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Worst Pain Severity Profiles of Oncology Patients Are Associated with Significant Stress and Multiple Co-Occurring Symptoms

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Abstract

Little is known about the associations between pain, stress, and co-occurring symptoms in oncology patients. Purpose was to identify subgroups of @distinct worst pain profiles and evaluate for differences among the subgroups in demographic and clinical characteristics, as well as stress and symptom scores. Oncology outpatients (n=1305) completed questionnaires prior to their second or third chemotherapy cycle. Worst pain intensity was assessed six times over two chemotherapy cycles using a 0 to 10 numeric rating scale. The 371 patients (28.4%) who had ≤1 occurrence of pain over the six assessments were classified as the None class. For the remaining 934 patients whose data were entered into the latent profile analysis, three distinct worst pain profiles were identified (i.e., Mild [12.5%], Moderate [28.6%], Severe [30.5%]). Compared to None class, Severe class had fewer years of education and a lower annual income; were less likely to be employed and married; less likely to exercise on a regular basis, had a higher comorbidity burden, and a worse functional status. Compared to None class, Severe class reported higher levels of general, disease-specific, and cumulative life stress and lower levels of resilience, as well as higher levels of depressive symptoms, anxiety, fatigue, sleep disturbance, and cognitive dysfunction. This study is the first to identify distinct worst pain profiles in a large sample of oncology patients receiving chemotherapy and associated risk factors.

Perspective: Unrelieved pain remains a significant problem for oncology patients receiving chemotherapy. High levels of stress and co-occurring symptoms contribute to a more severe pain profile in these patients.

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Keywords

pain; stress; resilience; cancer; fatigue; sleep disturbance; anxiety; latent profile analysis

INTRODUCTION

Unrelieved pain occurs in approximately 55% of oncology patients during active treatment and over 35% of these patients report moderate to severe pain.[111] Outpatients receiving chemotherapy can experience pain as a result of the cancer itself, associated treatments (e.g., chemotherapy-induced peripheral neuropathy, aromatase inhibitors-induced arthralgia, granulocyte-colony stimulating factors-induced bone pain), and/or other comorbid conditions (e.g., musculoskeletal disorders).[22, 77, 88, 108] Despite the tremendous symptom burden associated with unrelieved pain, as well as the significant decrements in quality of life (QOL) and overall survival,[114] numerous studies found that oncology outpatients do not receive adequate pain management.[24, 25, 38, 41]

Undertreated pain in outpatients receiving chemotherapy can have significant clinical consequences, including interruptions in treatment.[22] For example, pain associated with chemotherapy-induced peripheral neuropathy is the dose-limiting toxicity associated with numerous chemotherapeutic agents.[22] Emerging evidence suggests that compared to oncology patients without pain, fatigue, depressive symptoms, anxiety, sleep disturbance, and cognitive impairment are more common in patients with pain.[5, 50, 57, 102, 114] In addition, patients with two or more concurrent symptoms are more likely to report severe pain.[50, 57] However, little is known about the associations between pain and these common symptoms in outpatients receiving chemotherapy.

A growing body of evidence suggests that a large amount of inter-individual variability exists in patients' pain experiences depending on various demographic (e.g., age, gender, ethnicity), clinical (e.g., body mass index (BMI), comorbidities, functional status), and socioeconomic factors.[24, 29, 57, 88, 114] However, most of these studies used a variable-centered approach to evaluate for risks factors associated with more severe pain.

Perceived stress varies widely among individuals depending on their susceptibility to stress and their level of resilience.[33, 52, 117] These differences in responses to stress and resilience behaviors have a direct impact on shaping each individual's unique pain phenotype.[17] As noted in previous studies,[10, 58, 74, 99] higher levels of cumulative lifetime stress, as well as higher levels of perceived stress or post-traumatic stress disorder (PTSD) are associated with increased occurrence rates for a variety of chronic pain conditions. However, no studies were identified that evaluated for associations between pain intensity and various types of stress (i.e., general stress, cancer-related distress, cumulative lifetime stress) and resilience in outpatients undergoing chemotherapy.

Latent profile analysis (LPA) is a person-centered analytic approach that can be used to identify subgroups (i.e., latent classes) of patients with similar patterns.[6, 7, 56] Given the heterogeneous nature of pain in outpatients receiving chemotherapy, the use of LPA may provide insights into factors that contribute to inter-individual variability in their pain

experiences. Therefore, the purposes of this study, in a sample of oncology outpatients receiving chemotherapy (n=1305), were to: identify subgroups of patients with distinct worst pain profiles and evaluate for differences among the subgroups in demographic and clinical characteristics; as well as for differences in stress and resilience measures and the severity of multiple co-occurring symptoms. We hypothesized that, compared to patients without pain, patients who reported higher pain intensity scores would report higher levels of stress, lower levels of resilience, and a higher symptom burden.

METHODS

Patients and settings

This study is part of a larger, longitudinal study of the symptom experience of oncology outpatients receiving chemotherapy.[70] 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 (60.1% response rate) and 1305 rated their worst pain intensity six times over two chemotherapy cycles (i.e., prior to chemotherapy administration (assessments 1 and 4), approximately 1 week after chemotherapy administration (assessments 2 and 5), and approximately 2 weeks after chemotherapy administration (assessments 3 and 6); Figure 1). The remaining questionnaires described in this paper were completed at enrollment (i.e., prior to their second or third cycle of chemotherapy), Medical records were reviewed for disease and treatment information.

Instruments

Demographic and Clinical Measures—Patients completed a demographic questionnaire, Karnofsky Performance Status (KPS) scale,[48] Self-Administered Comorbidity Questionnaire (SCQ),[93] Alcohol Use Disorders Identification Test (AUDIT),[9] and a smoking history questionnaire. Medical records were reviewed for disease and treatment information.

Pain Measure—Worst pain severity was assessed using the Brief Pain Inventory (BPI).[32] Patients were asked to indicate whether they were generally bothered by pain (yes/no). If they were generally bothered by pain, they rated their worst pain severity in the past 24 hours using a 0 (no pain) to 10 (worst pain imaginable) numeric rating scale (NRS). Worst pain scores were selected for this LPA because this score has well established clinically meaningful cutpoints[84, 96, 98] and is used in national cancer pain management guidelines.[105]

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. [27]. Each item was rated on a 0 to 4 Likert scale (i.e., 0 = never, 1 = almost never, 2 = sometimes, 3 = fairly often, 4 = very often). Total PSS scores can range from 0 to 56. A score of ≥14.0 indicates a clinically meaningful level of general stress. The PSS has well established validity and reliability.[31] 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[44, 112] 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". Each item was rated on a 0 (not at all) to 4 (extremely) Likert scale. Three subscales evaluate levels of intrusion, avoidance, and hyperarousal perceived by patient. The total score can range from 0 to 88. Sum scores of ≥24 indicated clinically meaningful post traumatic symptomatology and scores of ≥33 indicate probable PTSD.[30] The IES-R has well established validity and reliability [23, 30, 104]. 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).[113] The LSC–R assesses whether each stressful event occurred, at what ages the events occurred, how many times each event occurred, how dangerous the event was, and whether the individual had an intense emotional reaction to the event(s). The total LSC–R score is obtained by summing the total number of events endorsed (range of 0 to 30 with 30 indicating endorsement of all of the events). If the patient endorsed an event, the patient was asked to indicate how much that stressor affected his/her life in the past year, from 1 (not at all) to 5 (extremely). 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 LSC-R has demonstrated good to moderate test–retest reliability and good criterion-related validity with diverse populations.[51, 59, 66] In this study, the total scores Kudar-Richardson 20 was 0.76.

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"; and "I believe I can achieve my goals, even if there are obstacles").[12, 28] Items are scored on a 5-point Likert scale ("not true at all" to "true nearly all of the time"). 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 (standard deviation [SD], 5.4),[11, 12] with an estimated minimal clinically important difference of 2.7.[81] The CDRS has well established validity and reliability in oncology patients.[2, 67, 90]. In this study, its Cronbach's alpha was 0.90.

Symptom Measures—The 20-item Center for Epidemiological Studies-Depression scale (CES-D) evaluates the major symptoms in the clinical syndrome of depression. A total score can range from 0 to 60, with scores of ≥16 indicating the need for individuals to seek clinical evaluation for major depression. The CES-D has well established validity and reliability.[13, 89, 97] In this study, its Cronbach's alpha was 0.89.

The 20 items on Spielberger State-Trait Anxiety Inventories (STAI-T and STAI-S) are rated from 1 to 4. 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. The STAI-S and STAI-T inventories have well established validity and reliability.[8, 49, 100] In the current study, the Cronbach's alphas for the STAI-T and STAI-S were 0.92 and 0.96, respectively.

The 18-item Lee Fatigue Scale (LFS) was designed to assess physical fatigue and energy.[62] Each item was rated on a 0 to 10 NRS. Total fatigue and energy scores are calculated as the mean of the 13 fatigue items and the 5 energy items, respectively. Higher scores indicate greater fatigue severity and higher levels of energy. Using separate LFS questionnaires, patients were asked to rate each item based on how they felt within 30 minutes of awakening (i.e., morning fatigue, morning energy) and prior to going to bed (i.e., evening fatigue, evening energy). The LFS has established cut-off scores for clinically meaningful levels of fatigue (i.e., ≥3.2 for morning fatigue, ≥5.6 for evening fatigue) and energy (i.e., ≤6.2 for morning energy, ≤3.5 for evening energy).[39] It was chosen for this study because it is relatively short, easy to administer, and has well established validity and reliability.[42, 62, 63, 71–73] In the current study, the Cronbach's alphas were 0.96 for morning and 0.93 for evening fatigue and 0.95 for morning and 0.93 for evening energy.

The 21-item General Sleep Disturbance Scale (GSDS) was designed to assess the quality of sleep in the past week. Each item was rated on a 0 (never) to 7 (everyday) NRS. The GSDS total score is the sum of the 21 items that can range from 0 (no disturbance) to 147 (extreme sleep disturbance). Higher total scores indicate higher levels of sleep disturbance. A GSDS total score of ≥43 indicates a significant level of sleep disturbance.[39] The GSDS has well-established validity and reliability.[60, 61, 72]. In the current study, its Cronbach's alpha was 0.83.

The 16-item Attentional Function Index (AFI) assesses an individual's perceived effectiveness in performing daily activities that are supported by attention and working memory.[21] A higher total mean score on a 0 to 10 NRS indicates greater capacity to direct attention.[21] Total scores are grouped into categories of attentional function (i.e., <5.0 low function, 5.0 to 7.5 moderate function, >7.5 high function).[20] The AFI has well established reliability and validity.[21] In this study, its Cronbach's alpha was 0.93.

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.[47] As was done for other symptoms,[4, 53, 75, 107, 110, 115, 116] LPA was used to identify unobserved subgroups of patients (i.e., latent classes) with distinct worst pain profiles over the six assessments, using the patients' ratings of worst pain severity. Before performing the LPA, patients who reported the occurrence of pain for ≤1 of the six assessments were identified and labeled as the "None" class (n=371, 28.4%). Then, the LPA was performed on the remaining 934 patients using MPlus™ Version 8.4.[80]

Typically, for longitudinal data, growth mixture modeling (GMM) or latent class growth modeling (LCGM) of change trajectories would be used to identify latent classes of individuals who change differently over time. However, the current data demonstrated a complex pattern of change because the assessments included a pre-treatment assessment, an immediate post-treatment assessment, and a second post-treatment assessment -- for two cycles of treatment. One would expect the trajectory of change for pain scores over two treatment cycles, measured over only six occasions, to have a pattern that looks like two inverted “V’s”. GMM is ideally suited to discover change patterns that differ among latent classes such as linear change, or linear and quadratic change, when the number of assessments is as small as six. More complex patterns require more assessments for reliable identification of latent classes with different change trajectories.

Therefore, we identified latent classes of patients based on their profiles of means, where the means were estimated from the same symptoms (i.e., worst pain) measured on six occasions. In order to incorporate the expected correlations among the repeated measures, we included covariances among measures that were one or two occasions apart (a covariance structure with a lag of two). In this way, we retained the within person correlation among the measures, at the same time that we focused on the patterns of means that distinguished the latent classes. We limited the covariance structure to a lag of two to accommodate the expected reduction in correlation that would be introduced by two treatments within each set of three measurement occasions, and to reduce model complexity.

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 (BIC), Vuong-Lo-Mendell-Rubin likelihood ratio test (VLRM), entropy, and latent class percentages that were large enough to be reliable.[79] Missing data were accommodated for with the use of the Expectation-Maximization (EM) algorithm.[78] This algorithm is appropriate because the data in this study met the assumption of “missingness at random.

Differences among the latent classes in demographic and clinical characteristics, stress and resilience measures, and symptom severity scores at enrollment were evaluated using analysis of variance, Kruskal-Wallis or Chi Square 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 possible pairwise comparisons).

RESULTS

Latent profile analysis

The 371 patients (28.4%) who had ≤1 occurrence of pain over the six assessments were classified as the None class. For the remaining 934 patients whose data were entered into the LPA, a three-class solution was selected because the 3-class solution fit the data better than the 2-class solution (Table 1). The BIC for the 3-class solution was lower than the BIC for the 2-class solution. In addition, the VLMR was significant for the 3-class solution. Although the BIC was smaller for the 4-class than for the 3-class solution, the VLMR for

4-classes was not significant. Figure 2 displays the trajectories of worst pain profiles for the four classes. The latent classes were named based on clinically meaningful cutoff scores (1–3 = Mild, 4–6 = Moderate, ≥7 = Severe).[96] Of the 1305 patients in this study, 28.4% did not report pain (None), 12.5% were in the Mild class, 28.6% in the Moderate class, and 30.5% in the Severe class.

Differences in demographic and clinical characteristics at enrollment

Compared to the other three classes, patients in the Severe class had fewer years of education, a lower annual household income, were more likely to be unemployed, had a higher number of comorbid conditions, a higher SCQ score, a lower functional status, and were more likely to self-report diagnoses of anemia and back pain. Compared to the None and Moderate classes, patients in the Severe class had a higher BMI, were less likely to exercise in a regular basis, and were more likely to self-report diagnoses of ulcer or stomach disease and depression. Compared to the None class, patients in the Moderate and Severe classes reported a higher number of previous cancer treatments and were more likely to self-report a diagnosis of rheumatoid arthritis (Table 2).

Differences in stress and resilience measures at enrollment

Compared to the other three classes, patients in the Severe class reported higher PSS, intrusion, avoidance, hyperarousal, and total IES-R, as well as LSC-R affected sum scores. Compared to the None class, patients in the Moderate class reported higher PSS and IES-R intrusion and hyperarousal scores. Compared to the None class, patients in the other three classes reported higher LSC-R PTSD sum and total scores. Compared to the None class, patients in the Severe pain reported lower CDRS scores (Table 3).

Differences in symptom scores at enrollment

Compared to the other three classes, patients in the Severe class reported higher levels of depressive symptoms, trait anxiety, state anxiety, morning fatigue, evening fatigue, sleep disturbance, and cognitive dysfunction. Compared to the None class, patients in the Moderate class reported higher levels of depressive symptoms, trait anxiety, state anxiety, morning fatigue, sleep disturbance, cognitive dysfunction, and decrements in morning energy (Table 4).

DISCUSSION

This study is the first to use LPA to identify subgroups of oncology patients undergoing chemotherapy with distinct pain profiles (see Figure 2). Consistent with our a priori hypothesis, compared to the patients without pain, patients in Moderate and Severe pain classes reported higher stress scores and a higher symptom burden (Table 5). Of note, over 70% of our patients reported pain and over 50% had moderate to severe pain. This occurrence rate is higher than the 55% reported in a meta-analysis of pain in oncology patients receiving treatment.[111] Given that our data were collected during the rise in discussions regarding the opioid epidemic in the United States,[69] these findings suggest that the undertreatment of pain in oncology patients remains a significant clinical problem.[41]

Demographic characteristics associated with worst pain profiles

Table 5 provides a summary of the common and distinct characteristics associated with the Low, Moderate, and Severe pain classes, compared to the None class. The remainder of this discussion places these comparisons within the context of the extant literature. Patients in the Severe class were more likely to be female, single, unemployed, had a lower annual household income, and were less likely to exercise on a regular basis. While findings regarding gender differences in pain occurrence and intensity among oncology patients are inconsistent,[1, 19, 34, 65] a growing body of preclinical evidence suggests that sexual dimorphism exists in the development of chemotherapy-induced peripheral neuropathy with female rats more likely to develop this adverse effect.[37, 101] Equally important, several chronic pain conditions (e.g., osteoarthritis[85] rheumatoid arthritis[76]) that occurred more frequently in our sample are more common in women. In addition, in one study of oncology outpatients,[18] women reported more hesitancy in using analgesics and had lower levels of adherence with their analgesic regimen. These findings suggest that female oncology patients are a high risk group that warrant careful assessments of both cancer and non-cancer related pain.

As noted previously,[15, 16] ongoing cancer treatments and unrelieved pain interfere with patients' employment and contribute to financial toxicity. In addition, chronic pain conditions (e.g., back pain) may result in significant disability which interferes with one's ability to work and remain employed. Finally, patients who are single may lack social support which is known to amplify patients' pain experiences.[43] These factors are likely to add to the stress that patients in the Severe class were experiencing.

Clinical characteristics associated with worst pain profiles

Compared to the None class, patients in the Moderate and Severe classes reported a higher number of comorbidities, a higher comorbidity burden, a higher number of previous cancer treatments, and higher occurrence rates for osteoarthritis, back pain, and rheumatoid arthritis. Not surprisingly, these patients reported not only statistically significant but clinically meaningful decrements in functional status (Cohen's d = 0.36 for the Moderate and 0.86 for the Severe classes).[26] Taken together and supported by previous findings from the general population,[86] multimorbidity is associated with more severe pain and significant decrements in functional performance. In addition, the receipt of chemotherapy may contribute to the development of comorbid conditions or make existing comorbidities worse.[40, 94] These findings suggest that oncology clinicians need to work with primary care providers to achieve the optimal management of the patient's cancer and co-occurring conditions, as well as their pain.

A higher BMI and lack of regular exercise were two modifiable characteristics associated with membership in the Severe pain class. While findings regarding the relationship between BMI and pain are inconsistent,[35, 106, 109] it is reasonable to hypothesize that in addition to unrelieved pain, a mean BMI in the overweight range; the higher occurrence rates for a number of painful comorbid conditions; and the lack of regular exercise are associated with a lower function status in the patients in the Severe class. In addition to pain management

interventions, these patients warrant referrals to dieticians and physical therapists to improve their level of physical functioning.

Stress and resilience characteristics associated with worst pain profiles

While patients in the Moderate and Severe classes had significantly higher general stress scores than those in the None class, all four classes had PSS scores that were above the clinically meaningful cutpoint. This finding is consistent with previous studies that noted that a cancer diagnosis and associated treatments are stressful experiences for most patients.[3]

In addition, compared to the None class, patients in the other three classes had significantly higher levels of disease-specific stress and cumulative life stress. While the mean IES-R total score in the Severe class did not exceed the clinically meaningful cutpoint, 42% of the patients in this class had scores above the cutpoint of 24 (i.e., partial PTSD) and 17% met the criteria for PTSD. While the LSC-R has not been used to assess cumulative life stress in oncology patients, the total score for the LSC-R is comparable to a community-based samples of Columbian (7.2 ± 3.8)[46] and Mexican (9.5 ± 4.2)[82] women and individuals who were dependent on prescription opioids (7.7 ± 0.6).[59] Our findings are consistent with previous reports that demonstrated positive associations between chronic pain and the extent of lifetime trauma exposures.[45, 58] As noted in two reviews,[17, 33] stress can decrease pain thresholds due to a heavy allostatic load and dysregulation of the neuroendocrine stress axes. In addition, early life stress is known to alter the responsiveness of the hypothalamic pituitary axis, as well as the functioning of the opioidergic, monoaminergic, endocannabinoid, and immune systems.[10]

In terms of resilience, while none of the latent classes had CDRS scores above the normative adult mean score in the United States of 31.8 (±5.4),[11, 12] their scores were consistent with a previous study of oncology patients[68] and higher than those reported by primary care patients with depressive symptoms.[87] While a behavioral response to stress, recent evidence suggests that a large amount of inter-individual variability exists in resilience. In addition, the active and unique biological mechanisms associated with resilience appear to buffer an individual's response to stress, not simply reverse pathophysiologic mechanisms.[14, 36, 91]

Multiple co-occurring symptoms associated with worst pain profiles

In terms of multiple co-occurring symptoms, it should be noted that all four classes reported severity ratings for decrements in morning and evening energy, as well as sleep disturbance that were above the clinically meaningful cutoff scores. Given that between 30% to 88% of oncology patient report sleep disturbance during treatment,[95] it is not surprising that these symptoms clustered together in our sample regardless of pain class.

Compared to the None class, patients in the Moderate and Severe classes reported a higher overall symptom burden (i.e., higher scores for depressive symptoms, state and trait anxiety, morning fatigue and sleep disturbance, as well as significant decrements in morning energy and cognitive function; Table 5). These findings suggest that dynamic and synergistic interactions occur between pain and multiple co-occurring symptoms. This hypothesis is consistent with a previous review that suggested that patients with multiple co-occurring

symptoms experience more severe pain due to the complex interactions among a variety of physiological, psychological, behavioral, and sociocultural factors.[83].

Perhaps most important, the Moderate and Severe classes reported higher levels of all three types of stress, in addition to multiple co-occurring symptoms. While these initial findings warrant confirmation, a growing body of evidence suggests that stress, pain, and other common symptoms associated with cancer and its treatment may share common underlying mechanisms including alterations in inflammatory cascades,[54, 55] disruptions in the hypothalamic-pituitary-adrenal axis,[64] and alterations in the gut brain axis.[92, 103] This hypothesis warrants investigation in future studies.

LIMITATIONS

Several limitations warrant consideration. Given that our sample was relatively homogenous in terms of gender and ethnicity, our findings may not generalize to more diverse racial and ethnic groups. Given that these patients were not recruited prior to the initiation of chemotherapy and not followed to the completion of treatment, longitudinal studies are needed to evaluate the relationships among pain, stress, and multiple co-occurring symptoms. While the sample size was large and the Bonferroni procedure for multiple comparisons was used, the post hoc comparisons may need to be interpreted with caution. Finally, detailed information on the causes of and treatments for pain were not available for our sample.

CONCLUSIONS

Despite these limitations, the findings from this study suggest that synergistic relationships occur between unrelieved pain, stress, and multiple co-occurring symptoms in oncology patients receiving chemotherapy. These complex relationships may make it difficult for clinicians to manage pain in these patients. Guided by our findings, clinicians need to perform a comprehensive evaluation of these multiple and interacting factors. Undoubtedly, patients whose profile matches our Severe class will require referrals to symptom management and psychological services.

Longitudinal studies are needed to identify the causal relationships between pain, stress, and multiple co-occurring symptoms. In addition, detailed characterization of both cancer and non-cancer pain problems are warranted in oncology patients undergoing chemotherapy. Finally, studies of the common and unique molecular mechanisms associated with pain, stress, resilience, and multiple co-occurring symptoms are warranted to be able to develop precision health interventions for these patients.

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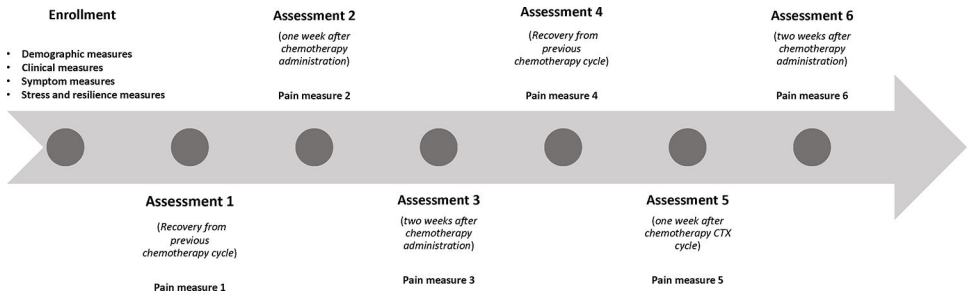

Figure 1 –.
Timeline for the study measures

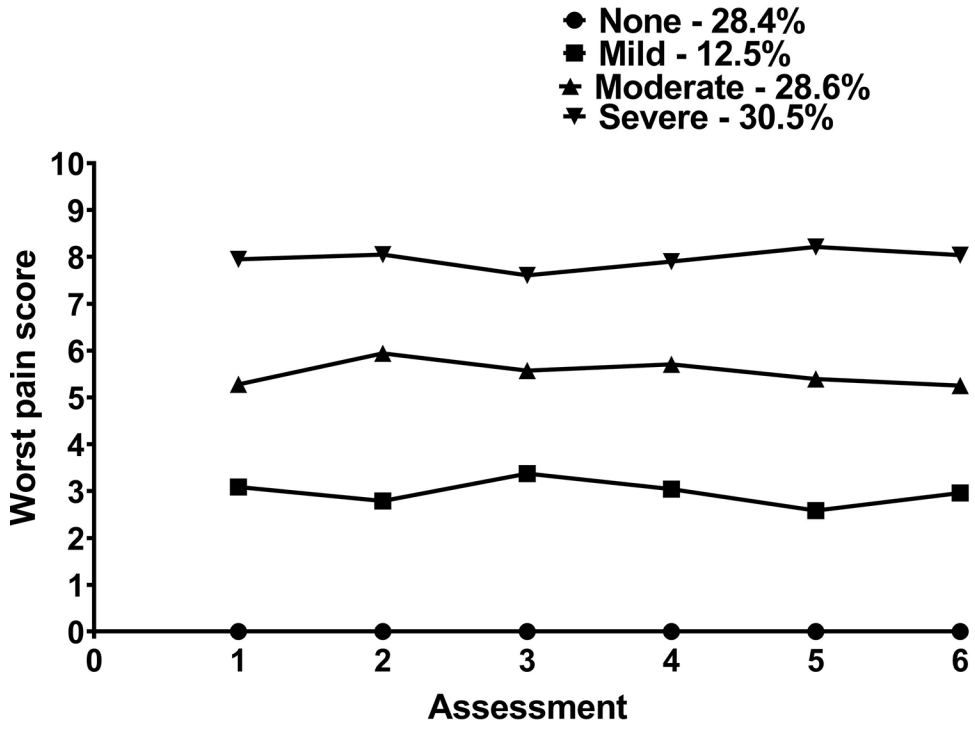

Figure 2 –.
Trajectories of worst pain severity for the four latent classes.

Table 1 –

Worst Pain Latent Profile Solutions and Fit Indices for One through Four Classes

Model	LL	AIC	BIC	Entropy	VLMR
1 Class	−7754.82	15557.64	15673.78	n/a	n/a
2 Class	−7544.66	15151.32	15301.35	0.71	420.31 $^{+}$
3 Class[a]	−7490.39	15056.78	15240.68	0.70	108.54 *
4 Class	−7441.09	14972.18	15189.96	0.73	ns

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

* p < .01

$^{+}$ p < .00005

[a]The 3-class solution was selected because the BIC for that solution was lower than the BIC for the 2-class solution. In addition, the VLMR was significant for the 3-class solution, indicating that three classes fit the data better than two classes. Although the BIC was smaller for the 4-class than for the 3-class solution, the VLMR for 4-classes was not significant, indicating that too many classes had been extracted. Further, the 4-class solution included a small predicted class (only 17 predicted cases; less than two-percent of the sample), raising the concern that the solution may not generalize to other samples.

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

Table 2 –

Differences in Demographic and Clinical Characteristics at Enrollment Among the Worst Pain Latent Classes

Characteristic	None (0) 28.4% (n=371)	Low (1) 12.5% (n=163)	Moderate (2) 28.6% (n=373)	Severe (3) 30.5% (n=398)	Statistics
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	
Age (years)	58.2 (11.9)	57.9 (12.0)	57.3 (12.4)	55.9 (12.8)	F = 2.37, p = .069
Education (years)	16.7 (3.2)	16.4 (3.0)	16.3 (2.9)	15.6 (2.9)	F = 7.57, p <.001 0, 1, and 2 > 3
Body mass index (kg/m^2)	25.5 (5.5)	26.4 (5.6)	25.9 (5.3)	27.1 (6.1)	F = 5.37, p = .001 0 and 2 < 3
Alcohol Use Disorders Identification Test score	3.0 (2.0)	2.9 (2.2)	3.0 (2.6)	3.0 (2.8)	F = 0.04, p = .988
Karnofsky Performance Status score	84.8 (11.5)	82.7 (11.9)	80.3 (11.4)	74.1 (12.3)	F = 54.03, p <.001 0, 1, and 2 > 3; 0 > 2
Number of comorbid conditions	1.9 (1.1)	2.2 (1.2)	2.4 (1.4)	3.0 (1.6)	F = 41.00, p <.001 0, 1, and 2 < 3; 0 < 1 and 2
Self-administered Comorbidity Questionnaire score	4.3 (2.4)	4.9 (2.6)	5.4 (2.9)	7.0 (3.8)	F = 55.23, p <.001 0, 1, and 2 < 3; 0 < 2
Time since diagnosis (years)	1.7 (3.2)	2.0 (3.7)	2.2 (4.3)	2.0 (4.2)	KW = 8.57, p = .036 0 < 2
Time since diagnosis (years, median)	0.4	0.43	0.43	0.45	
Number of prior cancer treatments	1.3 (1.3)	1.6 (1.5)	1.7 (1.6)	1.8 (1.5)	F = 6.16, p <.001 0 < 2 and 3
Number of metastatic sites including lymph node involvement[a]	1.1 (1.2)	1.3 (1.3)	1.3 (1.2)	1.3 (1.3)	F = 2.26, p = .080
Number of metastatic sites excluding lymph node involvement	0.7 (0.9)	0.9 (1.1)	0.8 (1.1)	0.8 (1.1)	F = 2.60, p = .051
MAX2 score	0.17 (0.08)	0.16 (0.08)	0.18 (0.08)	0.18 (0.08)	F = 3.90, p = .009 1 < 2 and 3
	% (n)	% (n)	% (n)	% (n)	
Gender (% female)	71.9 (266)	72.4 (118)	79.4 (296)	84.4 (336)	X^2 = 20.93, p <0.001 0 and 1 < 3
Self-reported ethnicity					X^2 = 23.83, p = .005

Characteristic	None (0) 28.4% (n=371)	Low (1) 12.5% (n=163)	Moderate (2) 28.6% (n=373)	Severe (3) 30.5% (n=398)	Statistics
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	
White	70.5 (260)	66.0 (107)	75.0 (276)	66.4 (259)	NS
Asian or Pacific Islander	12.5 (46)	16.7 (27)	12.5 (46)	10.0 (39)	NS
Black	6.8 (25)	7.4 (12)	6.5 (24)	8.2 (32)	NS
Hispanic, Mixed, or Other	10.3 (38)	9.9 (16)	6.0 (22)	15.4 (60)	2 < 3
Married or partnered (% yes)	69.6 (256)	70.4 (114)	64.7 (236)	55.8 (218)	X^2 = 19.42, p <.001 0 and 1 > 3
Lives alone (% yes)	18.8 (69)	19.1 (31)	21.6 (79)	25.6 (101)	X^2 = 6.02, p = .110
Currently employed (% yes)	42.2 (154)	38.0 (62)	37.3 (138)	26.2 (103)	X^2 = 22.96, p <.001 0, 1, and 2 > 3
Annual household income					
Less than $30,000 +	9.7 (32)	14.9 (21)	13.6 (45)	30.0 (110)	
$30,000 to $70,000	17.0 (56)	26.2 (37)	20.0 (66)	24.0 (88)	KW = 62.57, p <.001 0, 1, and 2 > 3
$70,000 to $100,000	19.7 (65)	13.5 (19)	19.7 (65)	13.9 (51)	
Greater than $100,000	53.6 (177)	45.4 (64)	46.7 (154)	32.2 (118)	
Child care responsibilities (% yes)	22.0 (80)	23.1 (37)	21.3 (78)	22.2 (86)	X^2 = 0.23, p = .973
Elder care responsibilities (% yes)	6.2 (21)	6.1 (9)	6.4 (22)	12.1 (43)	X^2 = 11.32, p = .010 0 < 3
Past or current history of smoking (% yes)	30.2 (110)	41.5 (66)	36.7 (135)	38.4 (151)	X^2 = 8.45, p = .038 no significant pairwise contrasts
Exercise on a regular basis (% yes)	77.7 (283)	68.4 (108)	72.4 (265)	63.4 (246)	X^2 = 19.63, p <.001 0 and 2 > 3
Specific comorbid conditions (% yes)	3.2 (12)	4.3 (7)	6.7 (25)	7.8 (31)	
Heart disease					X^2 = 8.65, p = .034 0 < 3
High blood pressure	29.1 (108)	32.5 (53)	27.6 (103)	33.7 (134)	X^2 = 4.00, p = .261
Lung disease	9.4 (35)	10.4 (17)	11.8 (44)	14.1 (56)	X^2 = 428, p = .233
Diabetes	7.0 (26)	7.4 (12)	9.1 (34)	11.8 (47)	X^2 = 6.08, p= .108
Ulcer or stomach disease	3.0 (11)	4.3 (7)	3.5 (13)	8.0 (32)	X^2= 13.31, p = .004 0 and 2 < 3
Kidney disease	0.8 (3)	0.0 (0)	1.9 (7)	2.3 (9)	X^2 = 5.75, p = .124
Liver disease	5.4 (20)	7.4 (12)	6.7 (25)	7.0 (28)	X^2 = 1.16, p = .763

Characteristic	None (0) 28.4% (n=371)	Low (1) 12.5% (n=163)	Moderate (2) 28.6% (n=373)	Severe (3) 30.5% (n=398)	Statistics
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	
Anemia or blood disease	8.4 (31)	8.6 (14)	11.0 (41)	19.1 (76)	X^2 = 24.85, p<.001 0, 1, and 2 < 3
Depression	10.5 (39)	16.0 (26)	18.5 (69)	29.1 (116)	X^2 = 44.70, p <.001 0 and 1 < 3; 2 < 3
Osteoarthritis	5.9 (22)	8.6 (14)	14.7 (55)	17.6 (70)	X^2 = 28.35, p <.001 0 and 1 < 3, 0 < 2
Back pain	7.3 (27)	21.5 (35)	27.1 (101)	43.7 (174)	X^2 = 135.07, p <.001 0, 1, and 2 < 3; 0 < 1 and 2
Rheumatoid arthritis	0.8 (3)	4.3 (7)	3.2 (12)	4.8 (19)	X^2 = 10.84, p = .013 0 < 2 and 3
Cancer diagnosis					X^2 = 26.18, p = .002
Breast cancer	38.5 (143)	37.4 (61)	44.5(166)	38.9 (155)	NS
Gastrointestinal cancer	35.6 (132)	39.3 (64)	24.7 (92)	27.1 (108)	0 and 1 > 2 and 3
Gynecological cancer	13.2 (49)	14.1 (23)	20.1 (75)	20.1 (80)	NS
Lung cancer	12.7 (47)	9.2 (15)	10.7 (40)	13.8 (55)	NS
Prior cancer treatment					
No prior treatment	29.2 (105)	25.8 (40)	23.7 (86)	21.8 (85)	
Only surgery, CTX, or RT	44.0 (158)	43.2 (67)	41.6 (151)	40.3 (157)	X^2 = 18.22, p = .033 no significant pairwise contrasts
Surgery and CTX, or surgery and RT, or CTX and RT	15.3 (55)	21.9 (34)	22.6 (82)	21.0 (82)	
Surgery and CTX and RT	11.4 (41)	9.0 (14)	12.1 (44)	16.9 (66)	
Metastatic sites					
No metastasis	34.8 (126)	27.7 (44)	31.6 (117)	32.4 (128)	
Only lymph node metastasis	22.4 (81)	22.0 (35)	21.1 (78)	22.8 (90)	X^2 = 4.29, p = .891
Only metastatic disease in other sites	19.1 (69)	23.9 (38)	22.7 (84)	20.3 (80)	
Metastatic disease in lymph nodes and other sites	23.8 (86)	26.4 (42)	24.6 (91)	24.6 (97)	
Receipt of targeted therapy					
No	73.5 (263)	66.0 (105)	71.7 (263)	68.2 (268)	X^2 = 4.26, p = .233
Yes	26.5 (95)	34.0 (54)	28.3 (104)	31.8 (125)	
CTX regimen					X^2 = 8.62, p = .196
Only CTX	73.5 (263)	66.0 (105)	71.7 (263)	68.2 (268)	

Characteristic	None (0) 28.4% (n=371)	Low (1) 12.5% (n=163)	Moderate (2) 28.6% (n=373)	Severe (3) 30.5% (n=398)	Statistics
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	
Only targeted therapy	2.5 (9)	5.7 (9)	2.7 (10)	2.3 (9)	
Both CTX and targeted therapy	24.0 (86)	28.3 (45)	25.6 (94)	29.5 (116)	
Cycle length					KW = 8.13, p = .043 No significant pairwise contrasts
14 day cycle	45.5 (166)	47.2 (76)	39.5 (146)	37.9 (149)	
21 day cycle	48.2 (176)	47.8 (77)	51.4 (190)	54.7 (215)	
28 day cycle	6.3 (23)	5.0 (8)	9.2 (34)	7.4 (29)	
Emetogenicity of the CTX regimen					KW = 17.49, p = .001 0 > 3
Minimal/low	14.8 (54)	17.4 (28)	20.8 (77)	24.1 (95)	
Moderate	60.8 (222)	66.5 (107)	57.6 (213)	61.2 (241)	
High	24.4 (89)	16.1 (26)	21.6 (80)	14.7 (58)	
Antiemetic regimen					X^2 = 10.57, p = .306
None	6.7 (24)	10.2 (16)	6.4 (23)	6.2 (24)	
Steroid alone or serotonin receptor antagonist alone	18.5 (66)	15.9 (25)	22.3 (80)	22.4 (87)	
Serotonin receptor antagonist and steroid	48.3 (172)	54.1 (85)	45.5 (163)	45.9 (178)	
NK-1 receptor antagonist and two other antiemetics	26.4 (94)	19.7 (31)	25.7 (92)	25.5 (99)	

[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, n/a = not applicable, NK-1 = neurokinin-1, NS = not significant, RT = radiation therapy, SD = standard deviation

Table 3 –

Differences in Stress and Resilience Measures at Enrollment Among the Worst Pain Latent Classes

Measures[a]	None (0) 28.4% (n=371)	Low (1) 12.5% (n=163)	Moderate (2) 28.6% (n=373)	Severe (3) 30.5% (n=398)	Statistics
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	
PSS total score (≥14.0)	16.0 (7.9)	17.6 (6.9)	18.5 (8.1)	20.8 (8.4)	F = 23.22, p <.001 0, 1, and 2 < 3; 0 < 2
IES-R total score (≥24)	15.5 (10.6)	15.9 (10.5)	17.9 (12.3)	23.4 (15.3)	F = 27.62, p <.001 0, 1, and 2 < 3
IES-R intrusion	0.7 (0.6)	0.8 (0.6)	0.9 (0.7)	1.1 (0.8)	F = 25.29, p <.001 0, 1, and 2 < 3; 0 < 2
IES-R avoidance	0.9 (0.6)	0.8 (0.6)	0.9 (0.7)	1.1 (0.7)	F = 9.59, p <.001 0, 1, and 2 < 3
IES-R hyperarousal	0.5 (0.5)	0.5 (0.5)	0.6 (0.6)	0.9 (0.8)	F = 33.48, p <.001 0, 1, and 2 < 3; 0 < 2
LSC-R total score (range 0–30)	4.8 (3.2)	6.1 (4.2)	6.3 (3.7)	6.9 (4.3)	F = 14.68, p <.001 0 < 1, 2, and 3
LSC-R affected sum (range 0–150)	8.3 (7.2)	11.7 (11.6)	11.9 (9.3)	15.0 (13.3)	F = 19.30, p <.001 0, 1, and 2 < 3; 0 < 1 and 2
LSC-R PTSD sum (range 0–21)	2.1 (2.3)	3.1 (3.3)	3.2 (2.8)	3.9 (3.4)	F = 17.39, p <.001 0 < 1, 2, and 3
CDRS total score (≥31.8)	31.1 (6.3)	29.6 (6.2)	30.3 (6.0)	29.3 (6.7)	F = 5.14, p = .002 0 > 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 at Enrollment Among the Worst Pain Latent Classes

Symptoms[a]	None (0) 28.4% (n=371)	Low (1) 12.5% (n=163)	Moderate (2) 28.6% (n=373)	Severe (3) 30.5% (n=398)	Statistics
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	
Depressive symptoms (≥16)	9.6 (8.0)	11.5 (8.7)	12.8 (9.2)	16.4 (10.8)	F = 34.26, p <.001 0, 1, and 2 < 3; 0 < 2
Trait anxiety (≥31.8)	31.6 (9.2)	34.4 (9.9)	35.4 (10.1)	38.3 (11.2)	F = 26.71, p <.001 0, 1, and 2 < 3; 0 < 1 and 2
State anxiety (≥32.2)	30.6 (10.6)	32.3 (11.7)	33.6 (11.9)	37.5 (13.7)	F = 21.04, p <.001 0, 1, and 2 < 3; 0 < 2
Morning fatigue (≥3.2)	2.4 (2.1)	2.6 (2.0)	3.0 (1.9)	4.2 (2.4)	F = 50.50, p <.001 0, 1, and 2 < 3; 0 < 2
Evening fatigue (≥5.6)	5.0 (2.3)	5.1 (2.1)	5.3 (1.9)	5.9 (2.0)	F = 15.30, p <.001 0, 1, and 2 < 3
Morning energy (≤6.2)	4.9 (2.4)	4.5 (2.4)	4.4 (2.1)	3.9 (2.1)	F = 10.50, p <.001 0 and 2 > 3; 0 > 2
Evening energy (≤3.5)	3.6 (2.1)	3.6 (2.1)	3.7 (1.9)	3.3 (2.0)	F = 3.75, p = .011 0 and 2 > 3
Sleep disturbance (≥43.0)	46.0 (18.6)	47.6 (18.7)	52.1 (19.0)	61.0 (20.2)	F = 41.93, p <.001 0, 1, and 2 < 3; 0 < 2
Attentional function (<5.0 = Low, 5 to 7.5 = Moderate, >7.5 = High)	7.0 (1.8)	6.7 (1.8)	6.4 (1.6)	5.8 (1.8)	F = 30.64, p <.001 0, 1, and 2 > 3; 0 > 2

Abbreviations: SD = standard deviation

[a]Clinically meaningful cutoff scores

Table 5 –

Characteristics Associated With Membership in the Mild, Moderate, and Severe Pain Group

Characteristic[a]	Mild pain	Moderate pain	Severe pain
Demographic Characteristics			
Fewer years of education			■
More likely to be female			■
Less likely to be married/partnered			■
More likely to have elder care responsibilities			■
Less likely to be employed			■
More likely to have a lower annual income			■
Less likely to exercise on a regular basis			■
Clinical Characteristics			
Higher body mass index			■
Lower functional status		■	■
Higher number of comorbidities	■	■	■
Higher comorbidity burden		■	■
Longer time since cancer diagnosis		■	
Higher number of cancer treatments		■	■
More likely to self-report heart disease			■
More likely to self-report stomach disease			■
More likely to self-report anemia			■
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 receive a chemotherapy regimen with lower emetogenicity			■
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		■	■

Characteristic[a]	Mild pain	Moderate pain	Severe pain
Higher trait anxiety	■	■	■
Higher state anxiety		■	■
Higher morning fatigue		■	■
Higher evening fatigue			■
Lower morning energy		■	■
Lower evening energy			■
Higher sleep disturbance		■	■
Lower attentional function		■	■

[a]Comparisons done with the None group

Abbreviation: PTSD = post-traumatic stress disorder