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Higher Stress And Symptom Severity Are Associated With Worse Depressive Symptom Profiles In Patients Receiving Chemotherapy

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Abstract

Purpose: Identify subgroups of patients with distinct depressive symptom profiles and evaluate for differences in demographic and clinical characteristics, levels of stress and resilience, and the severity of co-occurring symptoms.

Methods: Patients (n=1327) had a diagnosis of breast, gastrointestinal, gynecological, or lung cancer; had received chemotherapy within the preceding four weeks; and were scheduled to receive at least two additional cycles of chemotherapy. Demographic and clinical characteristics, stress, resilience, and co-occurring symptoms were evaluated at enrollment. Depressive symptoms were evaluated using the Center for Epidemiological Studies-Depression (CES-D) scale six times over two cycles of chemotherapy. Latent profile analysis (LPA) was used to identify subgroups of patients (i.e., latent classes) with distinct depressive symptom profiles using the six CES-D scores.

Results: Based on the LPA, 47.3% of the patients were classified as “None”; 33.6% as “Subsyndromal”; 13.8% as “Moderate”; and 5.3% as “High”. Compared to None class, patients in the other three classes had a lower functional status, a higher comorbidity burden, and a self-reported diagnosis of depression or back pain. Those patients with higher levels of depressive symptoms reported higher levels of stress, lower levels of resilience, and increased severity of co-occurring symptoms.

Conclusions: Inter-individual variability in depressive symptoms was associated with demographic and clinical characteristics, multiple types of stress and levels of resilience, as well as with the increased severity of multiple co-occurring symptoms. The risk factors associated with

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worse depressive symptom profiles can assist clinicians to identify high risk patients and initiate more timely supportive care interventions.

Keywords

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

INTRODUCTION

Clinically significant depression occurs in 17% to 45% of oncology patients receiving chemotherapy (Wen et al., 2019). Unresolved depressive symptoms can lead to decreased adherence with treatment (Li et al., 2017), longer hospitalizations (Li et al., 2017), a poorer prognosis (Reiche et al., 2004), and increased mortality (Li et al., 2017). For some patients, a cancer diagnosis is a significant stressor that serves as a catalyst for depressive symptoms (Wen et al., 2019). For others, acute and/or chronic stress are risk factors associated with the development of depressive symptoms (Reiche et al., 2004). Furthermore, due to its negative effects on various physiologic processes through activation of the sympathetic nervous system and hypothalamic-pituitary-adrenal axis, increased stress may result in inhibition of anti-tumor responses (Reiche et al., 2004) and more severe co-occurring symptoms (Weber and O'Brien, 2017). Higher levels of resilience can increase an individual's ability to respond adaptively to stressors (Osório et al., 2017). However, like stress, levels of resilience vary substantially among individuals. Therefore, concurrent evaluation of depressive symptoms, stress and resilience, as well as co-occurring symptoms, may provide a more complete picture of the relationships among these characteristics that can be used to identify patients who may benefit from additional screening or referrals to psychosocial support services.

Given that many factors contribute to the development and/or exacerbation of depressive symptoms during cancer treatment, an evaluation of inter-individual variability in patients' responses is warranted. This goal can be accomplished using a person-centered analytic approach (e.g., latent variable modeling) to identify oncology patients with distinct depressive symptom profiles. To date, only two longitudinal studies have used this approach to evaluate oncology patients receiving chemotherapy (Lam et al., 2013; Whisenant et al., 2020). In the first study of patients with advanced breast cancer (n=192) (Lam et al., 2013), four distinct depressive symptoms profiles (i.e., low-stable, recovering, high-stable, high-recovering) were identified from enrollment through 12 months after the initiation of chemotherapy. While no demographic or clinical characteristics were associated with any of the depressive symptom profiles, compared to the low-stable group, patients in the other three groups reported more cancer-related rumination, greater physical symptom distress, and were less optimistic. In the second study of patients with breast cancer (n=166) (Whisenant et al., 2020), two distinct depressive symptom profiles (i.e., consistently mild depressed mood, consistently moderate depressed mood) were identified during the second and third cycles of chemotherapy. Receipt of doxorubicin was the only characteristic associated with membership in the moderate depressed mood class.

Using various methods of regression analysis, five additional studies have evaluated for changes over time in depressive symptoms and associated characteristics in oncology patients receiving chemotherapy (Berger et al., 2020; Bergerot et al., 2017; Duc et al., 2017; Liu and Yang, 2019; Nakamura et al., 2021). In a study of patients with heterogeneous cancer types (n=260) (Duc et al., 2017), while 46% of patients had depressive symptoms prior to starting chemotherapy (i.e., enrollment); 44% (25% of whom did not report depressive symptoms at enrollment) had depressive symptoms after four cycles of chemotherapy. While pre-treatment depressive symptoms and poorer nutritional status were associated with an increased risk for depressive symptomatology during chemotherapy, effective chemotherapy treatment was associated with a decreased risk. In a second study of patients with heterogeneous cancer types (n=548) (Bergerot et al., 2017), depressive symptoms were highest at the start of chemotherapy and decreased over time. While women had higher depressive symptom scores at the initiation of chemotherapy, this association did not persist over time. In a study of patients with ovarian cancer (n=111) (Liu and Yang, 2019), depressive symptom scores decreased from prior to through the completion of treatment. In addition, younger age was associated with higher levels of depressive symptoms. In a study of patients with breast cancer (n=219) (Berger et al., 2020), while no demographic or clinical characteristics were evaluated, depressive symptom scores were higher at one month after the completion of chemotherapy compared to scores prior to and one year after initiation of treatment. In the final study of patients with breast cancer (n=256) (Nakamura et al., 2021), the occurrence of moderate, severe, or very severe depressive symptoms varied over the course of treatment and more severe depression was associated with limitations in social activities.

These studies provide valuable insights into inter-individual variability in depressive symptoms and associated risk factors. However, of the seven studies cited above (Berger et al., 2020; Bergerot et al., 2017; Duc et al., 2017; Lam et al., 2013; Liu and Yang, 2019; Nakamura et al., 2021; Whisenant et al., 2020), only two used latent variable modeling to identify subgroups of patients with distinct depressive symptom profiles (Lam et al., 2013; Whisenant et al., 2020); only two included patients with heterogeneous cancer types (Bergerot et al., 2017; Duc et al., 2017); only two evaluated for common co-occurring symptoms (Berger et al., 2020; Lam et al., 2013); and none assessed for associations between depressive symptoms and stress or resilience. Furthermore, the instruments used to measure depressive symptoms and co-occurring symptoms were not consistent across studies. In order to have a more comprehensive evaluation of inter-individual variability in depressive symptoms in oncology patients, studies need to include assessments of demographic and clinical characteristics, co-occurring symptoms, stress, and resilience. Therefore, the purposes of this study, in a sample of oncology patients (n=1327) who were receiving chemotherapy were to: identify subgroups of patients with distinct depressive symptom profiles and evaluate for differences in demographic and clinical characteristics, levels of stress and resilience, and the severity of common co-occurring symptoms. We hypothesized that patients with higher levels of depressive symptoms would report higher levels of stress, lower levels of resilience, and increased severity of multiple 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 (Miaskowski et al., 2014). 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 depressive symptom 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 1327 patients who had complete data on the depression measure were included in this analysis.

Instruments

Demographic and clinical measures—Patients completed a demographic questionnaire, Karnofsky Performance Status (KPS) scale (Karnofsky, 1977), Self-Administered Comorbidity Questionnaire (SCQ) (Sangha et al., 2003), Alcohol Use Disorders Identification Test (AUDIT) (Bohn et al., 1995), and a smoking history questionnaire. The toxicity of each patient's chemotherapy regimen was rated using the MAX2 score (Extermann et al., 2004). Medical records were reviewed for disease and treatment information.

Depressive symptoms measure—The 20-item Center for Epidemiological Studies-Depression scale (CES-D) evaluates the major symptoms in the clinical syndrome of depression (Radloff, 1977). 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. In this study, its Cronbach's alpha was 0.89.

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 (Cohen et al., 1983). 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 (Horowitz et al., 1979). 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) (Creamer et al., 2003). 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) (Wolfe and Kimmerling, 1997). 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") (Campbell-Sills and Stein, 2007). 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) (Campbell-Sills et al., 2009). 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: anxiety (Spielberger State-Trait Anxiety Inventories (STAI-T and STAI-S) (Spielberger et al., 1983)); morning and evening fatigue and morning and evening energy (Lee Fatigue Scale (LFS) (Lee et al., 1991)); sleep disturbance (General Sleep Disturbance Scale (GSDS) (Fletcher et al., 2008)) cognitive function (Attentional Function Index (AFI) (Cimprich et al., 2005)) and pain (Brief Pain Inventory (BPI) (Daut et al., 1983)).

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 (IBMCorp, 2020). Latent profile analysis (LPA) was used to identify unobserved subgroups of patients (i.e., latent classes) with distinct depressive symptom profiles over the six assessments, using the six CES-D scores. The LPA was performed using MPlus™ Version 8.4 (Muthen and Muthen, 1998–2020).

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 (Mravec et al.), Vuong-Lo-Mendell-Rubin likelihood ratio test (VLRM), entropy, and latent class percentages that were large enough to be reliable (Muthén and Muthén, 2009). Missing data were accommodated with the use of the Expectation-Maximization (EM) algorithm (Muthen and Shedden, 1999).

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 evaluated using a Bonferroni corrected p-value of <.008 (.05/6 possible 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.

In terms of latent class membership, 47.3% of the patients (n=628) were classified as “None”; 33.6% (n=446) as “Subsyndromal”; 13.8% (n=183) as “Moderate”; and 5.3% (n=70) as “High” (Figure 1). Classes were named based on established cutoff scores for the CES-D (Radloff, 1977).

Differences in demographic and clinical characteristics

Compared to the None class, patients in the Subsyndromal class were younger, more likely to be female, and had a lower annual household income. In addition, patients in the Subsyndromal class had a lower KPS score, a higher SCQ score, and were more likely to self-report a diagnosis of depression or back pain (Table 2).

Compared to the None class, patients in the Moderate class were younger, more likely to be female, more likely to live alone, more likely to have elder care responsibilities, had a lower annual household income, were less likely to be married partnered, and less likely to be employed. In addition, patients in the High class had a lower KPS score, a higher number of comorbidities, a higher SCQ score, a higher MAX2 score, a higher AUDIT score, were more likely to self-report a diagnosis of depression or back pain and were more likely to have an antiemetic regimen that included a neurokinin-1 (NK-1) receptor antagonist and two other antiemetics.

Compared to the None class, patients in the High class were less likely to be married or partnered, more likely to live alone, more likely to be Hispanic, and had a lower annual household income. In addition, patients in the High class had a lower KPS score, a higher number of comorbidities, a higher SCQ score, and were more likely to self-report a diagnosis of stomach disease, depression, or back pain. Additional post hoc comparisons are noted on Table 2.

Differences in stress and resilience measures

Significant differences in PSS total, IES-R total and subscale, and LSC-R PTSD sum scores at enrollment were found among the four latent classes in the expected pattern (i.e., None

< Subsyndromal < Moderate < High; Table 3). Compared to the None class, patients in the other three classes reported higher LSC-R total and LSC-R PTSD sum scores. In terms of resilience, significant differences in CDRS scores were found among the four latent classes in the expected pattern (i.e., None > Subsyndromal > Moderate > High).

Differences in co-occurring symptom scores

Significant differences in depressive symptoms, trait anxiety, state anxiety, sleep disturbance, and mean pain interference scores at enrollment were found among the four latent classes in the expected pattern (i.e., None < Subsyndromal < Moderate < High; Table 4). Compared to the None class, patients in the other three classes reported higher levels of morning and evening fatigue, lower levels of morning and evening energy, and lower levels of attentional function. Compared to the None class, a lower percentage of patients in the other three classes reported that they did not experience pain. Compared to the None class, a higher percentage of patients in Moderate and High classes reported the occurrence of both non-cancer and cancer pain and higher worst pain severity scores. Differences in the pain interference scores followed the expected pattern (i.e., None < Subsyndromal < Moderate < High).

DISCUSSION

This study is the first to use LPA to identify four subgroups of patients with distinct depressive symptom profiles, with concurrent evaluation of differences in levels of self-reported stress, resilience, and common co-occurring symptoms. Of note, 33.6% of the patients had subsyndromal levels and 19.1% had moderate or high levels of depressive symptoms. In a meta-analysis that evaluated self-reported depression in oncology patients (Krebber et al., 2014), the pooled mean prevalence of depressive symptoms was 24% across 38 studies that used the CES-D. As noted in this meta-analysis (Krebber et al., 2014), self-report measures are intended to screen for risk or severity of depressive symptoms and may overestimate depression. However, depressive symptoms in oncology patients may be missed because a diagnostic interview for depression is not practical in fast-paced oncology practices (Krebber et al., 2014). Therefore, the use of a self-report measure to screen for depression is recommended (Luckett et al., 2010) followed by a diagnostic interview and referral to psychological services (Krebber et al., 2014).

While in our study and similar to a previous report (Whisenant et al., 2020), our patients' depressive symptom scores remained relatively consistent, in previous studies, the trajectories of depressive symptoms varied over time (Duc et al., 2017; Lam et al., 2013; Nakamura et al., 2021); decreased but did not resolve (Bergerot et al., 2017; Liu and Yang, 2019); or were highest at the end of chemotherapy (Berger et al., 2020). These inconsistent findings may be related to the timing of assessments; the instruments used to assess depression; the presence of pretreatment depressive symptoms and/or other comorbid conditions; and/or the failure to account for inter-individual variability. However, both the high prevalence rates and stable trajectories of depressive symptoms among our latent classes may be related to differences in the severity of stress and co-occurring

symptoms. Therefore, the remainder of this discussion will focus on the characteristics that distinguished the Subsyndromal, Moderate, and High classes from the None class (Table 5).

Demographic and clinical characteristics associated with higher depressive symptom profiles

In terms of age, consistent with previous studies of oncology patients (Saracino et al., 2020a; Yang et al., 2020), patients in the Subsyndromal and Moderate classes were significantly younger than those in the None class. As noted previously (Saracino et al., 2020a), older oncology patients may endorse lower levels of depressive symptoms related to a variety of factors (e.g., a true increased sense of well-being as one ages, differing response styles in different age groups). Of note, in a recent confirmatory factor analysis of the CES-D (Saracino et al., 2020b), the authors concluded that the CES-D can be used to screen oncology patients and does not require scoring adjustments for patients' age.

Consistent with findings in the general population (Morssinkhof et al., 2020), a higher percentage of women were in the Subsyndromal and Moderate classes. The fact that a higher percentage of patients in the Moderate and High classes reported being single and living alone suggests that the lack of social support contributes to depressive symptoms. This hypothesis is supported by findings from a meta-analysis that noted that oncology patients with a strong social support network were less likely to report depressive symptoms (Wen et al., 2019). However, clinicians need to be mindful that patients with established support networks warrant ongoing evaluation because patients with depressive symptoms are at increased risk for declining social support over the trajectory of their cancer experience (Chang et al., 2019).

Compared to the None class, patients in the Subsyndromal class were more likely to be unemployed and patients in the other three classes reported a lower annual household income. This finding is important because oncology patients with lower incomes, who screen positive for depression, are less likely to receive referrals to psychology or psychiatry services (Hallet et al., 2020). In addition, patients in the Subsyndromal class were more likely to have elder care responsibilities. While not evaluated in oncology patients, in a study of family caregivers (Butler et al., 2005), elder care responsibilities increased the risk for depressive symptoms.

Consistent with previous reports (Bergerot et al., 2017; Duc et al., 2017), most of the cancer-specific characteristics (i.e., diagnosis, prior treatments, metastatic sites, type of regimen, chemotherapy cycle length) were not associated with latent class membership. However, the two clinical characteristics that were unique to the Moderate class (i.e., higher MAX2 score, receipt of an antiemetic regimen that included a NK-1 receptor antagonist and two other antiemetics) suggest that patients who were receiving a more toxic and/or emetogenic chemotherapy regimen may be at increased risk for depressive symptoms. Additional research is warranted that examines the relationship between chemotherapy regimens and psychological symptom trajectories.

Of note, compared to the None class, the four clinical characteristics that were common to the Subsyndromal, Moderate, and High classes (i.e., lower functional status, higher

comorbidity burden, self-reported diagnosis of depression or back pain) highlight the positive relationships between a higher comorbidity burden and more severe depressive symptom profiles. As noted in one review (Menear et al., 2015), compared to the general population, depressive symptoms were two to three times more common in patients with multiple co-morbidities. In addition, in a large cohort study of patients with breast cancer (Yang et al., 2017), similar associations were found.

In terms of back pain, while not evaluated in oncology patients, in a longitudinal study of twins (Fernandez et al., 2017), chronic back pain was associated with an increased risk for the development of depressive symptoms. In addition, as noted in two reviews of patients with breast cancer (Caplette-Gingras and Savard, 2008; Reich et al., 2008), individuals with a previous history of depression were more likely to develop depressive symptoms during cancer. These findings warrant careful consideration because in a study that compared patients who developed depressive symptoms and/or functional limitations after a cancer diagnosis to those who had a history of depressive symptoms and/or functional limitations at the time of diagnosis (Stommel et al., 2002), individuals with a history of either or both had a 2.6 times greater hazard of dying in the 19 months following the diagnosis. Therefore, comprehensive assessment and optimal management of comorbid conditions are essential components of oncology care that may have a significant impact on depressive symptoms as well as other important patient outcomes.

Stress and resilience characteristics associated with higher depressive symptom profiles

As noted in one review (Smith, 2015), while both acute and chronic stress can contribute to depressive symptoms in oncology patients, a need exists to evaluate multiple types of stress concurrently. In terms of global stress, our findings are consistent with previous studies of women with breast (Li et al., 2021a; Li et al., 2021b) and ovarian (Liu et al., 2017) cancer that found significant positive associations with depressive symptoms and perceived stress. In terms of cancer-specific stress, in our study, patients in the Subsyndromal and Moderate classes (i.e., 47.4% of the total sample) had IES-R total scores indicating post-traumatic symptomatology and those in the High class had IES-R scores indicative of probable PTSD. Our findings are consistent with a previous study of women with breast cancer (Kang et al., 2012), that found that IES scores were positively correlated with depressive symptoms.

In terms of cumulative life stress, our samples' LSC-R scores were similar to Americans with concurrent depression and substance-use disorders (Mahoney et al., 2015). In addition, our findings are consistent with a study of women with heterogeneous cancer types (Seib et al., 2018), that found that both recent and lifetime stressors were positively associated with depressive symptoms. As noted by the authors in this study (Seib et al., 2018), the "stress sensitization hypothesis" supports these findings because previous stressors may increase a patient's susceptibility to the deleterious psychological impacts of the cancer experience. However, this association warrants additional investigation because in a study of women with breast cancer (Kazlauskiene and Bulotiene, 2020), patients with a history of traumatic events were less likely to report PTSD symptoms during cancer treatment. The authors hypothesized that patients with a history of stress may have developed more adaptive ways to cope with their cancer. Taken together, these findings suggest that multiple types of

stress (i.e., global, cancer-specific, cumulative life stress) warrant assessment in oncology patients undergoing chemotherapy because unrelieved stress can prevent adoption and/or continuation of healthy behaviors (Stults-Kolehmainen and Sinha, 2014). Equally important, the use of stress reduction interventions can increase oncology patients' quality of life and prolong their survival (Mravec et al., 2020b).

In terms of resilience, patients in the Subsyndromal, Moderate, and High classes had resilience scores below the normative mean score for adults in the United States (Campbell-Sills et al., 2009). As noted in a recent review (Tamura et al., 2021), resilience levels of oncology patients decrease as the number and/or severity of symptoms increase which may explain the findings from our study. More specifically, in a study of patients with breast cancer (Ristevska-Dimitrovska et al., 2015), a significant negative correlation was found between depression and resilience. The authors hypothesized that resilience may be protective against depressive symptoms. In contrast, in a study of patients with prostate cancer (Sharpley et al., 2018), in those individuals who reported chronic stress, this inverse relationship between depressive symptoms and resilience was absent. Given these conflicting findings, clinicians need to assess for depressive symptoms and the impact of stress and resiliency on individual patients as they plan personalized interventions (Sharpley et al., 2018).

Multiple co-occurring symptoms associated with higher depressive symptom profiles

While oncology patients are known to experience multiple symptoms (Cooley and Siefert, 2016), our findings support previous research that found positive associations between higher levels of depressive symptoms and other common symptoms (Doong et al., 2015; Grotmol et al., 2019; Mercadante et al., 2019). For example, in a large study of patients with heterogeneous types of advanced cancer (Grotmol et al., 2019), after controlling for disease, treatment status, and prognosis, depressive symptoms were associated with a higher number of co-occurring symptoms. In addition, depressive symptoms, pain, fatigue, and sleep disturbances are known to cluster together in oncology patients (Doong et al., 2015). Furthermore, the co-occurrence of depressive symptoms and anxiety is associated with an increase in the severity of other co-occurring symptoms (Mercadante et al., 2019). For clinicians, diagnosis and management of depressive symptoms in the context of multiple co-occurring symptoms may present challenges because many of the symptoms of cancer and/or cancer treatments (e.g., fatigue, insomnia) are part of the diagnostic criteria for depression (Akechi et al., 2003).

Of note, for over 50% of our patients, the management of the most common symptoms associated with cancer treatment appears to be inadequate. The presence of psychological symptoms may make it more difficult to achieve adequate symptom control (Mercadante et al., 2019). Clinicians should remain vigilant in assessing multiple symptoms and aim to identify the root cause(s) of the various symptoms in order to prescribe targeted interventions. Furthermore, additional research is warranted to understand the underlying mechanism(s) for these common and co-occurring symptoms.

Limitations

Some limitations warrant consideration. First, stress and resilience measures were evaluated at only one timepoint. Future studies should evaluate for changes in depressive symptoms, as well as stress and resilience over time. Second, the sample was relatively homogenous in terms gender, ethnicity, education, and income which may limit the generalizability of our findings. Third, information on medications used to treat depression 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 a possible underestimation of depression in this sample.

Conclusion

In patients receiving chemotherapy, inter-individual variability in depressive symptoms was associated with multiple types of stress, as well as with the increased severity of multiple co-occurring symptoms. In oncology patients, depressive symptoms are often not diagnosed (Grotmol et al., 2019). If left untreated, this symptom can have significant deleterious effects (Li et al., 2017; Reiche et al., 2004). Therefore, the risk factors associated with worse depressive symptom profiles can assist clinicians to identify high risk patients and initiate more timely supportive care interventions.

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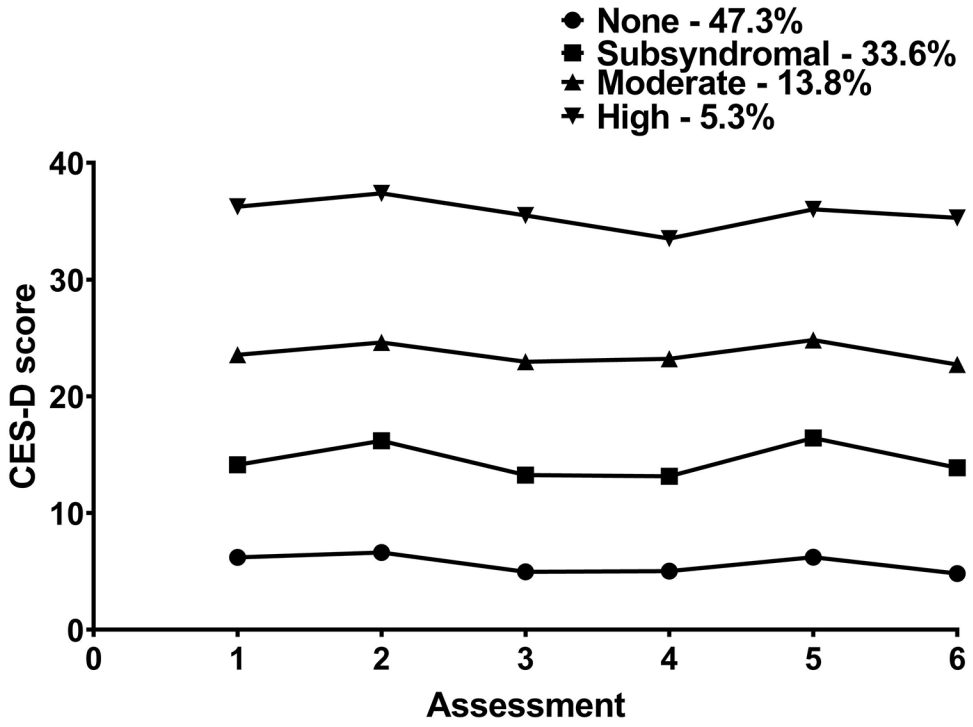

Fig. 1.
Trajectories of depressive symptoms for the four latent classes.

Table 1 –

Center for Epidemiologic Studies-Depression Scale: Latent Profile Solutions and Fit Indices for One through Five Classes

Model	LL	AIC	BIC	Entropy	VLMR
1 Class	−23141.03	46324.07	46433.07	n/a	n/a
2 Class	−22590.30	45236.61	45381.95	0.87	1101.46 $^{+}$
3 Class	−22288.65	44647.30	44828.97	0.84	603.31 **
4 Class [a]	−22165.43	44414.86	44632.87	0.83	246.44 *
5 Class	−22072.61	44243.22	44497.56	0.83	ns

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

* $p < .05$

** $p < .001$

$^{+}$ $p < .00005$

[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 Depression Latent Classes

Characteristic	None (0) 47.3% (n=628)	Subsyndromal (1) 33.6% (n=446)	Moderate (2) 13.8% (n=183)	High (3) 5.3% (n=70)	Statistics
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	
Age (years)	59.0 (12.1)	55.6 (12.2)	55.2 (13.3)	55.3 (10.4)	F = 9.25, p < 0.001 0 > 1 and 2
Education (years)	16.2 (3.0)	16.4 (3.1)	15.9 (3.0)	15.8 (3.1)	F = 1.56, p = 0.196
Body mass index (kg/m^2)	26.1 (5.3)	25.9 (5.6)	26.9 (6.6)	26.8 (6.2)	F = 1.71, p = 0.164
Alcohol Use Disorders Identification Test score	2.9 (2.2)	2.7 (2.1)	3.7 (3.6)	3.0 (2.5)	F = 4.45, p = 0.004 0 and 1 < 2
Karnofsky Performance Status score	85.1 (11)	77.0 (11.7)	73.4 (12.4)	70.2 (10.6)	F = 86.05, p < 0.001 0 > 1; 0 and 1 > 2 and 3
Number of comorbid conditions	2.2 (1.3)	2.4 (1.4)	2.8 (1.6)	3.5 (1.7)	F = 24.27, p < 0.001 0 and 1 < 2 and 3; 2 < 3
Self-administered Comorbidity Questionnaire score	4.8 (2.7)	5.6 (3.0)	6.5 (3.7)	8.2 (4.4)	F = 37.14, p < 0.001 0 < 1 < 2 < 3
Time since diagnosis (years)	2.1 (3.9)	1.8 (3.7)	2.2 (3.8)	2.0 (5.2)	KW = 3.49, p = 0.321
Time since diagnosis (years, median)	0.42	0.41	0.45	0.44	
Number of prior cancer treatments	1.6 (1.5)	1.5 (1.4)	1.8 (1.5)	1.8 (1.5)	F = 2.15, p = 0.092
Number of metastatic sites including lymph node involvement[a]	1.3 (1.2)	1.2 (1.3)	1.3 (1.3)	1.2 (1.1)	F = 0.08, p = 0.969
Number of metastatic sites excluding lymph node involvement	0.8 (1.0)	0.8 (1.0)	0.8 (1.1)	0.7 (1.0)	F = 0.27, p = 0.844
MAX2 score	0.16 (0.08)	0.18 (0.08)	0.19 (0.08)	0.17 (0.08)	F = 5.63, p = 0.001 0 < 2
	% (n)	% (n)	% (n)	% (n)	

Characteristic	None (0) 47.3% (n=628)	Subsyndromal (1) 33.6% (n=446)	Moderate (2) 13.8% (n=183)	High (3) 5.3% (n=70)	Statistics
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	
Gender (% female)	72.8 (457)	80.7 (359)	85.8 (157)	85.7 (60)	$X^2 = 20.69$, $p < 0.001$ 0 < 1 and 2
Self-reported ethnicity					$X^2 = 22.45$, $p = 0.008$
White	69.3 (431)	72.2 (317)	69.8 (125)	55.7 (39)	1 > 3
Asian or Pacific Islander	13.3 (83)	11.8 (52)	8.9 (16)	17.1 (12)	NS
Black	8.8 (55)	5.2 (23)	6.1 (11)	7.1 (5)	NS
Hispanic, Mixed, or Other	8.5 (53)	10.7 (47)	15.1 (27)	20.0 (14)	0 < 3
Married or partnered (% yes)	70.8 (438)	65.2 (288)	48.6 (86)	43.3 (31)	$X^2 = 42.71$, $p < 0.001$ 0 and 1 > 2 and 3
Lives alone (% yes)	17.1 (106)	22.1 (98)	29.4 (52)	37.1 (26)	$X^2 = 23.75$, $p < 0.001$ 0 < 2 and 3
Currently employed (% yes)	41.0 (254)	33.3 (143)	21.9 (40)	25.7 (18)	$X^2 = 27.06$, $p < 0.001$ 0 and 1 > 2
Annual household income					
Less than $30,000 +	11.8 (65)	17.1 (69)	35.7 (60)	40.6 (26)	KW = 52.92, $p < 0.001$ 0 < 1; 0 and 1 < 2 and 3
$30,000 to $70,000	19.3 (107)	25.7 (104)	16.1 (27)	21.9 (14)	
$70,000 to $100,000	18.6 (103)	16.1 (65)	16.7 (28)	7.8 (5)	
Greater than $100,000	50.3 (278)	41.1 (166)	31.5 (53)	29.7 (19)	
Child care responsibilities (% yes)	19.8 (122)	23.2 (101)	25.3 (45)	29.4 (20)	$X^2 = 5.31$, $p = 0.151$
Elder care responsibilities (% yes)	6.5 (37)	7.5 (30)	14.4 (24)	6.2 (4)	$X^2 = 11.62$, $p = 0.009$ 0 < 2
Past or current history of smoking (% yes)	32.5 (201)	36.5 (159)	39.4 (71)	41.4 (29)	$X^2 = 4.94$, $p = 0.177$
Exercise on a regular basis (% yes)	75.0 (465)	67.4 (293)	68.2 (120)	63.6 (42)	$X^2 = 10.02$, $p = 0.018$ No significant pw contrasts
Specific comorbid conditions (% yes)					
Heart disease	5.3 (33)	7.2 (32)	4.9 (9)	1.4 (1)	$X^2 = 4.65$, $p = 0.199$

Characteristic	None (0) 47.3% (n=628)	Subsyndromal (1) 33.6% (n=446)	Moderate (2) 13.8% (n=183)	High (3) 5.3% (n=70)	Statistics
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	
High blood pressure	31.5 (198)	28.0 (125)	29.5 (54)	34.3 (24)	$X^2 = 2.12$, $p = 0.548$
Lung disease	9.6 (60)	12.1 (54)	12.6 (23)	20.0 (14)	$X^2 = 7.72$, $p = 0.052$
Diabetes	9.7 (61)	7.0 (31)	8.7 (16)	14.3 (10)	$X^2 = 5.12$, $p = 0.163$
Ulcer or stomach disease	3.7 (23)	5.4 (24)	4.9 (9)	12.9 (9)	$X^2 = 11.80$, $p = 0.008$ 0 < 3
Kidney disease	1.0 (6)	1.6 (7)	1.1 (2)	5.7 (4)	$X^2 = 10.32$, $p = 0.016$ No significant pw contrasts
Liver disease	7.2 (45)	5.6 (25)	6.6 (12)	5.7 (4)	$X^2 = 1.12$, $p = 0.772$
Anemia or blood disease	9.2 (58)	14.6 (65)	14.8 (27)	18.6 (13)	$X^2 = 11.19$, $p = 0.011$ No significant pw contrasts
Depression	6.5 (41)	19.3 (86)	42.6 (78)	71.4 (50)	$X^2 = 252.64$, $p < 0.001$ 0 < 1 < 2 < 3
Osteoarthritis	11.8 (74)	9.6 (43)	18.6 (34)	12.9 (9)	$X^2 = 9.88$, $p = 0.020$ No significant pw contrasts
Back pain	19.7 (124)	27.8 (124)	31.7 (58)	48.6 (34)	$X^2 = 35.38$, $p < 0.001$ 0 < 1, 2, and 3; 1 < 3
Rheumatoid arthritis	3.2 (20)	2.7 (12)	2.2 (4)	8.6 (6)	$X^2 = 7.58$, $p = 0.056$
Cancer diagnosis					
Breast cancer	38.9 (244)	39.5 (176)	43.7 (80)	50.0 (35)	
Gastrointestinal cancer	33.1 (208)	30.5 (136)	25.1 (46)	20.0 (14)	$X^2 = 13.66$, $p = 0.135$
Gynecological cancer	16.1 (101)	17.5 (78)	22.4 (41)	15.7 (11)	
Lung cancer	11.9 (75)	12.6 (56)	8.7 (16)	14.3 (10)	
Prior cancer treatment					
No prior treatment	26.5 (161)	26.8 (117)	18.4 (33)	18.8 (13)	
Only surgery, CTX, or RT	40.8 (248)	41.4 (181)	46.9 (84)	42.0 (29)	$X^2 = 18.49$, $p = 0.026$ No significant pw contrasts
Surgery and CTX, or surgery and RT, or CTX and RT	21.1 (128)	20.1 (88)	15.6 (28)	17.4 (12)	
Surgery and CTX and RT	11.7 (71)	11.7 (51)	19.0 (34)	21.7 (15)	
Metastatic sites					
No metastasis	31.0 (192)	33.9 (150)	33.5 (60)	31.9 (22)	$X^2 = 3.36$, $p = 0.948$

Characteristic	None (0) 47.3% (n=628)	Subsyndromal (1) 33.6% (n=446)	Moderate (2) 13.8% (n=183)	High (3) 5.3% (n=70)	Statistics
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	
Only lymph node metastasis	21.6 (134)	21.7 (96)	21.8 (39)	27.5 (19)	
Only metastatic disease in other sites	22.7 (141)	19.9 (88)	20.1 (36)	18.8 (12)	
Metastatic disease in lymph nodes and other sites	24.7 (153)	24.6 (109)	24.6 (44)	21.7 (15)	
Receipt of targeted therapy					
No	66.2 (407)	73.5 (321)	73.2 (131)	72.5 (50)	$X^2 = 7.81$, p = 0.050
Yes	33.8 (208)	26.5 (116)	26.8 (48)	27.5 (19)	
CTX regimen					
Only CTX	66.2 (407)	73.5 (321)	73.2 (131)	72.5 (50)	$X^2 = 8.69$, p = 0.192
Only targeted therapy	3.4 (21)	2.3 (10)	2.8 (5)	4.3 (3)	
Both CTX and targeted therapy	30.4 (187)	24.3 (106)	24.0 (43)	23.2 (16)	
Cycle length					
14 day cycle	43.5 (272)	41.3 (182)	41.4 (75)	30.9 (21)	$X^2 = 6.34$, p = 0.386
21 day cycle	49.0 (306)	50.8 (224)	53.6 (97)	61.8 (42)	
28 day cycle	7.5 (47)	7.9 (35)	5.0 (9)	7.4 (5)	
Emetogenicity of the CTX regimen					
Minimal/low	20.2 (126)	17.4 (77)	20.4 (37)	26.5 (18)	$X^2 = 6.70$, p = 0.349
Moderate	61.9 (387)	60.6 (268)	59.1 (107)	60.3 (41)	
High	17.9 (112)	21.9 (97)	20.4 (37)	13.2 (9)	
Antiemetic regimen					$X^2 = 24.65$, p = 0.003
None	8.5 (52)	6.0 (26)	5.7 (10)	6.0 (4)	NS
Steroid alone or serotonin receptor antagonist alone	21.2 (130)	17.6 (76)	23.0 (40)	28.4 (19)	NS
Serotonin receptor antagonist and steroid	49.2 (301)	51.4 (222)	37.9 (66)	34.3 (23)	1 > 2
NK-1 receptor antagonist and two other antiemetics	21.1 (129)	25.0 (108)	33.3 (58)	31.3 (21)	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 Depression Latent Classes

Measures[a]	None (0) 47.3% (n=628)	Subsyndromal (1) 33.6% (n=446)	Moderate (2) 13.8% (n=183)	High (3) 5.3% (n=70)	Statistics
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	
PSS total score (range 0–56)	13.6 (5.9)	20.4 (6.4)	25.7 (6.1)	31.9 (7.0)	F= 328.89, p < 0.001 0 < 1 < 2 < 3
IES-R total score (≥24)	12.4 (8.5)	20.5 (10.8)	27.5 (12.9)	42.8 (16.9)	F= 235.20, 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= 220.82, p < 0.001 0 < 1 < 2 < 3
IES-R avoidance	0.7 (0.6)	1.0 (0.6)	1.2 (0.7)	1.7 (0.9)	F= 59.71, p < 0.001 0 < 1 < 2 < 3
IES-R hyperarousal	0.3 (0.3)	0.7 (0.5)	1.1 (0.7)	2.0 (0.9)	F= 297.49, p < 0.001 0 < 1 < 2 < 3
LSC-R total score (range 0–30)	5.2 (3.2)	6.4 (4.0)	7.4 (4.7)	8.8 (5.1)	F= 25.12, p < 0.001 0 < 1, 2 and 3; 1 < 3
LSC-R affected sum (range 0–150)	8.8 (7.6)	12.4 (10.6)	17.1 (14.1)	24.1 (14.8)	F= 55.01, p < 0.001 0 < 1 < 2 < 3
LSC-R PTSD sum (range 0–21)	2.3 (2.4)	3.4 (3.1)	4.2 (3.6)	5.5 (3.9)	F= 31.83, p < 0.001 0 < 1, 2, and 3; 1 and 2 < 3
CDRS total score (range 0–40)	32.4 (5.5)	29.3 (6.0)	26.7 (6.5)	23.2 (5.9)	F= 83.06, p < 0.001 0 > 1 > 2 > 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 Depression Latent Classes

Symptoms[a]	None (0) 47.3% (n=628)	Subsyndromal (1) 33.6% (n=446)	Moderate (2) 13.8% (n=183)	High (3) 5.3% (n=70)	Statistics
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	
Depressive symptoms (≥16)	6.1 (4.1)	14.4 (5.4)	23.8 (6.4)	36.5 (7.5)	F = 1119.37, p < 0.001 0 < 1 < 2 < 3
Trait anxiety (≥31.8)	28.5 (5.9)	37.0 (7.5)	46.1 (7.9)	56.4 (8.2)	F = 561.58, p < 0.001 0 < 1 < 2 < 3
State anxiety (≥32.2)	26.5 (7.0)	35.8 (9.7)	45.2 (9.9)	59.4 (11.9)	F = 444.77, p < 0.001 0 < 1 < 2 < 3
Morning fatigue (≥3.2)	2.0 (1.7)	3.7 (2.0)	4.6 (2.2)	6.0 (2.1)	F = 181.09, p < 0.001 0 < 1, 2, and 3; 1 < 3
Evening fatigue (≥5.6)	4.6 (2.1)	5.7 (1.9)	6.2 (2.0)	7.1 (1.7)	F = 60.19, p < 0.001 0 < 1, 2, and 3; 1 and 2 < 3
Morning energy (≤6.2)	5.0 (2.3)	4.1 (2.0)	3.8 (2.1)	3.0 (2.0)	F = 31.79, p < 0.001 0 > 1, 2, and 3; 1 > 3
Evening energy (≤3.5)	3.9 (2.0)	3.4 (1.9)	3.0 (2.0)	2.6 (2.1)	F = 16.87, p < 0.001 0 > 1, 2, and 3
Sleep disturbance (≥43.0)	42.4 (17.3)	58.2 (17.3)	64.0 (17.5)	77.7 (16.7)	F = 158.70, p < 0.001 0 < 1 < 2 < 3
Attentional function (<5.0 = Low, 5 to 7.5 = Moderate, >7.5 = High)	7.4 (1.4)	5.9 (1.5)	4.9 (1.5)	4.3 (1.7)	F = 205.20, p < 0.001 0 > 1 > 2; 0 and 1 > 3
	% (n)	% (n)	% (n)	% (n)	
Types of pain					X^2 = 108.16, p < 0.001
None	36.3 (225)	23.7 (103)	14.0 (25)	5.8 (4)	0 > 1; 0 and 1 > 2 and 3
Only non-cancer pain	18.7 (116)	14.7 (64)	11.7 (21)	8.7 (6)	NS
Only cancer pain	24.1 (149)	28.0 (122)	30.7 (55)	23.2 (16)	NS
Both non-cancer and cancer pain	20.8 (129)	33.6 (146)	43.6 (78)	62.3 (43)	0 < 1, 2, and 3; 1 and 2 < 3

Symptoms[a]	None (0) 47.3% (n=628)	Subsyndromal (1) 33.6% (n=446)	Moderate (2) 13.8% (n=183)	High (3) 5.3% (n=70)	Statistics
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	
Worst pain intensity score	5.5 (2.5)	6.1 (2.5)	6.9 (2.2)	7.2 (2.5)	F = 15.39, p < 0.001 0 and 1 < 2 and 3
Mean pain interference score	2.0 (1.9)	3.3 (2.4)	4.5 (2.5)	5.5 (2.8)	F = 73.46, p < 0.001 0 < 1 < 2 < 3

Abbreviations: NS = not significant, SD = standard deviation

[a]Clinically meaningful cutoff scores

Table 5 –

Characteristics Associated with Membership in the Subsyndromal, Moderate, and High Classes

Characteristic[a]	Subsyndromal	Moderate	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 elder care responsibilities		■	
Clinical Characteristics			
Lower functional status	■	■	■
Higher number of comorbidities		■	■
Higher comorbidity burden	■	■	■
Higher MAX2 score		■	
More likely to have a higher AUDIT score		■	
More likely to self-report stomach disease			■
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	■	■	■
Lower morning energy	■	■	■

Characteristic[a]	Subsyndromal	Moderate	High
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 None class

Abbreviation: PTSD = post-traumatic stress disorder