores

In terms of the SF-12 (Table 4), compared to the Both Normal class, the other four classes reported lower scores for the physical functioning, role physical, bodily pain, general health, vitality, and PCS scales. In addition, compared to the Both Normal class, the Both Low, Low PF+High CF, and Moderate PF+Low CF classes reported lower scores for the social functioning, and role emotional scales. In terms of the MQOLS-PV, compared to the Both Normal class, the other four classes reported lower scores for the physical, psychological, and spiritual well-being subscales, as well as its total QOL score.

DISCUSSION

Building on our previous work with older adults that identified three distinct joint PF and CF profiles,[11] using a large sample with an age range from 19 to 90 years, five distinct joint PF and CF profiles were identified. However, direct comparisons between the previous[11] and current analysis are not possible given the differences in the number and types of profiles.

Of note, using clinically meaningful cutpoints for the PF and CF measures, over 70% of our sample had moderate to severe decrements in one or both of these extremely important PROs. It is interesting to note that 19.8% of the sample had high levels of CF with severe impairments in PF and 26.7% had low levels of CF and only moderate impairments in PF. The fact that decrements in PF did not parallel decrements in CF is supported by research that demonstrates that a significant amount of heterogeneity exists in the biological effects of cancer[49] as well as in the physiological reserves of oncology patients.[50] Equally important, a variety of social determinants of health (e.g., lower socioeconomic status), living and working conditions, and/or availability of social and community resources can influence PF and CF in oncology patients.[51]

Table 5 summarizes the differences in demographic, clinical, and symptom characteristics and QOL outcomes between each of the distinct PF and CF profiles compared to the Both Normal class. Given the complexity of the findings, the initial sections of the Discussion will place some of the common risk factors associated with decrements in PF and CF within the context of the extant literature for the individual PROs. Subsequent sections of the Discussion will provide hypotheses regarding the factors that contribute to two of the individual profiles (i.e., Changing and Both Low); summarize study limitations; and provide recommendations for clinical practice and research.

Demographic and Clinical Characteristics

Compared to the Both Normal class, being unemployed and having a lower annual income were risk factors for membership in all of the classes except the Changing class. In terms of PF, this result is consistent with a systematic review that found that economic instability contributed to the development of frailty because it disrupts individuals' social activities and impairs the development of social relationships.[52] In terms of CF, findings from several studies suggest that having financial stability is the most protective and conducive factor to maintain cognitive abilities because of greater exposure to stimuli, engagement with others, and the performance of activities that involve cognitive challenges and repetition.[53, 54] As noted by Zeng and colleagues,[53] CF is a complex longitudinal process that is intertwined with socioeconomic conditions and exhibits considerable heterogeneity.

Compared to the Both Normal class, being female and not being married or partnered were associated with membership in the Both Low and Moderate PF+Low CF classes. In terms of gender differences in PF[55] and CF,[56] findings across studies of oncology patients are inconsistent. In terms of marital status, our result is consistent with a study of adults in the United States that found that being unmarried was associated with decreases in social and emotional support and increases in cognitive decline.[54] Equally important, the lack of social support may decrease patients' participation in social[57] and physical[58] activities that results in decrements in PF.

Compared to the Both Normal class, the lack of regular exercise was associated with membership in the Very Low PF+Low CF and Low PF+High CF classes. Consistent with systematic reviews of individuals with[7] and without cancer,[13, 59] decrements in CF are associated with declines in physical activity. It is reasonable to hypothesize that decreases in physical activity, that have a negative impact on muscle mass and strength, contribute to functional decline.[60] It is important to note that exercise has beneficial effects on brain health and CF.[13, 32, 61] Regardless of the type of exercise, neuroprotective effects are observed in terms of memory

and progression of neurodegenerative diseases.[62] The resultant neuroplasticity associated with exercise is at least in part due to the increased expression and release of a variety of neurotrophic and growth factors (e.g., brain-derived neurotrophic factor).[63] While exercise is recommended to decrease cancer-related fatigue, clinicians need to prescribe an exercise regimen to maintain or improve both PF and CF.

Compared to the Both Normal class, the other three classes reported lower KPS scores. In addition, except for the Changing class, membership in the other three classes was associated with a higher number of comorbidities, a higher comorbidity burden, and a self-reported diagnosis of back pain. These results are consistent with a recent International Society of Geriatric Oncology report that identified inter-relationships among baseline impairments in PF and CF and a higher number of comorbidities and functional decline.[55] While the contribution of specific comorbidities to declines in PF and CF warrant detailed evaluation in oncology patients, in recent systematic reviews and meta-analyses, evidence suggests that impairments in PF[64] and CF[65] occur in patients with chronic low back pain.

Common Symptoms

As shown in Table 5, for the majority of the symptoms, compared to the Both Normal class, the other four classes reported higher severity scores. However, the pattern of these differences in terms of clinically meaningful cutoff scores warrants consideration (Table 3). For the two classes with Low CF, their scores for depression and trait and state anxiety indicate clinically meaningful levels of these symptoms. These findings are consistent with two cross-sectional studies of patients with breast cancer[66, 67] and one longitudinal study of older adults[68] that suggest that depressive symptoms increase the risk for accelerations in cognitive decline. Given that depressive symptoms are a modifiable risk factor for both CF and PF, treatment for depression, as well as cognitive training and exercise, may delay cognitive decline by enhancing neuroplasticity and neurogenesis.[32, 61] While less well studied than depression,

higher levels of anxiety were associated with cognitive decline in patients with breast cancer[57] and decrements in PF in patients with advanced stage lung cancer.[69]

A similar pattern was observed for the two classes with low CF, in that, their morning and evening fatigue scores and morning and evening energy scores indicated clinically meaningful levels of fatigue as well as decrements in energy. While diurnal variations in fatigue and energy were not evaluated, these findings are consistent with a previous study of women who were assessed prior to breast cancer surgery.[70] Across the three subscales of the AFI (i.e., effective action, attentional lapses, interpersonal effectiveness), higher levels of fatigue and lower levels of energy were associated with worse cognitive performance. Given this finding, future research needs to evaluate the relationships between changes in PF and the various dimensions of CF (e.g., attention, multi-tasking) using subjective and objective measures of both PROs.

It is interesting to note that compared to the Both Normal class, the other four classes, with varying levels of PF and CF, had clinically meaningful levels of sleep disturbance. While a number of reviews have concluded that sleep disturbance is a risk factor for cognitive dysfunction,[71, 72] the exact mechanisms that underlie this relationship are unknown. In terms of PF, in a cross-sectional study of older adults with cancer,[73] 40% had sleep disturbance. In a multivariate analysis, patients with sleep disturbance had a 1.96 increase in the odds of having impairments in instrumental ADLs and a 2.43 increase in the odds of having limitations in physical activity.

Similar to sleep disturbance, compared to the Both Normal class, the other four classes had higher rates of both cancer and non-cancer pain. In addition, across these four classes, worst pain intensity scores were in the moderate to severe range. In terms of CF, as noted in one systematic review of the neuroimmunology of cancer and associated symptoms,[74] findings from both preclinical and clinical studies suggest that neuroimmune interactions contribute to the development of pain and CF in patients with cancer. In terms of PF, in a nation-wide survey

of oncology outpatients in Taiwan,[75] 50.6% of them reported pain. As these patients' disease progressed (e.g., increased number of metastatic sites, additional cancer treatments) the occurrence of pain was associated with increased impairments in PF.

QOL Outcomes

As shown in Tables 4 and 5, except for the MQOLS-PV spiritual well-being subscale, for the majority of the QOL domains, compared to the Both None class, the other four classes reported significantly lower scores. Of note for both the PCS and MCS summary scores, patients in the Low CF classes had scores below the normative score of 50 for the general population of the United States.[36] Overall, our results are consistent with a previous report of patients with head and neck cancer that found that deficits in various aspects of function were associated with significant declines in QOL following treatment.[76] In addition, our results are consistent with a systematic review that found that even mild cognitive difficulties, especially when they are persistent and untreated, can have significant functional consequences.[77] These authors noted that cognitive impairments have negative effects on return to work, interpersonal relationships, leisure activities, and overall QOL.

Individual Latent Classes

While albeit small in size (5.4% of the sample), the characteristics of the Changing class warrants some consideration. Some of the characteristics that were unique to this class included: being younger; having a fewer number of cancer treatments and metastatic sites; being less likely to have gastrointestinal cancer and metastatic disease; having a higher MAX2 score (increased toxicity of the chemotherapy regimen), and receiving a more emetogenic chemotherapy regimen. In addition, this class had clinically meaningful levels of state and trait anxiety, evening fatigue, and sleep disturbance and decrements in morning and evening energy prior to their second or third cycle of chemotherapy. Equally important, both the AFI and MCS scores at enrollment were within the normal ranges. In contrast the PCS scores at enrollment for the Changing class were below the clinically meaningful cutoff. Taken together, these

findings suggest that these patients were receiving relatively toxic chemotherapy and inadequate symptom management interventions that had a greater impact on their PF than on their CF.

As noted in Leidy's functional status framework,[16] one hypothesis for the changing PF scores in this class is that when these patients are exposed to a stressor (i.e., receipt of chemotherapy), they experience a decline in functional capacity and a depletion of physical reserves that results in decrements in performance. This framework suggests that functional performance is a dynamic outcome that responds to stress through the establishment of new equilibria. In terms of variations in CF, plausible hypotheses for the dynamic changes in AFI scores include these patients' ability to rapidly respond to the stress of chemotherapy[18] and/or higher levels of cognitive reserve and resilience.[78]

The Both Low class, that constituted 18.4% of this sample, appears to be an extremely high risk group. As shown in Table 5, compared to the Both High class, these patients had the largest number of risk factors. Particularly noteworthy are the higher occurrence rates for almost all of the comorbid conditions on the SCQ and that these patients had an average of 3.3 chronic conditions. Equally important, this class's mean self-reported KPS score was 67.9 and 42% had a score of less than 60. A KPS score of 60 equates with "I require occasional assistance, but am able to care for most of my personal needs".[33] In addition, all of the symptom scores on Table 3 indicated clinically meaningful levels of depression, anxiety, fatigue, sleep disturbance, and pain, as well as significant decrements in energy. The extremely low scores on the majority of the SF-12 subscales corroborate the extremely low levels of both PF and CF in these patients.

Based on these findings, one can hypothesize that if assessed using a measure like the Clinical Frailty Scale (CFS),[79] these patients would meet the criteria for being frail (i.e., a state of increased vulnerability resulting from age-associated declines in reserve and function across multiple physiological systems, such that the ability to cope with every day or acute stressors is

compromised[80]). Consistent with the frailty model,[81] that suggests that the underlying mechanisms for frailty include chronic low-grade inflammation, as well as energy imbalances and anabolic deficiency, in addition to multimorbidity and decrements in PF and CF, these patients may be malnourished and/or have sarcopenia. These findings suggest that patients undergoing chemotherapy, with similar risk factors as the Both Low class, warrant screening for frailty.

Limitations

A number of limitations warrant consideration. Given that the sample was primarily female, White, and well-educated and had a relatively high annual income, future studies need to recruit more diverse samples and evaluate additional social determinants of health (e.g., medical discrimination, environmental stressors). While valid and reliable self-report measures were used to assess PF and CF, future studies need to assess both outcomes using objective measures and examine associations among these measures. In addition, pretreatment and post-treatment of both outcomes warrant evaluation to be able determine if membership in each of the latent classes persists over time. Equally important, additional information is warranted on the effects of specific comorbid conditions and pharmacologic and non-pharmacologic symptom management interventions on both PF and CF.

Implications for Clinical Practice and Research

As noted in a recent qualitative study of oncology patients,[82] PF, CF, social function, and physical health are the most important components of QOL. In particular, for older adults with cancer, maintaining their cognitive status and independence, staying in their own home, and maintaining contact with both family members and their community are important aspects of QOL. Therefore findings from the current study suggest that clinicians need to use simple subjective and objective measures to evaluate PF (e.g., KPS score, gait speed[3]) and CF (AFI, trail making test[3]) on a routine basis. In addition, given that clinically meaningful severity scores for a large number of common symptoms were associated with poorer PF and CF,

individualized symptom management interventions need to be developed and their effects on the targeted symptom and these important PROs need to be evaluated on an ongoing basis. Given the benefits of exercise for both PF[83] and CF,[84] high risk patients warrant referral to physical therapy for tailored exercise prescriptions that take into account patients' level of disability.

Future studies need to evaluate the impact of family and social relationships, caregiver characteristics, and community resources on older adults' PF and CF. In addition, studies that investigate the effects of stress and psychological resilience on PF and CF will provide important information on potentially modifiable risk factors that can be targeted to improve these PROs.[85] Equally important, the mechanisms that underlie changes in PF and CF as independent and combined PROs warrant evaluation. Finally, longitudinal studies are needed, using analytic techniques like parallel process growth modeling,[86] to determine which outcome is driving improvements, maintenance, or worsening of PF and CF in patients undergoing cancer treatments.

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Table 1 – Latent Profile Solutions and Fit Indices for One through Six Classes for Physical Component Summary Scores[a] AND Attentional Index Scores Over Six Assessments

Model	LL	AIC	BIC	Entropy	VLMR
1 Class	-34561.30	69238.61	69539.84	n/a	n/a
2 Class	-33904.78	67951.55	68320.31	0.77	1313.05[†]
3 Class	-33601.09	67370.18	67806.45	0.82	607.379[‡]
4 Class	-33370.33	66934.67	67438.45	0.80	461.51[‡]
5 Class[b]	-33206.95	66633.90	67205.21	0.82	582.92[*]
6 Class	-33082.37	66410.75	67049.57	0.82	ns

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

*p < .001; [†]p = .0001; [‡]p < .00005

[a]Physical Component Summary scores from the Medical Outcomes Study-Short Form 12

[b]The 5-class solution was selected because the BIC for that solution was lower than the BIC for the 4-class solution. In addition, the VLMR was significant for the 5-class solution, indicating that five classes fit the data better than four classes. Although the BIC was smaller for the 6-class than for the 5-class solution, the VLMR was not significant for the 6-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

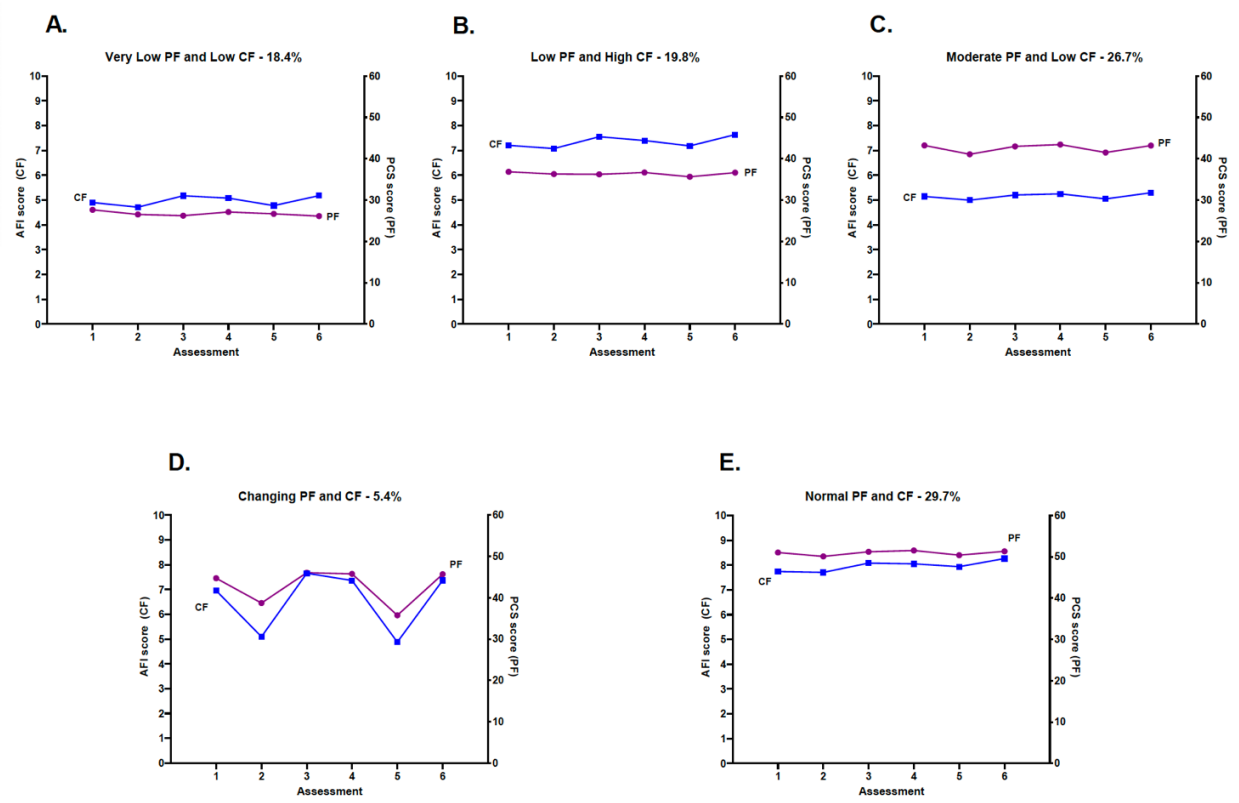

Figure 1- Trajectories for the PCS and AFI scores

Table 2 – Differences in Demographic and Clinical Characteristics Among the Physical Function and Cognitive Function Latent Classes at Enrollment

Characteristic	Very Low PF and Low CF (1) 18.4% (n=245)	Low PF and High CF (2) 19.8% (n=264)	Moderate PF and Low CF (3) 26.7% (n=355)	Changing PF and CF (4) 5.4% (n=72)	Normal PF and CF (5) 29.7% (n=395)	Statistics
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	
Age (years)	58.4 (12.4)	59.9 (10.7)	55.3 (13.2)	51.4 (13.2)	57.1 (11.7)	F = 10.22, p <.001 1 > 3 and 4; 2 > 3, 4, and 5; 4 < 5
Education (years)	15.8 (3.1)	16.1 (2.8)	16.1 (3.0)	16.6 (2.8)	16.6 (3.1)	F = 3.04, p = .017 1 < 5
Body mass index (kg/m^2)	26.9 (6.3)	26.6 (5.4)	26.0 (5.8)	25.4 (4.1)	25.8 (5.5)	F = 2.20, p = .067
Alcohol Use Disorders Identification Test score	2.7 (2.8)	2.7 (2.3)	3.3 (2.8)	2.9 (2.3)	3.0 (2.1)	F = 1.50, p = .202
Karnofsky Performance Status score (KPS)	67.9 (10.0)	79.1 (11.5)	79.8 (11.0)	79.0 (12.5)	88.3 (8.9)	F = 138.81, p < .001 1 < 2, 3, 4, and 5; 2, 3, and 4 < 5
Number of comorbid conditions	3.3 (1.6)	2.5 (1.5)	2.3 (1.3)	1.9 (1.1)	1.9 (1.2)	F = 36.77, p <.001 1 > 2, 3, 4, and 5; 2 > 4 and 5; 3 > 5
Self-administered Comorbidity Questionnaire score	7.7 (3.8)	5.7 (3.1)	5.4 (3.0)	4.3 (2.2)	4.2 (2.3)	F = 58.65 , p <.001 1 > 2, 3, 4, and 5; 2 and 3 > 4 and 5
Time since diagnosis (years)	2.6 (5.5)	2.3 (3.9)	1.7 (3.2)	1.2 (3.0)	1.8 (3.2)	KW = 17.11, p < .002 4 < 1, 2, and 3
Time since diagnosis (years, median)	0.45	0.46	0.42	0.32	0.41	
Number of prior cancer treatments	1.9 (1.6)	1.7 (1.5)	1.6 (1.5)	1.0 (1.0)	1.5 (1.5)	F = 6.51, p < .001 1, 2 and 3 > 4; 1 > 5
Number of metastatic sites including lymph node involvement[a]	1.5 (1.4)	1.4 (1.3)	1.1 (1.2)	0.7 (0.9)	1.2 (1.1)	F = 7.55, p <.001 1 > 3, 4, and 5; 2 > 4; 4 < 5
Number of metastatic sites excluding lymph node involvement	1.0 (1.2)	1.0 (1.1)	0.7 (1.0)	0.3 (0.7)	0.7 (1.0)	F = 9.71, p <.001 1 > 3, 4, and 5; 2 > 3 and 4; 4 < 5
MAX2 score	0.18 (0.08)	0.16 (0.08)	0.18 (0.08)	0.22 (0.08)	0.17 (0.08)	F = 8.16, p < .001 1, 2, 3, and 5 < 4
	% (n)	% (n)	% (n)	% (n)	% (n)	
Gender (% female)	83.7 (205)	73.1 (193)	82.2 (291)	91.7 (66)	71.1 (281)	X^2 = 30.48, p <.001 1 > 2 and 5 2 < 4; 3 > 5
Self-reported ethnicity						
White	63.1 (152)	71.7 (185)	71.6 (252)	70.4 (50)	70.0 (275)	
Asian or Pacific Islander	14.1 (34)	11.2 (29)	12.2 (43)	16.9 (12)	12.0 (47)	
Black	6.6 (16)	8.9 (23)	5.7 (20)	2.8 (2)	8.7 (34)	
Hispanic, Mixed, or Other	16.2 (39)	8.1 (21)	10.5 (37)	9.9 (7)	9.4 (37)	X^2 = 18.20, p = .110

Characteristic	Very Low PF and Low CF (1) 18.4% (n=245)	Low PF and High CF (2) 19.8% (n=264)	Moderate PF and Low CF (3) 26.7% (n=355)	Changing PF and CF (4) 5.4% (n=72)	Normal PF and CF (5) 29.7% (n=395)	Statistics
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	
Married or partnered (% yes)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	X^2 = 25.32, p <.001 1 and 3 < 5
Lives alone (% yes)	28.8 (70)	22.3 (57)	23.1 (81)	16.7 (12)	16.1 (63)	X^2 = 16.15, p = .003 1 > 5
Currently employed (% yes)	17.2 (42)	30.5 (80)	32.9 (116)	47.9 (34)	49.4 (191)	X^2 = 77.00, p <.001 1 < 2, 3, 4, and 5; 2 and 3 < 5
Annual household income Less than $30,000+ $30,000 to $70,000 $70,000 to $100,000 Greater than $100,000	 32.1 (70) 25.2 (55) 12.4 (27) 30.3 (66)	 14.0 (33) 22.5 (53) 22.0 (52) 41.5 (98)	 22.5 (74) 22.2 (73) 15.5 (51) 39.8 (131)	 10.3 (7) 19.1 (13) 23.5 (16) 47.1 (32)	 10.0 (34) 17.1 (58) 16.5 (56) 56.5 (192)	KW = 64.42, p < .001 1 < 2, 3, 4, and 5 2 and 3 < 5
Child care responsibilities (% yes)	19.3 (46)	18.4 (47)	26.3 (93)	32.4 (23)	20.8 (80)	X^2 = 11.52, p = .021 no significant pairwise contrasts
Elder care responsibilities (% yes)	10.1 (22)	8.9 (21)	10.2 (33)	1.5 (1)	5.2 (19)	X^2 = 11.11, p = .025 no significant pairwise contrasts
Past or current history of smoking (% yes)	38.2 (92)	37.2 (97)	37.5 (131)	38.0 (27)	29.5 (114)	X^2 = 8.05, p = .090
Exercise on a regular basis (% yes)	52.5 (125)	67.8 (177)	73.0 (252)	79.4 (54)	81.0 (315)	X^2 = 62.53, p < .001 1 < 2, 3, 4, and 5; 2 < 5
Specific comorbid conditions (% yes)						
Heart disease	9.4 (23)	8.0 (21)	5.6 (20)	0.0 (0)	2.8 (11)	X^2 = 19.49, p < .001 1 and 2 > 5
High blood pressure	37.1 (91)	34.5 (91)	24.5 (87)	20.8 (15)	29.4 (116)	X^2 = 16.50, p = .002 1 > 3
Lung disease	18.0 (44)	14.0 (37)	10.4 (37)	2.8 (2)	7.6 (30)	X^2 = 23.74, p < .001 1 > 4 and 5
Diabetes	15.1 (37)	12.5 (33)	5.9 (21)	0.0 (0)	7.1 (28)	X^2 = 28.26, p < .001 1 and 2 > 3 and 4; 1 > 5
Ulcer or stomach disease	5.7 (14)	3.8 (10)	6.5 (23)	4.2 (3)	3.8 (15)	X^2 = 4.07, p = .396
Kidney disease	2.4 (6)	1.5 (4)	1.4 (5)	2.8 (2)	0.5 (2)	X^2 = 5.15, p = .273
Liver disease	9.4 (23)	9.1 (24)	3.9 (14)	2.8 (2)	5.6 (22)	X^2 = 12.47, p = .014 no significant pairwise contrasts
Anemia or blood disease	20.0 (49)	10.2 (27)	11.3 (40)	11.1 (8)	10.1 (40)	X^2 = 16.67, p = .002 1 > 2, 3, and 5

Characteristic	Very Low PF and Low CF (1) 18.4% (n=245)	Low PF and High CF (2) 19.8% (n=264)	Moderate PF and Low CF (3) 26.7% (n=355)	Changing PF and CF (4) 5.4% (n=72)	Normal PF and CF (5) 29.7% (n=395)	Statistics
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	
Depression	34.3 (84)	13.3 (35)	27.9 (99)	15.3 (11)	7.1 (28)	$X^2 = 96.85$, $p < .001$ 1 > 2, 4 and 5; 3 > 2 and 5
Osteoarthritis	18.0 (44)	14.0 (37)	11.0 (39)	9.7 (7)	8.4 (33)	$X^2 = 14.90$, $p = .005$ 1 > 5
Back pain	51.0 (125)	23.9 (63)	23.4 (83)	18.1 (13)	14.7 (58)	$X^2 = 111.05$, $p < .001$ 1 > 2 ,3, 4 and 5; 2 and 3 > 5
Rheumatoid arthritis	6.1 (15)	3.8 (10)	2.0 (7)	2.8 (2)	1.8 (7)	$X^2 = 11.79$, $p = .019$ 1 > 5
Cancer diagnosis						$X^2 = 47.84$, $p < .001$
Breast cancer	38.0 (93)	35.2 (93)	43.4 (154)	54.2 (39)	40.3 (159)	2 < 4
Gastrointestinal cancer	23.7 (58)	36.4 (96)	27.6 (98)	9.7 (7)	37.0 (146)	1 < 2 and 5; 4 < 2, 3, and 5
Gynecological cancer	21.2 (52)	16.3 (43)	19.2 (68)	25.0 (18)	12.9 (51)	NS
Lung cancer	17.1 (42)	12.1 (32)	9.9 (35)	11.1 (8)	9.9 (39)	NS
Prior cancer treatment						$X^2 = 37.37$, $p < .001$
No prior treatment	20.1 (48)	24.6 (63)	24.1 (84)	29.2 (21)	28.1 (107)	NS
Only surgery, CTX, or RT	39.7 (95)	37.5 (96)	42.5 (148)	61.1 (44)	42.3 (161)	1, 2, 3, and 5 < 4
Surgery and CTX, or surgery and RT, or CTX and RT	20.1 (48)	23.4 (60)	20.7 (72)	5.6 (4)	19.4 (74)	1, 2, 3, and 5 > 4
Surgery and CTX and RT	20.1 (48)	14.5 (37)	12.6 (44)	4.2 (3)	10.2 (39)	1 > 4 and 5
Metastatic sites						$X^2 = 30.52$, $p = .002$
No metastasis	29.3 (71)	29.1 (76)	35.3 (124)	51.4 (37)	30.4 (118)	1, 2 and 5 < 4
Only lymph node metastasis	21.1 (51)	19.2 (50)	22.8 (80)	29.2 (21)	22.2 (86)	NS
Only metastatic disease in other sites	23.1 (56)	24.9 (65)	18.2 (64)	5.6 (4)	22.7 (88)	1, 2, and 5 > 4
Metastatic disease in lymph nodes and other sites	26.4 (64)	26.8 (70)	23.6 (83)	13.9 (10)	24.7 (96)	NS
CTX regimen						$X^2 = 15.63$, $p = .048$
Only CTX	67.9 (163)	65.6 (170)	76.0 (263)	72.2 (52)	68.5 (265)	NS
Only targeted therapy	2.5 (6)	2.3 (6)	2.9 (10)	0.0 (0)	4.4 (17)	NS
Both CTX and targeted therapy	29.6 (71)	32.0 (83)	21.1 (73)	27.8 (20)	27.1 (105)	2 > 3
Cycle length						KW = 10.86, $p = .028$
14 day cycle	34.2 (83)	45.5 (120)	44.0 (153)	25.7 (18)	45.2 (178)	no significant pairwise contrasts OK
21 day cycle	58.4 (142)	45.5 (120)	48.9 (170)	72.9 (51)	47.7 (188)	
28 day cycle	7.4 (18)	9.1 (24)	7.2 (25)	1.4 (1)	7.1 (28)	
Emetogenicity of the CTX regimen						KW = 24.30, $p < .001$
Minimal/low	23.5 (57)	20.5 (54)	19.5 (68)	4.3 (3)	19.3 (76)	4 > 1, 2, 3, and 5
Moderate	59.3 (144)	65.9 (174)	57.6 (201)	60.0 (42)	61.9 (244)	
High	17.3 (42)	13.6 (36)	22.9 (80)	35.7 (25)	18.8 (74)	

Characteristic	Very Low PF and Low CF (1) 18.4% (n=245)	Low PF and High CF (2) 19.8% (n=264)	Moderate PF and Low CF (3) 26.7% (n=355)	Changing PF and CF (4) 5.4% (n=72)	Normal PF and CF (5) 29.7% (n=395)	Statistics
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	
Antiemetic regimen						
None	6.4 (15)	6.6 (17)	7.0 (24)	1.5 (1)	9.1 (35)	
Steroid alone or serotonin receptor antagonist alone	21.7 (51)	21.3 (55)	19.9 (68)	20.6 (14)	19.9 (77)	
Serotonin receptor antagonist and steroid	46.4 (109)	49.6 (128)	48.0 (164)	39.7 (27)	48.2 (186)	$X^2 = 13.19$, p = .356
NK-1 receptor antagonist and two other antiemetics	25.5 (60)	22.5 (58)	25.1 (86)	38.2 (26)	22.8 (88)	

[a]Total number of metastatic sites evaluated was 9.
[+]Reference group
Abbreviations: CF = cognitive function, CTX = chemotherapy, kg = kilograms, KW = Kruskal Wallis, m^2 = meters squared, PF = physical function, pw = pairwise, NK-1 = neurokinin-1, NS = not significant, RT = radiation therapy, SD = standard deviation

Table 3 – Differences in Common Symptom Severity Scores Among the Physical Function and Cognitive Function Latent Classes at Enrollment

Symptoms[a]	Very Low PF and Low CF (1) 18.4% (n=245)	Low PF and High CF (2) 19.8% (n=264)	Moderate PF and Low CF (3) 26.7% (n=355)	Changing PF and CF (4) 5.4% (n=72)	Normal PF and CF (5) 29.7% (n=395)	Statistics
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	
Depressive symptoms (≥16.0)	19.0 (10.1)	9.7 (7.3)	17.8 (9.9)	9.8 (7.8)	7.4 (6.2)	F = 114.67, p <.001 1 and 3 > 2, 4, and 5; 2 > 5
Trait anxiety (≥31.8)	40.8 (10.6)	31.0 (7.9)	40.9 (10.4)	33.6 (8.8)	29.8 (7.7)	F = 103.46, p <.001 1 and 3 > 2, 4, and 5; 4 > 5
State anxiety (≥32.2)	39.4 (13.3)	29.6 (10.5)	39.4 (12.5)	32.9 (11.3)	28.7 (9.4)	F = 63.42, p <.001 1 and 3 > 2, 4, and 5; 4 > 5
Morning fatigue (≥3.2)	4.7 (2.3)	2.5 (1.9)	4.1 (2.0)	2.8 (2.1)	1.8 (1.7)	F = 112.28, p <.001 1 > 2, 3, 4, and 5; 2, 3, and 4 > 5; 3 > 2 and 4
Evening fatigue (≥5.6)	6.2 (1.8)	5.0 (2.2)	6.0 (1.9)	5.7 (2.2)	4.4 (2.1)	F = 41.57, p <.001 1, 2, 3, and 4 > 5; 1, 3, and 4 > 2
Morning energy (≤6.2)	3.3 (1.9)	4.4 (2.2)	4.1 (1.9)	4.5 (2.2)	5.3 (2.4)	F = 35.19, p <.001 1, 2, 3, and 4 < 5; 1 < 2, 3, and 4
Evening energy (≤3.5)	2.9 (1.9)	3.5 (2.0)	3.3 (2.0)	3.5 (2.0)	4.2 (2.0)	F = 16.89, p <.001 1, 2, and 3 < 5; 1 < 2
Sleep disturbance (≥43.0)	64.7 (19.7)	48.9 (18.3)	59.7 (16.8)	50.4 (18.5)	41.3 (17.9)	F = 80.37, p < .001 1 > 2, 3, 4, and 5; 3 > 2, 4, and 5 2 and 4 > 5
Types of pain						X^2 = 206.70, p < .001
None	4.6 (11)	24.2 (63)	25.9 (90)	21.4 (15)	46.2 (180)	1 < 2, 3, 4, and 5; 2, 3, and 4 < 5
Only cancer pain	29.2 (70)	16.9 (83)	26.2 (91)	37.1 (26)	19.0 (74)	1, 2, and 4 > 5
Only non-cancer pain	10.0 (24)	26.9 (44)	15.3 (53)	11.4 (8)	19.7 (77)	1 < 5
Both non-cancer and cancer pain	56.3 (135)	26.9 (70)	32.6 (113)	30.0 (21)	15.1 (59)	1 > 2, 3, 4, and 5; 2, 3, and 4 > 5
For those patients with pain	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	
Worst pain intensity score Mild – 1 to 3 Moderate – 4 to 6 Severe – 7 to 10	7.3 (2.1)	6.0 (2.5)	5.8 (2.5)	5.5 (2.8)	5.1 (2.5)	F = 20.60, p <.001 1 > 2, 3, 4, and 5; 2 > 5

Symptoms[a]	Very Low PF and Low CF (1) 18.4% (n=245)	Low PF and High CF (2) 19.8% (n=264)	Moderate PF and Low CF (3) 26.7% (n=355)	Changing PF and CF (4) 5.4% (n=72)	Normal PF and CF (5) 29.7% (n=395)	Statistics
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	
Mean pain interference score	5.0 (2.5)	2.7 (2.1)	3.1 (2.3)	2.1 (2.2)	1.5 (1.6)	F = 72.44, p <.001 1 > 2, 3, 4, and 5; 2 > 5; 3 > 4 and 5

Abbreviations: CF = cognitive function, PF = physical function, SD = standard deviation

[a]Clinically meaningful cutoff scores are in parentheses when available

Table 4 - Differences in Quality of Life Outcomes Among the Physical Function and Cognitive Function Latent Classes at Enrollment

Domains	Very Low PF and Low CF (1) 18.4% (n=245)	Low PF and High CF (2) 19.8% (n=264)	Moderate PF and Low CF (3) 26.7% (n=355)	Changing PF and CF (4) 5.4% (n=72)	Normal PF and CF (5) 29.7% (n=395)	Statistics
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	
Medical Outcomes Study – Short Form 12						
Physical functioning	16.5 (19.4)	36.4 (25.2)	54.3 (28.4)	58.2 (32.1)	84.1 (21.3)	F = 310.08, p < .001 1 < 2, 3, 4, and 5; 2, 3, and 4 < 5; 2 < 3 and 4
Role physical	22.8 (19.1)	47.4 (25.0)	44.6 (22.2)	65.8 (25.6)	78.1 (20.0)	F = 262.56, p < .001 1 < 2, 3, 4 and 5; 2, 3 and 4 < 5; 2 and 3 < 4
Bodily pain	44.1 (29.6)	76.9 (24.4)	76.1 (25.0)	82.2 (24.7)	92.7 (14.1)	F = 163.64, p < .001 1 < 2, 3, 4 and 5; 2, 3, and 4 <5
General health	37.8 (27.7)	56.8 (26.6)	64.1 (25.0)	74.4 (21.3)	78.3 (19.6)	F = 111.65, p < .001 1 < 2 < 3 < 4 and 5
Vitality	24.3 (23.3)	44.6 (23.9)	37.0 (23.4)	56.2 (22.4)	64.4 (20.5)	F = 136.67, p < .001 1 < 2, 3, 4 and 5 2>3; 2<4 and 5 3 < 4 and 5
Social functioning	41.4 (29.0)	70.1 (27.5)	59.4 (28.4)	78.3 (27.8)	85.4 (21.1)	F = 114.96, p < .001 1 < 2, 3, 4 and 5; 3 < 2, 4, and 5; 2 < 5
Role emotional	60.9 (30.9)	83.0 (25.0)	61.9 (26.6)	84.8 (24.0)	90.1 (15.9)	F = 92.61, p < .001 1 < 2, 4, and 5; 3 < 2, 4, and 5; 2 < 5
Mental health	64.1 (21.9)	79.2 (17.3)	61.7 (21.4)	76.4 (16.8)	79.9 (16.4)	F = 61.59, p < .001 1 < 2, 4, and 5; 3 < 2, 4, and 5
Physical component summary score	27.4 (6.6)	36.5 (6.8)	43.2 (6.8)	44.9 (8.2)	51.1(5.3)	F = 514.81, p < .001 1 < 2 < 3, 4, and 5; 3 and 4 < 5
Mental component summary score	45.3 (11.1)	53.8 (8.5)	42.6 (10.4)	52.8 (8.6)	53.0 (7.3)	F = 85.38, p < .001 1 < 2, 4, and 5; 1 > 3; 3 < 2, 4, and 5
Multidimensional Quality of Life Scale – Cancer						
Physical well-being	5.1 (1.6)	6.8 (1.6)	6.1 (1.6)	6.5 (1.6)	7.9 (1.4)	F = 138.81, p < .001 1 < 2, 3, 4, and 5; 2 ,3, and 4 < 5; 3 < 2

Domains	Very Low PF and Low CF (1) 18.4% (n=245)	Low PF and High CF (2) 19.8% (n=264)	Moderate PF and Low CF (3) 26.7% (n=355)	Changing PF and CF (4) 5.4% (n=72)	Normal PF and CF (5) 29.7% (n=395)	Statistics
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	
Psychological well-being	4.4 (1.6)	6.0 (1.8)	4.6 (1.6)	5.8 (1.8)	6.5 (1.6)	F = 89.46, p < .001 1 < 2, 4, and 5; 2, 3, and 4 < 5; 3 < 2 and 4
Social well-being	4.3 (1.8)	6.0 (1.8)	5.0 (1.8)	5.9 (1.7)	7.0 (1.6)	F = 103.78, p < .001 1 < 2, 3, 4, and 5; 2, 3, and 4 < 5; 3 < 2, and 4
Spiritual well-being	5.3 (2.2)	5.5 (2.1)	5.3 (1.9)	5.6 (1.9)	5.6 (2.1)	F = 1.21, p = .305
Total quality of life score	4.7 (1.3)	6.1 (1.3)	5.1 (1.2)	5.9 (1.3)	6.7 (1.2)	F = 130.22, p < .001 1 < 2, 3, 4, and 5; 3 < 2 and 4; 2, 3, and 4 < 5

Abbreviations: CF = cognitive function, PF = physical function, SD = standard deviation

Table 5 – Characteristics Associated with Membership in the Four Physical and Cognitive Function Classes With Deficits Compared to the Normal Physical and Cognitive Function Class

Characteristic[a]	Very Low Physical Function and Low Cognitive Function	Low Physical Function and High Cognitive Function	Moderate Physical Function and Low Cognitive Function	Changing Physical Function and Changing Cognitive Function
Demographic Characteristics				
Older age		■		
Younger age				■
Lower education	■			
More likely to be female	■		■	
Less likely to be married/partnered	■		■	
More likely to live alone	■			
Less likely to be employed	■	■	■	
More likely to have a lower annual income	■	■	■	
Less likely to exercise on a regular basis	■	■		
Clinical Characteristics				
Lower functional status	■	■	■	■
Higher number of comorbidities	■	■	■	
Higher comorbidity burden	■	■	■	
Higher number of cancer treatments	■			
Higher number of metastatic sites with and without lymph node involvement	■			
Lower number of metastatic sites with and without lymph node involvement				■
Higher MAX2 score				■
More likely to self-report heart disease	■	■		
More likely to self-report lung disease	■			
More likely to report diabetes	■			
More likely to report anemia or blood disease	■			
More likely to self-report depression	■		■	
More likely to self-report osteoarthritis	■			
More likely to self-report back pain	■	■	■	
More likely to self-report rheumatoid arthritis	■			
Less likely to have gastrointestinal cancer	■			■
More likely to have had only surgery, radiation therapy, or chemotherapy				■
More likely to not have metastatic disease				■

Characteristic[a]	Very Low Physical Function and Low Cognitive Function	Low Physical Function and High Cognitive Function	Moderate Physical Function and Low Cognitive Function	Changing Physical Function and Changing Cognitive Function
More likely to have a more emetogenic chemotherapy regimen				■
Symptom Characteristics				
Higher trait anxiety	■		■	■
Higher state anxiety	■		■	■
Higher depressive symptoms	■	■	■	
Higher morning fatigue	■	■	■	■
Higher evening fatigue	■	■	■	■
Lower morning energy	■	■	■	■
Lower evening energy	■	■	■	
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	■	■	■	
Medical Outcomes Study – Short Form-12				
Lower physical functioning	■	■	■	■
Lower role physical	■	■	■	■
Lower bodily pain	■	■	■	■
Lower general health	■	■	■	■
Lower vitality	■	■	■	■
Lower social functioning	■	■	■	
Lower role emotional	■	■	■	
Lower mental health	■		■	
Lower physical component summary score	■	■	■	■
Lower mental component summary score	■		■	
Multidimensional Quality of Life Scale - Cancer				
Lower physical well-being	■	■	■	■
Lower psychological well-being	■	■	■	■
Lower social well-being	■	■	■	■
Lower overall quality of life	■	■	■	■

[a]Comparisons done with the Normal Physical Function and Normal Cognitive Function (i.e., Both Normal) class

■ – Indicates the presence of the risk factor compared to the Normal Physical Function and Normal Cognitive Function (i.e., Both Normal) class

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