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Anxiety Profiles Are Associated With Stress, Resilience And Symptom Severity In Outpatients Receiving Chemotherapy

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Abstract

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Authors contributions

All authors contributed to the study conception and design. Data analysis was performed by Steven M. Paul and Bruce A. Cooper. The first draft of the manuscript was written by Kate Oppegaard and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript. All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Conflicts of interest

The authors have no relevant financial or non-financial interests to disclose.

Availability of code

Not applicable.

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 to publish

Not applicable.

Purpose: The purposes of this study, in a sample of oncology patients (n=1326) receiving chemotherapy, were to: identify subgroups of patients with distinct anxiety profiles and evaluate for differences in demographic and clinical characteristics, stress and resilience measures, and severity of co-occurring symptoms (i.e., depression, sleep disturbance, attentional function, fatigue, pain).

Methods: Patients completed self-report questionnaires a total of six times over two cycles of chemotherapy. Severity of state anxiety was evaluated using the Spielberger State Anxiety Inventory and resilience was assessed using the Connor Davidson Resilience Scale. Symptoms were assessed using the Center for Epidemiologic Studies Depression Scale, General Sleep Disturbance Scale, Lee Fatigue Scale, Attentional Function Index and Brief Pain Inventory.

Results: Based on the findings from the latent profile analysis that utilized the six assessments of state anxiety, 47.7% of the patients were classified as “Low”, 28.3% as “Moderate”, 19.5% as “High”, and 4.5.% as “Very High”. Anxiety levels remained relatively stable across the six timepoints. Compared to the Low class, membership in the Moderate, High, and Very High classes was associated with a number of characteristics (e.g., younger age, female gender, lower functional status, more comorbidities). Those patients with higher levels of anxiety reported higher levels of stress, lower levels of resilience, and increased severity of co-occurring symptoms.

Conclusion: Our findings suggest that a substantial number of oncology patients may warrant referral to psychological services. Clinicians need to perform systematic assessments of anxiety, stress, and common symptoms and initiate appropriate interventions to enhance resilience and coping.

Keywords

anxiety; cancer; distress; latent profile analysis; stress; resilience

INTRODUCTION

Anxiety in patients with cancer results in treatment delays[1] and significant decrements in quality of life[2]. In addition, it may have a negative impact on both disease recurrence and survival[1]. Anxiety and stress are inextricably linked[3]. A cancer diagnosis and associated events are stressful experiences[3] that may be influenced by an individual’s level of resilience (i.e., the ability to respond to or adapt to stress)[4]. However, both responses to stress and levels of resilience vary considerably among individuals. An evaluation of the relationships among anxiety, stress, and resilience in oncology patients is important because of the negative physiologic effects of stress[5], as well as its role in the development of multiple co-occurring symptoms[2].

While the subject of several systematic reviews[6,7], little is known about inter-individual variability in anxiety and its association with stress and resilience in oncology patients. Only two longitudinal studies have used a person-centered analytic approach (i.e., latent variable modeling) to evaluate for subgroups of patients with distinct anxiety profiles during chemotherapy[8,9]. In the first study of patients with advanced breast cancer[8], four anxiety profiles (i.e., low-stable, delayed, recovering, high-stable) were identified from prior to through 12 months after the initiation of chemotherapy. Anxiety was assessed using the

7-item anxiety subscale of the Hospital Anxiety and Depression Scale. No demographic or clinical characteristics were associated with any of these anxiety profiles. In the logistic regression analysis, compared to the low-stable class, patients in the other three classes had higher levels of unmet psychological supportive care needs, higher levels of physical symptom distress and rumination, and lower levels of optimism.

In the second longitudinal study of patients with breast cancer[9], participants completed a single-item anxiety measure (i.e., “During the past 24 hours did you experience anxiety?”) on a daily basis to evaluate anxiety over the course of the second and third cycles of chemotherapy. Two distinct anxiety classes (i.e., consistently mild anxiety and consistently moderate anxiety) were identified. Membership in the moderate anxiety class was associated with a lower level of education, receipt of doxorubicin, and spending more hours lying down. Differences in the anxiety measures and timing of the assessments may explain the inconsistent findings. However, the identification of subgroups of patients with different anxiety profiles supports the use of this person-centered analytic approach.

Using regression-based analytic approaches, five additional studies have evaluated for changes over time in anxiety and associated characteristics in patients receiving chemotherapy[10–14]. In a study of patients with breast or colorectal cancer[10], trait and state anxiety levels decreased over six chemotherapy cycles. While no associations were found with any demographic or clinical characteristics, higher levels of anxiety were associated with a higher symptom burden throughout treatment. However, this association was no longer present when patients’ level of trait anxiety at the initiation of treatment was factored into the analysis.

In a second study of patients with heterogenous types of cancer[11], anxiety was highest at the start of treatment and decreased over time. Higher levels of anxiety were associated with younger age and female gender. In another study of patients with ovarian cancer[12], anxiety levels increased from the initiation to the end of treatment. Higher levels of anxiety were associated with younger age and being single. In a fourth study of patients with breast cancer[13], while no associated characteristics were evaluated, anxiety was highest at the start of treatment and decreased over twelve months. In the final study of patients with breast cancer[14], the occurrence of moderate, severe, and very severe anxiety varied over the course of treatment. Higher levels of anxiety were associated with being unmarried, having a lower Karnofsky Performance Status score, and having more limitations in social activities. However, in the multivariate analysis, having more limitations in social activities was the only characteristic that remained significant.

While these studies provide useful information on risk factors for and changes in anxiety in patients receiving chemotherapy, the findings are inconsistent. Of these seven studies[8–14], only two used latent variable modeling to identify subgroups of patients with distinct anxiety profiles[8,9], In addition, in five of these studies[8,9,12–14], the majority of the patients were women; the number of demographic and clinical characteristics evaluated were limited; and only three reported on associations with co-occurring symptoms[8,10,13]. In addition, different instruments were used to assess anxiety and co-occurring symptoms. Finally, given the strong associations between anxiety and stress in oncology patients[5],

none of these studies measured stress and/or resilience. Therefore, the purposes of this study, in a sample of oncology patients (n=1326) who were receiving chemotherapy were to: identify subgroups of patients with distinct anxiety profiles and to evaluate for differences in demographic and clinical characteristics, stress and resilience measures, and the severity of common co-occurring symptoms. We hypothesized that, compared to patients with lower levels of anxiety, those with higher levels of anxiety would report higher levels of stress, lower levels of resilience, and increased severity of co-occurring symptoms.

METHODS

Patients and settings

This study is part of a larger, longitudinal study of the symptom experience of oncology outpatients receiving chemotherapy[15]. 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. The major reason for refusal was being overwhelmed with their cancer treatment.

Study procedures

The study was approved by the Institutional Review Board at each of the study sites. Of the 2234 patients approached, 1343 consented to participate. These patients completed questionnaires, a total of six times over two chemotherapy cycles (i.e., prior to chemotherapy administration, approximately 1 week after chemotherapy administration, and approximately 2 weeks after chemotherapy administration). A total of 1326 patients, who completed the anxiety measures, were included in this analysis.

Measures

Demographic and clinical measures—Patients completed a demographic questionnaire, Karnofsky Performance Status (KPS) scale[16], Self-Administered Comorbidity Questionnaire (SCQ)[17], Alcohol Use Disorders Identification Test (AUDIT) [18], and a smoking history questionnaire. The toxicity of each patient's chemotherapy regimen was rated using the MAX2 score[19], Medical records were reviewed for disease and treatment information.

Anxiety measures—The 20-items on the Spielberger State-Trait Anxiety Inventories (STAI-T and STAI-S) were rated from 1 to 4 [20]. The STAI-S measures a person's temporary anxiety response to a specific situation or how anxious or tense a person is "right now" in a specific situation. The STAI-T measures a person's predisposition to anxiety as part of one's personality. Cut-off scores of ≥31.8 and ≥32.2 indicate high levels of trait and state anxiety, respectively [20]. In the current study, the Cronbach's alphas for the STAI-T and STAI-S were 0.92 and 0.96, respectively.

Stress and resilience measures—The 14-item Perceived Stress Scale (PSS) was used as a measure of global perceived stress according to the degree that life circumstances are appraised as stressful over the course of the previous week[21]. In this study, its Cronbach's alpha was 0.85.

The 22-item Impact of Event Scale-Revised (IES-R) was used to measure cancer-related distress[22]. Patients rated each item based on how distressing each potential difficulty was for them during the past week "with respect to their cancer and its treatment". Three subscales evaluate levels of intrusion, avoidance, and hyperarousal perceived by the patient. Sum scores of ≥24 indicate clinically meaningful post traumatic symptomatology and scores of ≥33 indicate probable post-traumatic stress disorder (PTSD)[23]. In this study, the Cronbach's alpha for the IES-R total score was 0.92.

The 30-item Life Stressor Checklist-Revised (LSC-R) is an index of lifetime trauma exposure (e.g., being mugged, the death of a loved one, a sexual assault)[24]. The total LSC–R score is obtained by summing the total number of events endorsed. If patients endorsed an event, they were asked to indicate how much that stressor affected their life in the past year. These responses were averaged to yield a mean "Affected" score. In addition, a PTSD sum score was created based on the number of positively endorsed items (out of 21) that reflect the DSM-IV PTSD Criteria A for having experienced a traumatic event.

The 10-item Connor-Davidson Resilience Scale (CDRS) evaluates a patient's personal ability to handle adversity (e.g., "I am able to adapt when changes occur"; "I tend to bounce back after illness, injury, or other hardships")[4]. Total scores range from 0 to 40, with higher scores indicative of higher self-perceived resilience. The normative adult mean score in the United States is 31.8 (±5.4)[25]. In this study, its Cronbach's alpha was 0.90.

Other symptom measures—An evaluation of other common symptoms was done using valid and reliable instruments. The symptoms and their respective measures were: depressive symptoms (Center for Epidemiological Studies-Depression scale (CES-D)[26]) morning and evening fatigue and morning and evening energy (Lee Fatigue Scale (LFS)[27]); sleep disturbance (General Sleep Disturbance Scale (GSDS)[28]) cognitive function (Attentional Function Index (AFI)[29]) and pain (Brief Pain Inventory (BPI)[30]).

Data analysis

Descriptive statistics and frequency distributions were generated for sample characteristics at enrollment using the Statistical Package for the Social Sciences (SPSS) version 27[31]. Latent profile analysis (LPA) was used to identify unobserved subgroups of patients (i.e., latent classes) with distinct anxiety profiles over the six assessments, using the patients' state anxiety scores. The LPA was performed using MPlus™ Version 8.4[32].

Estimation was carried out with full information maximum likelihood with standard error 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[33], Vuong-Lo-Mendell-Rubin likelihood ratio test (VLRM), entropy, and latent class percentages that were

large enough to be reliable[34], Missing data were accommodated for with the use of the Expectation-Maximization (EM) algorithm[35].

Differences among the latent classes in demographic and clinical characteristics, stress and resilience measures, and symptom severity scores were evaluated using parametric and nonparametric tests. A p-value of <.05 was considered statistically significant. Post hoc contrasts were done using a Bonferroni corrected p-value of <.008 (.05/6 pairwise comparisons).

RESULTS

Latent profile analysis

Table 1 displays the fit indices for the one- through five-class solutions. The 4-class solution was selected because the BIC for that solution was lower than the BIC for the 3-class solution. In addition, the VLMR was significant for the 4-class solution, indicating that four classes fit the data better than three classes. Although the BIC was smaller for the 5-class than for the 4-class solution, the VLMR for 5-classes was not significant, indicating that too many classes had been extracted.

As shown in Figure 1, 47.7% (n=633) of the patients were classified as “Low”, 28.3% (n=375) as “Moderate”, 19.5% (n=258) as “High”, and 4.5.% (n=60) as “Very High”. Classes were named based on clinically meaningful cutoff scores for the STAI-S[20].

Differences in demographic and clinical characteristics

Compared to the Low class, patients in the Moderate class were younger, had a higher SCQ score, a lower KPS score, and were more likely to self-report a diagnosis of depression or back pain (Table 2). Compared to the Low class, patients in the High class were younger, more likely to be female, more likely to be Hispanic, less likely to be married or partnered, more likely to live alone, less likely to be employed, more likely to have a lower annual household income, and more likely to have childcare responsibilities. In addition, patients in the High class reported a higher number of comorbid conditions, a higher SCQ score, a higher MAX2 score, a lower KPS score, were more likely to self-report a diagnosis of depression or back pain and were more likely to have an antiemetic regimen that contained a neurokinin-1 receptor antagonist and two other antiemetics.

Compared to the Low class, patients in the Very High class were less likely to be married or partnered and more likely to have a lower annual household income. In addition, patients in the Very High class reported a higher number of comorbid conditions, a higher SCQ score, a lower KPS score, and were more likely to have a self-reported diagnosis of ulcer or stomach disease, kidney disease, anemia or blood disease, depression, or back pain.

Differences in stress and resilience

Significant differences in PSS total, IES-R subscales and total, and LSC-R affected sum scores were found among the four latent classes in the expected pattern (i.e., Low < Moderate < High < Very High) (Table 3). Compared to the Low class, patients in the High and Very High classes reported higher LSC-R total scores. Compared to the Low class,

patients in the other three classes reported higher LSC-R PTSD sum scores. In terms of resilience, compared to the Low class, patients in the other three classes reported lower CDRS scores.

Differences in co-occurring symptoms

The four classes had significantly different levels of trait and state anxiety in the expected pattern (i.e., Low < Moderate < High < Very High). In addition, significant differences in depressive symptoms, morning fatigue, sleep disturbance, and mean pain interference scores were found among the four classes in the expected pattern (i.e., Low < Moderate < High < Very High). Compared to the Low class, patients in the other three classes reported higher levels of evening fatigue, less morning energy, less evening energy, and lower AFI scores. Compared to the Low class, patients in the High and Very High classes reported higher worst pain intensity scores. Compared to the Low class, a lower percentage of patients in the other three classes reported that they did not experience pain. Compared to the Low class, a higher percentage of patients in the other three classes reported the occurrence of both non-cancer and cancer-related pain (Table 4).

DISCUSSION

This study is the first to use LPA to identify subgroups of oncology patients with distinct anxiety symptom profiles and evaluate for associations with stress, resilience, and multiple co-occurring symptoms. Of note, 52.3% of the patients reported moderate to very high levels of anxiety. Our overall occurrence rate is higher than the 5% to 47% reported in previous longitudinal studies of patients receiving chemotherapy[8–14]. These wide occurrence rates may be related to heterogeneity in both the types of cancer that were evaluated, the timing of the assessments, and/or the instruments used to assess anxiety.

In terms of the directionality of the changes in anxiety levels over a course of chemotherapy, findings from previous studies are inconsistent (e.g., decreases following the initiation of chemotherapy[10,11,13], increases after first treatment[12], and variable trajectories[14]). In contrast, in our study, for all four classes, anxiety levels remained relatively stable across the two cycles of chemotherapy. Differences across studies may be related to the timing and duration of the assessments and whether pretreatment levels of anxiety were taken into consideration in the trajectory analyses. However, a common feature, across our and previous studies[8,9,11,13], is that high levels of anxiety can persist for extended periods of time.

Demographic and clinical characteristics and worse anxiety profiles

Our findings are consistent with previous research that found that younger age, female gender, and being single were associated with higher levels of anxiety[11,12]. However, our study provides new insights into a number of common characteristics that were associated with membership in the Moderate, High, and Very High classes (Table 5). Compared to the Low class, the four common characteristics among the Moderate, High, and Very High classes were a higher SCQ score, self-reported diagnoses of depression and back pain, and a lower functional status. All of these characteristics are associated with a higher comorbidity

burden. This finding is consistent with a previous review that noted that patients with higher levels of anxiety had disproportionately higher rates of comorbid conditions[36]. In addition, a higher level of comorbidity is associated with a poorer functional status[37]. These findings warrant careful consideration because patients with cancer and multiple comorbidities are less likely to receive curative treatment, have a poorer quality of life, experience higher health care costs, and have decreased survival rates[37]. Taken together, patients with these characteristics warrant evaluation for optimal management of their comorbid conditions and persistent anxiety.

Stress and resilience characteristics and worse anxiety profiles

While previous research established associations between anxiety and stress[3], findings from our study highlight the complex relationships among anxiety and three distinct forms of stress (i.e., self-reported global stress, cancer-specific stress, lifetime stress exposure). In terms of global stress, our findings are consistent with previous reports of patients with cancer[38]. In terms of cancer-specific stress, patients in the High class had IES-R sum scores suggestive of post traumatic symptomatology and patients in the Very High class had scores indicative of probable PTSD[23]. Our findings are consistent with a recent review that noted that 7.3% to 13.8% of oncology patients meet the criteria for PTSD and that an additional 10% to 20% of patients meet the criteria for subsyndromal PTSD[3]. As noted in this review[3], and consistent with the significant differences in the number and effects of lifetime trauma exposure among our anxiety groups, the positive associations between trauma history and greater likelihood of experiencing cancer-related traumatic distress likely contribute to the relatively high IES-R scores in our sample. While challenges exist in the diagnosis of cancer-related PTSD, our findings support the need for implementation of stress reduction interventions, with the goal of reducing intrusive thoughts and anxiety[39]. Additional research on the efficacy of these types of interventions, as well as greater integration of effective interventions into practice, are warranted.

Compared to normative data for adults in the United States[4], patients in the Moderate, High, and Very High classes had clinically meaningful decrements in resilience. In addition, consistent with previous reports of oncology patients[40], higher levels of anxiety were associated with lower levels of resilience. Resilience is often described as an individual's ability to thrive despite hardship[4], It is considered a characteristic that can be modified to promote a more successful adaptation to cancer[41]. While findings across studies are inconsistent[41], a number of demographic characteristics, coping strategies, personality traits, and levels of social support can influence levels of resilience in patients with cancer. In addition, because the use of strategies to increase resilience may facilitate post traumatic growth following a cancer diagnosis[39], clinicians need to suggest that patients engage in restorative activities (e.g., mindfulness exercises)[39].

Multiple co-occurring symptoms and worse anxiety profiles

Consistent with the limited amount of research on the positive associations between anxiety and symptom burden[8,10], patients in the Moderate, High, and Very High classes reported clinically meaningful increases or decrements (i.e., energy, cognitive function) in all of the symptoms that were assessed in this study (Table 4). While it is recognized that

oncology patients experience multiple co-occurring symptoms[2], our findings suggest that over 50% of our patients were not receiving adequate symptom management. Furthermore, our findings support previous research that demonstrates relatively high rates for the co-occurrence of anxiety and depression[42]. In patients with psychiatric disorders, the co-occurrence of these two symptoms can have deleterious consequences including the need for increases in medication doses, delays in response to treatments, and increased probability of suicide[42]. Equally important, anxiety and depression have bi-directional relationships with the occurrence and severity of fatigue, sleep disturbances, and cognitive impairments[43]. Additional research is warranted to determine the common and distinct mechanisms that underlie these common and co-occurring symptoms in oncology patients.

Study limitations

Despite numerous strengths (e.g., concurrent evaluation of stress and symptoms), some limitations warrant consideration. First, stress and resilience measures were evaluated at only one timepoint. Future studies need to evaluate for changes in anxiety, as well as stress and resilience, over time. Second, the sample was relatively homogenous in terms ethnicity, gender, education, and income. The inclusion of a more diverse sample would increase the generalizability of our findings. Third, information on medications used to treat anxiety was not obtained and may have assisted with the interpretation of our findings. Lastly, the major reason for refusal to participate was being overwhelmed with cancer treatment which suggests an underestimation of anxiety in this sample.

Conclusion

Our study adds to the existing literature that demonstrates that anxiety is a common symptom in patients with cancer[44]. Anxiety, unrelieved stress, and the burden of cancer and its treatments can increase patients' vulnerability to the overlapping and deleterious effects of these problems[3,5]. Based on our findings, one can hypothesize that co-occurring symptoms may develop and/or exacerbate these problems[2] and may contribute to an inordinate symptom burden.

Based on our findings, clinicians need to perform systematic assessments of anxiety, stress, and common symptoms and initiate appropriate interventions. It should be noted that patients who screen positive for significant levels of anxiety and/or depressive symptoms should undergo a diagnostic interview to evaluate for needed interventions. In addition, findings from this study suggest that a substantial number of patients may warrant referral to psychological services. Future studies need to evaluate for differences in psychosocial adjustment characteristics (e.g., personality and coping) among the anxiety profiles to guide the development of interventions. Finally, an evaluation of the molecular mechanisms associated with a worse anxiety profile may provide targets for interventions.

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Availability of data and material

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

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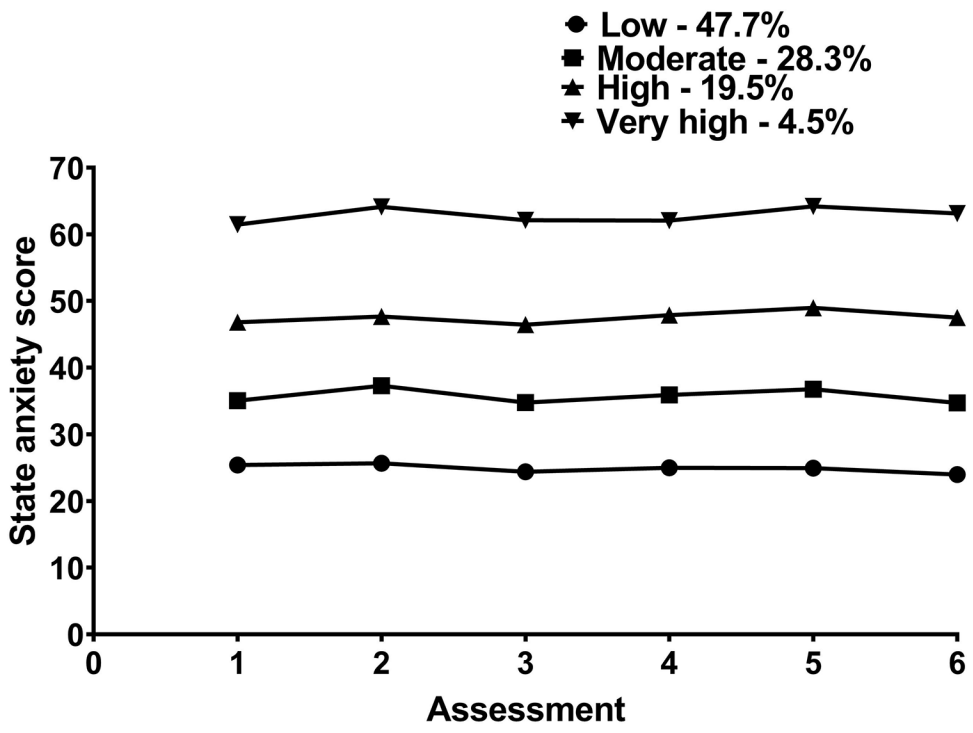

Fig. 1.
Trajectories of state anxiety for the four latent classes.

Table 1

Spielberger State Anxiety Scale: Latent Profile Solutions and Fit Indices for One through Five Classes

Model	LL	AIC	BIC	Entropy	VLMR
1 Class	−24650.12	49342.24	49451.23	n/a	n/a
2 Class	−24047.25	48150.50	48295.82	0.85	1205.74 $^{+}$
3 Class	−23796.96	47663.92	47845.56	0.87	500.58 $^{+}$
4 Class[a]	−23673.74	47431.48	47649.46	0.83	246.44 *
5 Class	−23599.59	47297.19	47551.49	0.84	ns

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

* p < .05;

$^{+}$ p < .00005

[a]The 4-class solution was selected because the BIC for that solution was lower than the BIC for the 3-class solution. In addition, the VLMR was significant for the 4-class solution, indicating that four classes fit the data better than three classes. Although the BIC was smaller for the 5-class than for the 4-class solution, the VLMR for 5-classes was not significant, indicating that too many classes had been extracted.

Abbreviations: AIC = Akaike's Information Criterion; BIC = Bayesian Information Criterion; LL = log-likelihood; n/a = not applicable; ns = not significant, VLMR = Vuong-Lo-Mendell-Rubin likelihood ratio test for the K vs. K-1 model

Table 2

Differences in Demographic and Clinical Characteristics Among the Anxiety Latent Classes

Characteristic	Low (0) 47.7% (n=633)	Moderate (1) 28.3% (n=375)	High (2) 19.5% (n=258)	Very High (3) 4.5% (n=60)	Statistics
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	
Age (years)	59.2 (11.5)	55.9 (12.9)	54.2 (13.0)	55.6 (10.3)	F = 12.73, p <0.001 0 > 1 and 2
Education (years)	16.3 (3.0)	16.3 (3.0)	15.9 (3.1)	16.1 (3.3)	F = 1.36, p = 0.254
Body mass index (kg/m^2)	26.1 (5.3)	26.1 (5.8)	26.4 (6.0)	26.4 (6.3)	F = 0.30, p = 0.824
Alcohol Use Disorders Identification Test score	2.8 (2.1)	3.0 (2.5)	3.2 (3.0)	3.1 (3.3)	F = 1.04, p = 0.375
Karnofsky Performance Status score	84.1 (11.4)	78.0 (12.2)	75.1 (12.2)	70.4 (11.4)	F = 54.32, p <0.001 0 > 1 > 2 > 3
Number of comorbid conditions	2.2 (1.3)	2.4 (1.4)	2.6 (1.5)	3.4 (1.7)	F = 15.20, p <0.001 0, 1, 2 < 3; 0 < 2
Self-administered Comorbidity Questionnaire score	4.9 (2.8)	5.6 (3.2)	6.1 (3.4)	8.0 (4.3)	F = 23.84, p <0.001 0, 1, and 2 < 3; 0 < 1 and 2
Time since diagnosis (years)	1.9 (3.5)	2.4 (4.5)	2.0 (4.1)	0.8 (1.2)	KW; p = 0.194
Time since diagnosis (years, median)	0.42	0.42	0.45	0.38	
Number of prior cancer treatments	1.6 (1.5)	1.6 (1.5)	1.7 (1.5)	1.5 (1.4)	F = 0.51, p = 0.678
Number of metastatic sites including lymph node involvement[a]	1.2 (1.2)	1.3 (1.2)	1.2 (1.3)	1.1 (1.0)	F = 1.30, p = 0.272
Number of metastatic sites excluding lymph node involvement	0.8 (1.0)	0.9 (1.1)	0.8 (1.1)	0.6 (0.8)	F = 1.59, p = 0.190
MAX2 score	0.17 (0.08)	0.18 (0.08)	0.19 (0.09)	0.17 (0.08)	F = 4.17, p = 0.006 0 < 2
	% (n)	% (n)	% (n)	% (n)	
Gender (% female)	73.6 (465)	79.7 (299)	83.7 (216)	86.7 (52)	X^2 =15.35, p = 0.002 0 < 2
Self-reported ethnicity					X^2 = 24.30, p = 0.004

Characteristic	Low (0) 47.7% (n=633)	Moderate (1) 28.3% (n=375)	High (2) 19.5% (n=258)	Very High (3) 4.5% (n=60)	Statistics
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	
White	72.0 (450)	69.5 (258)	66.1 (168)	58.3 (35)	NS
Asian or Pacific Islander	12.3 (77)	14.8 (55)	9.1 (23)	13.3 (8)	NS
Black	7.5 (47)	5.7 (21)	7.9 (20)	11.7 (7)	NS
Hispanic, Mixed, or Other	8.2 (51)	10.0 (37)	16.9 (43)	16.7 (10)	0 < 2
Married or partnered (% yes)	69.1 (431)	65.7 (243)	55.7 (14)	45.0 (27)	X^2 = 24.35, p <0.001 0 > 2; 0 and 1 > 3
Lives alone (% yes)	18.5 (115)	21.6 (80)	27.2 (69)	31.7 (19)	X^2 = 11.85, p = 0.008 0 < 2
Currently employed (% yes)	40.1 (250)	33.1 (123)	26.1 (67)	31.7 (19)	X^2 = 16.96, p = 0.001 0 > 2
Annual household income					
Less than $30,000 +	12.1 (67)	18.0 (60)	28.5 (69)	41.8 (23)	
$30,000 to $70,000	19.8 (110)	23.4 (78)	21.9 (53)	20.0 (11)	KW; <0.001 0 and 1 < 2 and 3
$70,000 to $100,000	20.1 (112)	14.4 (48)	15.7 (38)	3.6 (2)	
Greater than $100,000	48.0 (267)	44.3 (148)	33.9 (82)	34.5 (19)	
Child care responsibilities (% yes)	19.5 (121)	21.8 (79)	28.9 (73)	25.0 (15)	X^2 = 9.50, p = 0.023 0 < 2
Elder care responsibilities (% yes)	6.4 (37)	9.8 (33)	9.4 (22)	5.4 (3)	X^2 = 4.62, p = 0.202
Past or current history of smoking (% yes)	33.2 (207)	34.0 (125)	40.7 (103)	44.1 (26)	X^2 = 6.75, p = 0.080
Exercise on a regular basis (% yes)	73.6 (461)	71.1 (261)	64.6 (159)	66.7 (38)	X^2 = 7.47, p = 0.058
Specific comorbid conditions (% yes)					
Heart disease	5.5 (35)	7.7 (29)	3.5 (9)	1.7 (1)	X^2 = 7.19, p = 0.066
High blood pressure	31.6 (200)	27.7 (104)	29.5 (76)	35.0 (21)	X^2 = 2.39, p = 0.496
Lung disease	9.6 (61)	12.8 (48)	11.2 (29)	20.0 (12)	X^2 = 7.11, p = 0.068
Diabetes	9.2 (58)	8.0 (30)	8.5 (22)	15.0 (9)	X^2 = 3.19, p = 0.363
Ulcer or stomach disease	4.1 (26)	5.1 (19)	4.7 (12)	13.3 (8)	X^2 = 10.06, 0.018 0 < 3
Kidney disease	0.9 (6)	1.6 (6)	1.2 (3)	6.7 (4)	X^2 = 12.90, p = 0.005 0 < 3
Liver disease	6.8 (43)	7.2 (27)	5.0 (13)	3.3 (2)	X^2 = 2.30, p = 0.512

Characteristic	Low (0) 47.7% (n=633)	Moderate (1) 28.3% (n=375)	High (2) 19.5% (n=258)	Very High (3) 4.5% (n=60)	Statistics
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	
Anemia or blood disease	10.1 (64)	13.6 (51)	13.2 (34)	23.3 (14)	$X^2 = 10.36$, p = 0.016 0 < 3
Depression	8.5 (54)	18.1 (68)	38.8 (100)	55.0 (33)	$X^2 = 159.72$, p <0.001 0 < 1; 0 and 1 < 2 and 3
Osteoarthritis	11.7 (74)	12.8 (48)	11.2 (29)	13.3 (8)	$X^2 = 0.53$, p = 0.913
Back pain	19.4 (123)	27.7 (104)	32.6 (84)	50.0 (30)	$X^2 = 38.73$, p <0.001 0 < 1, 2, and 3; 1 < 3
Rheumatoid arthritis	3.6 (23)	1.9 (7)	4.3 (11)	1.7 (1)	$X^2 = 3.97$, p = 0.265
Cancer diagnosis					
Breast cancer	39.3 (249)	39.7 (149)	43.4 (112)	43.3 (26)	
Gastrointestinal cancer	33.0 (209)	28.8 (108)	27.9 (72)	25.0 (15)	$X^2 = 6.62$, p = 0.676
Gynecological cancer	16.3 (103)	20.0 (75)	16.3 (42)	16.7 (10)	
Lung cancer	11.4 (72)	11.5 (43)	12.4 (32)	15.0 (9)	
Prior cancer treatment					
No prior treatment	26.3 (162)	24.9 (91)	22.0 (55)	25.0 (15)	
Only surgery, CTX, or RT	40.8 (252)	40.5 (148)	45.6 (114)	46.7 (28)	
Surgery and CTX, or surgery and RT, or CTX and RT	21.6 (133)	20.3 (74)	17.2 (43)	10.0 (6)	$X^2 = 11.37$, p = 0.251
Surgery and CTX and RT	11.3 (70)	14.2 (52)	15.2 (38)	18.3 (11)	
Metastatic sites					
No metastasis	33.3 (209)	28.5 (106)	36.1 (91)	32.2 (19)	
Only lymph node metastasis	21.1 (132)	22.0 (82)	22.2 (56)	30.5 (18)	
Only metastatic disease in other sites	22.0 (138)	22.3 (83)	18.3 (46)	15.3 (9)	$X^2 = 9.16$, p = 0.422
Metastatic disease in lymph nodes and other sites	23.6 (148)	27.2 (101)	23.4 (59)	22.0 (13)	
Receipt of targeted therapy					
No	68.0 (422)	70.3 (258)	73.8 (186)	72.9 (43)	$X^2 = 3.23$, p = 0.358
Yes	32.0 (199)	29.7 (109)	26.2 (66)	27.1 (16)	
CTX regimen					
Only CTX	68.0 (422)	70.3 (258)	73.8 (186)	72.9 (43)	$X^2 = 4.94$, p = 0.551

Characteristic	Low (0) 47.7% (n=633)	Moderate (1) 28.3% (n=375)	High (2) 19.5% (n=258)	Very High (3) 4.5% (n=60)	Statistics
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	
Only targeted therapy	3.4 (21)	2.5 (9)	2.4 (6)	5.1 (3)	
Both CTX and targeted therapy	28.7 (178)	27.2 (100)	23.8 (60)	22.0 (13)	
Cycle length					
14 day cycle	44.9 (283)	40.3 (150)	37.4 (95)	36.2 (21)	KW = 4.46, p = 0.216
21 day cycle	47.6 (300)	53.0 (197)	55.1 (140)	55.2 (32)	
28 day cycle	7.5 (47)	6.7 (25)	7.5 (19)	8.6 (5)	
Emetogenicity of the CTX regimen					
Minimal/low	19.7 (124)	16.9 (63)	22.8 (58)	22.4 (13)	KW = 4.41, p = 0.220
Moderate	62.7 (395)	61.1 (228)	55.9 (142)	63.8 (37)	
High	17.6 (111)	22.0 (82)	21.3 (54)	13.8 (8)	
Antiemetic regimen					X^2 = 18.00, p = 0.035
None	8.3 (51)	6.0 (22)	7.1 (17)	3.5 (2)	NS
Steroid alone or serotonin receptor antagonist alone	21.4 (132)	20.1 (74)	19.5 (47)	21.1 (12)	NS
Serotonin receptor antagonist and steroid	50.2 (310)	47.6 (175)	42.3 (102)	40.4 (23)	NS
NK-1 receptor antagonist and two other antiemetics	20.2 (125)	26.4 (97)	31.1 (75)	35.1 (20)	0 < 2

[a] Total number of metastatic sites evaluated was 9.

[+] Reference group

Abbreviations: CTX = chemotherapy, kg = kilograms, KW = Kruskal Wallis, m^2 = meters squared, pw = pairwise, NK-1 = neurokinin-1, NS = not significant, RT = radiation therapy, SD = standard deviation

Table 3

Differences in Stress and Resilience Measures Among the Anxiety Latent Classes

Measures[a]	Low (0) 47.7% (n=633)	Moderate (1) 28.3 (n=375)	High (2) 19.5 (258)	Very High (3) 4.5% (n=60)	Statistics
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	
PSS total score (range 0–56)	13.6 (5.8)	19.8 (6.2)	25.5 (6.2)	32.4 (7.6)	F = 346.85, p<0.001 0 <1 < 2 < 3
IES-R total score (≥24)	12.5 (8.4)	19.9 (10.4)	27.2 (13.2)	43.0 (18.4)	F = 222.63, p<0.001 0 < 1 < 2 < 3
IES-R intrusion	0.6 (0.5)	1.0 (0.6)	1.4 (0.7)	2.2 (0.9)	F = 209.15, p<0.001 0 < 1 < 2 < 3
IES-R avoidance	0.8 (0.6)	1.0 (0.6)	1.2 (0.7)	1.7 (0.9)	F = 59.48, p<0.001 0 < 1 < 2 < 3
IES-R hyperarousal	0.3 (0.3)	0.7 (0.5)	1.1 (0.7)	2.0 (1.0)	F= 269.33, p<0.001 0 < 1 < 2 < 3
LSC-R total score (range 0–30)	5.5 (3.4)	6.1 (4.1)	6.9 (4.5)	8.4 (5.1)	F= 11.30, p<0.001 0 < 2; 0 and 1 < 3
LSC-R affected sum (range 0–150)	9.5 (8.1)	12.1 (11.1)	15.6 (13.0)	23.0 (16.2)	F = 33.95, p<0.001 0 < 1 < 2 < 3
LSC-R PTSD sum (range 0–21)	2.6 (2.6)	3.2 (3.1)	3.8 (3.3)	5.2 (4.2)	F = 16.19, p<0.001 0 < 1 and 2; 0, 1, and 2 < 3
CDRS total score (range 0–40)	32.9 (5.0)	29.3 (5.7)	25.8 (6.7)	23.6 (6.4)	F = 129.21, p<0.001 0 > 1; 0 and 1 > 2 and 3

Abbreviations: CDRS = Connor Davidson Resilience Scale, IES-R = Impact of Event Scale – Revised, LSC-R = Life Stressor Checklist-Revised, PSS = Perceived Stress Scale, PTSD = post-traumatic stress disorder, SD = standard deviation

[a]Clinically meaningful cutoff scores or range of scores

Table 4

Differences in Co-Occurring Symptom Severity Scores Among the Anxiety Latent Classes

Symptoms[a]	Low (0) 47.7% (n=633)	Moderate (1) 28.3% (n=375)	High (2) 19.5% (n=258)	Very High (3) 4.5% (n=60)	Statistics
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	
Depressive symptoms (≥16)	7.0 (5.3)	13.8 (6.8)	21.2 (8.6)	33.4 (10.0)	F= 466.34, p<0.001 0 < 1< 2 < 3
Trait anxiety (≥31.8)	27.9 (5.3)	36.7 (7.1)	46.0 (8.1)	55.4 (8.2)	F= 665.84, p<0.001 0 < 1< 2 < 3
State anxiety (≥32.2)	25.2 (5.3)	35.2 (7.7)	47.1 (8.2)	61.9 (10.1)	F= 949.27, p<0.001 0 < 1< 2 < 3
Morning fatigue (≥3.2)	2.2 (1.8)	3.4 (2.1)	4.5 (2.3)	5.5 (2.3)	F= 113.88, p<0.001 0 < 1< 2 < 3
Evening fatigue (≥5.6)	4.8 (2.2)	5.4 (1.9)	6.2 (2.0)	6.9 (1.9)	F= 36.24, p<0.001 0 < 1; 0 and 1 < 2 and 3
Morning energy (≤6.2)	4.9 (2.3)	4.1 (2.0)	3.8 (2.1)	3.2 (2.3)	F= 23.60, p<0.001 0 > 1 and 2; 0 and 1 > 3
Evening energy (≤3.5)	3.9 (2.1)	3.4 (1.8)	3.3 (2.0)	2.5 (2.0)	F= 11.42, p<0.001 0 > 1 and 2; 0 and 1 > 3
Sleep disturbance (≥43.0)	44.6 (18.9)	55.4 (18.0)	62.7 (17.5)	73.2 (18.6)	F= 90.33, p<0.001 0 < 1< 2 < 3
Attentional function (<5.0 = Low, 5 to 7.5 = Moderate, >7.5 = High)	7.3 (1.5)	6.1 (1.6)	5.1 (1.6)	4.6 (1.9)	F= 143.43, p<0.001 0 > 1; 0 and 1 > 2 and 3
	% (n)	% (n)	% (n)	% (n)	% (n)
Types of pain					X^2 = 80.85, p<0.001
None	35.3 (220)	24.4 (90)	17.2 (43)	8.5 (5)	0 > 1, 2, and 3; 1 > 3
Only non-cancer pain	17.9 (112)	14.9 (55)	13.2 (33)	11.9 (7)	NS
Only cancer pain	24.7 (154)	28.5 (105)	28.8 (72)	18.6 (11)	NS
Both non-cancer and cancer pain	22.1 (138)	32.2 (119)	40.8 (102)	61.0 (36)	0 < 1, and 2 < 3
For patients with pain	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	
Worst pain intensity score	5.6 (2.5)	6.1 (2.4)	6.6 (2.6)	7.5 (2.2)	F= 10.75, p<0.001 0 < 2 and 3; 1 < 3
Mean pain interference score	2.1 (2.0)	3.3 (2.4)	4.1 (2.6)	5.3 (2.9)	F= 52.74, p<0.001 0 < 1< 2 < 3

Abbreviations: SD = standard deviation

[a]Clinically meaningful cutoff scores

Table 5

Characteristics Associated with Membership to the Moderate, High, and Very High subgroups

Characteristic[a]	Moderate	High	Very High
Demographic Characteristics			
More likely to be younger	■	■	
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		■	■
More likely to be Hispanic		■	
More likely to report childcare responsibilities		■	
Clinical Characteristics			
Lower functional status	■	■	■
Higher number of comorbidities		■	■
Higher comorbidity burden	■	■	■
Higher MAX2 score		■	
More likely to self-report stomach disease			■
More likely to self-report kidney disease			■
More likely to self-report anemia			■
More likely to self-report depression	■	■	■
More likely to self-report back pain	■	■	■
More likely to have an antiemetic regimen of NK-1 receptor antagonist and two other antiemetics		■	
Stress and Resilience Measures			
Higher Perceived Stress Scale score	■	■	■
Higher Impact of Event Scale-Revised total score	■	■	■
Higher Impact of Event Scale-Revised intrusion score	■	■	■
Higher Impact of Event Scale-Revised avoidance score	■	■	■
Higher Impact of Event Scale-Revised hyperarousal score	■	■	■
Higher Life Stressor Checklist-Revised total score		■	■
Higher Life Stressor Checklist-Revised affected sum score	■	■	■
Higher Life Stressor Checklist-Revised PTSD sum score	■	■	■
Lower Connor Davidson Resilience Scale total score	■	■	■
Symptom Characteristics			
Higher depressive symptoms	■	■	■
Higher trait anxiety	■	■	■
Higher state anxiety	■	■	■
Higher morning fatigue	■	■	■
Higher evening fatigue	■	■	■

Characteristic[a]	Moderate	High	Very High
Lower morning energy	■	■	■
Lower evening energy	■	■	■
Higher sleep disturbance	■	■	■
Lower attentional function	■	■	■
Less likely to report no pain	■	■	■
More likely to report both non-cancer and cancer pain	■	■	■
More likely to report a worse pain intensity score		■	■
More likely to report a worse mean pain interference score	■	■	■

[a]Comparisons done with the Low subgroup

Abbreviation: PTSD = post-traumatic stress disorder