Title

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Journal

Journal of Pain and Symptom Management, 63(1)

ISSN

0885-3924

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Publication Date

2022

DOI

10.1016/j.jpainsymman.2021.07.018

Peer reviewed

Published in final edited form as:

J Pain Symptom Manage. 2022 January ; 63(1): 42–51. doi:10.1016/j.jpainsymman.2021.07.018.

Determination of Cutpoints for Symptom Burden in Oncology Patients Receiving Chemotherapy

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Abstract

Context: Cutpoints can be used as a threshold for screening symptom(s) that warrant intervention(s) and for monitoring patients' responses to these interventions.

Objectives: In a sample of oncology patients undergoing chemotherapy, study purposes were to determine the optimal cutpoints for low, moderate, and high symptom burden and determine if these cutpoints distinguished among the symptom groups in any demographic, clinical, and stress characteristics, as well as QOL outcomes.

Methods: Total of 1329 patients completed a modified version of the Memorial Symptom Assessment Scale (38 symptoms). Using the methodology of Serlin and colleagues, cutpoints were created using symptom occurrence rates and cancer-specific quality of life (QOL) scores. Cutpoints were validated using measures of stress and resilience and a generic measure of QOL (i.e., Medical Outcomes Study Short Form 12 (SF-12)).

Results: Of the 25 possible cutpoints evaluated, the optimal cutpoint, with the largest between category F statistic, was CP8,15 (Low = 0 to 8, Moderate = 9 to 15, High = 16 to 38 symptoms). Percentage of patients in the Low, Moderate, and High cutpoint groups were 25.3%, 36.3%, and 38.4%, respectively. Significant differences were found among the symptom burden groups in global, cancer-specific, and cumulative life stress (i.e., Low < Moderate < High) and resilience and SF-12 (i.e., Low > Moderate > High) scores.

Conclusion: Our findings provide evidence for clinically meaningful cutpoints that can be used to guide symptom assessment and management. These cutpoints may be used to establish alert thresholds for electronic monitoring of symptoms in oncology patients.

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Conflicts of interest: The authors have no conflicts of interest to declare.

Keywords

symptom burden; cutpoints; chemotherapy; cancer; symptoms; severity

INTRODUCTION

As noted by Shi and colleagues,[1] cutpoints can be used as a threshold for screening symptom(s) that warrant intervention(s) and for monitoring patients' responses to these interventions. Pain[2,3] and fatigue[4,5] associated with cancer and its treatments are the two symptoms with the most research on cutpoints. Confirmation of cutpoints for mild, moderate, and severe levels of these two symptoms have led to their incorporation into clinical practice guidelines for pain[6] and fatigue.[7]

While most of the research on cutpoints has focused on single symptoms using ratings of symptom severity,[2–5,8,9] it is well known that oncology patients rarely experience a single symptom. In fact, patients undergoing cancer treatment report between 10 and 12 concurrent symptoms.[10,11] Only one study was identified that determined the optimal cutpoint for a low versus a high symptom burden in 110 patients with advanced cancer.[12] Using the procedures of Serlin and colleagues[3] and occurrence ratings for 32 symptoms from the Memorial Symptom Assessment Scale (MSAS),[13] a cutpoint of ≤12 symptoms (i.e., 0 to 12 is low, 13 to 32 is high) was the optimal cutpoint for the total number of symptoms. Significant differences in depression, anxiety, and quality of life (QOL) scores validated this cutpoint. Of note, psychological symptoms had higher occurrence rates in the high symptom group.

As noted in our previous report of symptom cutpoints for patients with advanced cancer,[12] as well as in the work of Serlin and colleagues,[3] the theoretical basis for using changes in QOL scores to establish cutpoints for a higher symptom burden is that total number of symptoms has a non-linear relationship with QOL (as does pain severity and interference[2,3]). Therefore, we hypothesized that a significant decrease in QOL scores would occur as the total number of symptoms increased. Said another way, clinically meaningful differences in symptom burden would be negatively associated with statistically significant differences in overall QOL. In addition, given the growing body of literature on the associations between higher levels of stress and an increase in symptom burden in oncology patients,[14–17] we used measures of global, disease-specific, and cumulative life stress to validate the symptom cutpoints. Therefore, in a large sample of oncology patients undergoing chemotherapy (n=1329), the purposes of this study were to determine the optimal cutpoints for low, moderate, and high symptom burden using a range of potential cutpoints and to determine if these cutpoints distinguished among the symptom groups in any demographic, clinical, and stress characteristics, as well as QOL outcomes. In addition, differences among the cutpoint groups in symptom occurrence rates were evaluated.

METHODS

Patients and settings

This analysis is part of a longitudinal study of the symptom experience of oncology outpatients receiving chemotherapy.[10] 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, and 1329 provided complete data for the cutpoint analysis. Patients completed paper and pencil questionnaires, prior to their second or third cycle of chemotherapy.

Instruments

Demographic and Clinical Measures—Patients completed a demographic questionnaire (e.g., age, education, marital status, self-reported ethnicity), Karnofsky Performance Status (KPS) scale,[18] Self-Administered Comorbidity Questionnaire (SCQ),[19] Alcohol Use Disorders Identification Test (AUDIT),[20] and a smoking history questionnaire. Medical records were reviewed for disease and treatment information. Toxicity of the chemotherapy regimen was evaluated using the MAX2 score.[21]

Measures Used to Create the Cutpoints—A modified version of the Memorial Symptom Assessment Scale (MSAS) was used to evaluate the occurrence, severity, frequency, and distress of 38 symptoms commonly associated with cancer and its treatment.[13] In addition to the original 32 MSAS symptoms included in 1994, the following six common symptoms were assessed: hot flashes, chest tightness, difficulty breathing, abdominal cramps, increased appetite, and weight gain. Using the MSAS, patients were asked to indicate whether or not they had experienced each symptom in the past week (i.e., symptom occurrence), as well as frequency, severity, and distress.

Quality of Life-Patient Version (QOL-PV) is a 41-item instrument that assesses four dimensions of QOL (i.e., physical, psychological, social, and spiritual well-being) in cancer patients, as well as a total QOL score. Each item was rated on a 0 to 10 numeric rating scale (NRS) with higher scores indicating a better QOL.[22]

Measures Used to Validate the Cutpoints—The 14-item Perceived Stress Scale (PSS) is a measure of global perceived stress according to the degree that life circumstances are appraised as stressful over the course of the previous week.[23] Total PSS scores can range from 0 to 56. 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.[24,25] 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 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.[26] 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).[27] 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). If patients endorsed an event, they were asked to indicate how much that stressor affected their life in the past year (i.e., 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 10-item Connor-Davidson Resilience Scale (CDRS) evaluates a patient’s personal ability to handle adversity.[28,29] Items are scored on a 5-point Likert scale. 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),[29] with an estimated minimal clinically important difference of 2.7.[30] In this study, its Cronbach’s alpha was 0.90.

The 12-item Medical Outcomes Study-Short Form-12 (SF-12) was used as a generic measure of overall health status and QOL. The individual items on the SF-12 were evaluated and the instrument was scored into two components, namely physical component summary (PCS) score and mental component summary (MCS) scores. These scores can range from 0 to 100. Higher PCS and MCS scores indicate a better QOL.[31] The SF-12 was used as a second QOL measure to validate the cutpoint’s impact of symptom burden on QOL.

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 (IBM Corporation, Armonk, NY). Symptom occurrence rates were generated for each of the symptoms evaluated on the MSAS. Total number of symptoms was calculated by summing the number of symptoms based on a positive response to any one of the four dimensions (i.e., occurrence, frequency, severity, or distress).

Cutpoints that divided the sample into low, moderate, and high number of symptoms were created using the analytic strategy of Serlin and colleagues.[3] Twenty-five categorical variables, that represented the twenty-five possible combinations of cutpoints between 5 and 9, were created (Table 1) and were related to the mean total score on the QOL-PV, using

analysis of variance (ANOVA). The criterion that was used to determine the optimal set of cutpoints for low, moderate, and high symptom burden was the ANOVA that yielded the largest F ratio for the between category effects.

Differences among the symptom cutpoint groups in demographic and clinical characteristics, symptom occurrence rates, stress and resilience measures, and SF-12 scores were evaluated using ANOVA, 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 <.017 (.05/3 possible pairwise comparisons).

RESULTS

Cutpoint calculations

As shown in Table 1, of the 25 possible cutpoints evaluated, the optimal cutpoint with the largest between category F statistic was CP8,15 (i.e., Low = 0 to 8, Moderate = 9 to 15, High = 16 to 38 symptoms). Using this cutpoint, of the 1,329 patients in the study, 25.3% were in the Low (mean of 5.4 ±2.2 symptoms), 36.3% were in the Moderate (mean of 12.2 ±2.0 symptoms), and 38.4% (mean of 21.2 ±4.8 symptoms) were in the High symptom cutpoint group.

Differences in demographic and clinical characteristics

As shown in Table 2, differences in age and KPS scores among the three groups followed the same pattern (Low > Moderate > High). In addition, differences among the three groups in gender, SCQ scores, and a self-reported diagnosis of back pain followed the same pattern (Low < Moderate < High). Compared to the other two groups, patients in the High group were less likely to be married/partnered, less likely to be employed, more likely to have a lower annual household income, more likely to self-report a diagnosis of anemia and depression, and had a higher MAX2 score. Compared to the Low group, patients in the other two groups were more likely to have elder care responsibilities and less likely to have gastrointestinal cancer.

Differences in Symptom Occurrence Rates

Differences in the rank order of symptom occurrence rates for the three symptom groups are listed in Table 3. For all of the symptoms, significant differences in occurrence rates were found among the three groups (all p <.05). Post hoc contrasts followed the same pattern (Low < Moderate < High). Lack of energy, difficulty sleeping, pain, hair loss, feeling drowsy, and difficulty concentrating were among the top ten symptoms across the three groups.

Differences in Stress and Resilience Scores

For all of the stress measures, differences in scores among the three groups followed the same pattern (Low < Moderate < High). For the CDRS scores, differences among the three groups followed the same pattern (Low > Moderate > High; Table 4).

Differences in QOL Scores

As expected, significant differences were found among the three groups in the total QOL-PV score, as well as for three of the four subscales (i.e., physical, psychological, and social well-being, Figure 1). Differences among the three groups followed the same pattern (Low > Moderate > High; all p<.001). In terms of the PCS and MCS scores, significant differences were found among the three groups and followed the same pattern (Low > Moderate > High, both p <.001, Figure 2).

DISCUSSION

This study is the first to determine distinct symptom cutpoints in oncology patients undergoing chemotherapy. While our previous study with only 110 patients with advanced cancer found two cutpoints (i.e., 0 to 12 and 13 to 32),[12] with a larger sample and a total of 38 symptoms, three distinct cutpoints were determined using total QOL-PV scores to distinguish among the groups. Of note, in patients who were assessed prior to their second or third cycle of chemotherapy (i.e., theoretically a time of recovery from their previous cycle), 36.3% of the sample was categorized as having a Moderate and 38.4% as having a High symptom burden.

Significant differences among the three cutpoint groups in the global (PSS), disease-specific (IES-R), and cumulative life (LSC-R) stress provide support for the validity of these cutpoints. It is interesting to note that the scores for all three of the stress measures were significantly different among the three cutpoint groups. While it is well known that cancer and its treatment impose a significant stress on patients,[32] our findings provide new evidence of the association between three different types of stress and a progressively higher symptom burden. In terms of global stress, differences among the three cutpoint groups in PSS scores represent clinically meaningful differences (i.e., Cohen's d = 0.48 to 0.96). In addition, the PSS scores in our sample are similar to scores reported for stressed (20.2) and non-stressed (12.0) cancer survivors during COVID-19.[17] In terms of the IES-R total score, while none of the cutpoint groups exceeded the clinically meaningful cutoff score of ≥24, 44.4% of patients in the High group exceeded this threshold and 23.0% met the criteria for probable PTSD. For the LSC-R total score, while the High group reported scores similar to patients with a prescription opioid use disorder (7.7),[33] their scores were lower than those reported by older adults in prison (11.0).[34] While the CDRS scores for both the Moderate and High groups were below the normative score of 31.8 for the general United States population, the difference in resilience scores between the Low and High groups represents a clinically meaningful difference.[29] Taken together, these cross-sectional findings suggest potential overlapping mechanisms for the relationships between stress and symptom burden. Candidate mechanisms for future investigation include: alterations in the hypothalamic-pituitary-adrenal axis,[35] alterations in neuroendocrine pathways,[36] alterations in inflammatory pathways,[37,38] and alterations in the gut-brain-microbiome axis.[39–41]

Additional validation of the symptom cutpoint groups comes from the PCS and MCS findings. While the PCS scores for all three groups were below the normative score of 50.0 for the general population, only the Moderate and High groups' MCS scores were below this value. Of note, compared to the Low group, patients in both the Moderate and High groups

had clinically meaningful decrements in PCS (Cohen's d = 0.45 and 0.88, respectively) and MCS (Cohen's d = 0.41 and 0.95, respectively) scores.[42,43] These relatively large effect sizes suggest that when patients cross over into the Moderate and High symptom groups, they may notice decrements in their QOL.[12]

Across the three cutpoint groups, fatigue, difficulty sleeping, and pain were among the top five symptoms. This finding is not surprising given that previous reports have noted the high occurrence rates for each of these symptoms[44–46] and that these symptoms are known to cluster together in oncology patients.[11] While the occurrence rates for all of the symptoms were significantly different among the three groups (i.e., Low < Moderate < High), similar to our previous report of patients with advanced cancer,[12] psychological symptoms (e.g., worrying) were more likely to be among the symptoms with the highest occurrence rates in the Moderate and High classes. As noted previously,[12] this finding supports the hypothesis that psychological symptoms may significantly impact patients' QOL.

In terms of differences in demographic characteristics our findings are consistent with previous reports that found that a higher symptom burden was associated with younger age,[47] self-reported female gender,[48] as well as a lower annual income and being unemployed.[49] While a lower functional status and higher level of comorbidity are consistently associated with a higher symptom burden,[47] some of the clinical characteristics that differentiated among the cutpoint groups may assist with the identification of high risk patients. For example, a higher MAX2 score, a measure of the overall toxicity of the chemotherapy regimen,[21] was found for the High group. In addition, higher rates of self-reported anemia, depression, and back pain were found in the High group. Clinicians need to include an evaluation of these chronic medical conditions in their assessments of oncology patients.

Several limitations warrant consideration. While this large sample included heterogenous types of cancers, it was relatively homogenous in terms of gender, education, and ethnicity. Therefore, our findings may not generalize to patients from more diverse ethnic and socioeconomic backgrounds. In addition, given that the primary reason patients gave for declining participation was being too overwhelmed with cancer treatment, our findings may underestimate patients' symptom burden. While we used a comprehensive symptom assessment instrument with 38 symptoms, cutpoints for symptom burden will change depending on the number of symptoms on the measure. Additional research is warranted to determine the optimal number of symptoms to include on a symptom assessment instrument and to confirm or refute our findings. Given the cross-sectional design, future studies need to determine if symptom cutpoints change over time. In addition, differences in symptom cutpoints based on cancer diagnoses and/or treatments warrant investigation. Finally, future studies need to evaluate the impact of total number of symptoms versus the severity or distress from a few symptoms on patients' overall symptom burden.

Despite these limitations, our findings provide evidence for clinically meaningful cutpoints that can be used to guide symptom assessment and management. Recent evidence supports the use of symptom cutpoints to establish alert thresholds for electronic monitoring of symptoms in oncology patients.[50,51] In fact, this type of monitoring of common and

actionable symptoms is known to improve adherence with treatments, as well as increase patients' QOL and improve overall survival.[50,52] Given that many of these electronic monitoring systems have patients report the occurrence of multiple co-occurring symptoms followed by severity ratings of the symptoms that they are experiencing, optimal cutpoints for low, moderate, and high levels of symptom burden can be used to alert clinicians to patients who warrant time sensitive interventions.

Funding:

This study was funded by a grant from the National Cancer Institute (CA134900). Ms. Harris and Oppegaard are supported by a grant from the National Institute of Nursing Research (T32NR016920). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. Dr. Miaskowski is an American Cancer Society Clinical Research Professor. Ms. Harris is supported by a grant from the American Cancer Society. Ms. Oppegaard and Shin are supported by a grant from the Oncology Nursing Foundation.

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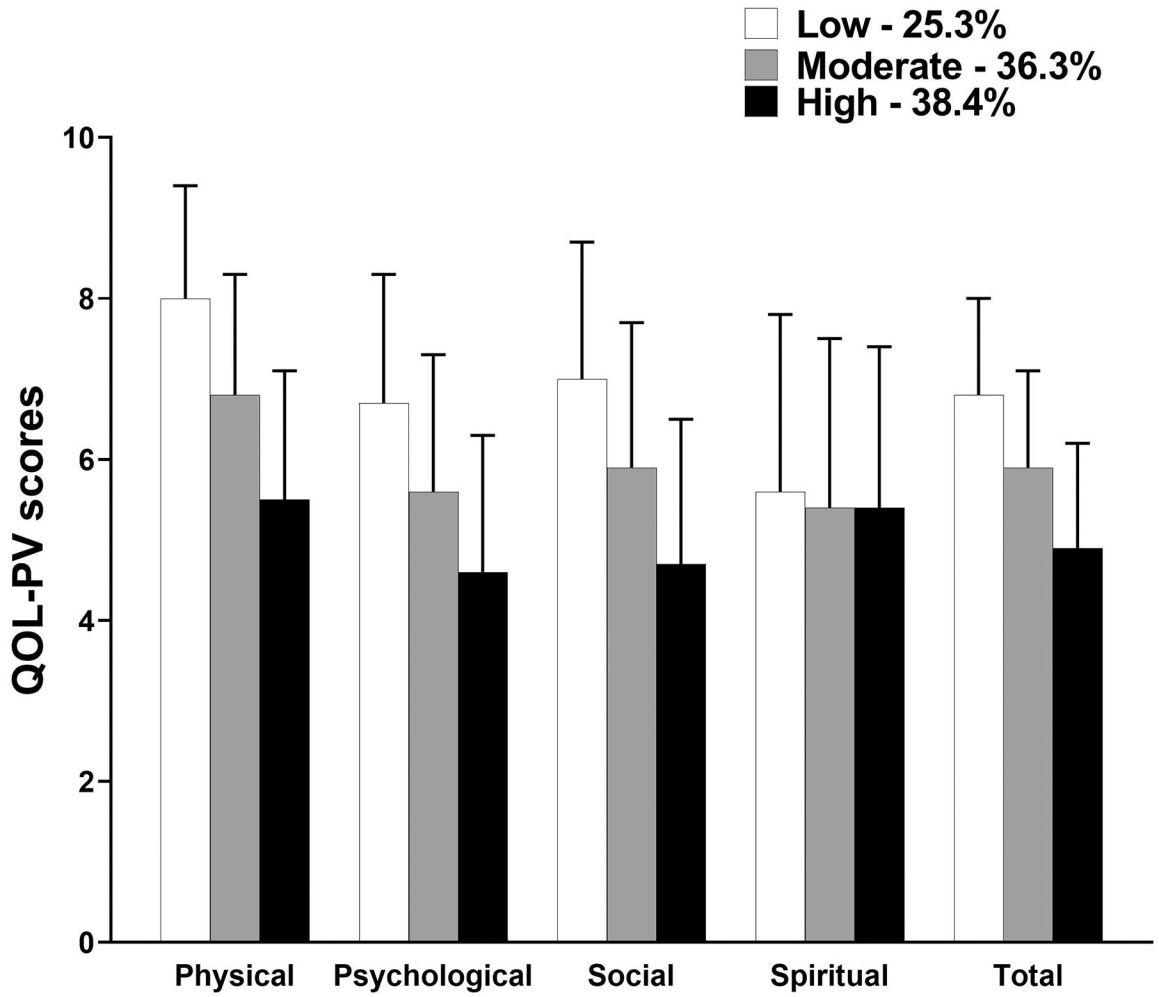

Figure 1 –.

Differences among the three cutpoint groups in subscale and total scores on the Quality of Life-Patient Version (QOL-PV). All values are plotted as means and standard deviations. Except for spiritual well-being (p=.322), significant differences were found among the three cutpoint groups for the other three subscales and total QOL scores (all p<.001; Low > Moderate > High).

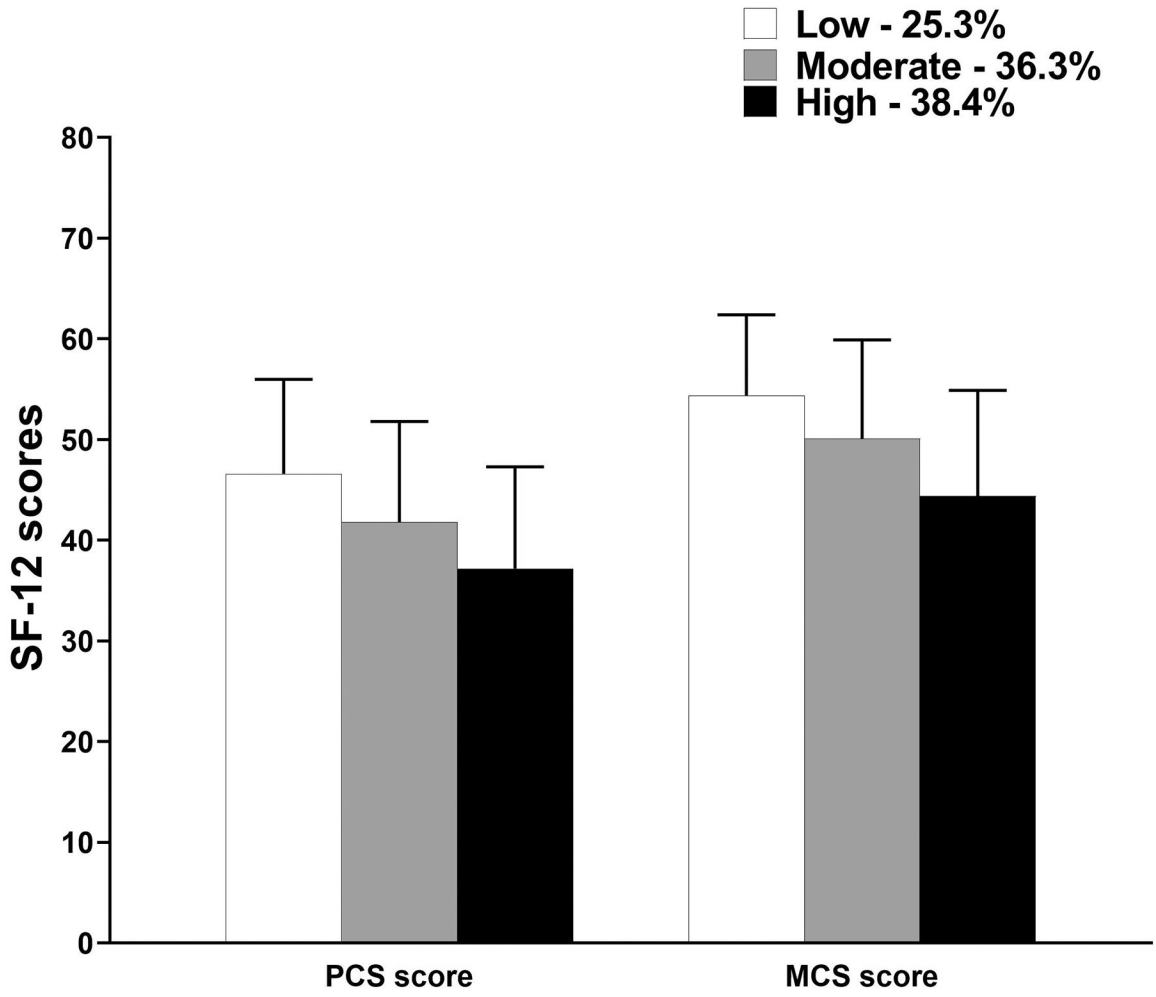

Figure 2 -

Differences among the three cutpoint groups in Physical Component Summary (PCS) and Mental Component Summary (MCS) scores from Medical Outcomes Study-Short Form-12 (SF-12). All values are plotted as means and standard deviations. Significant differences were found among the three cutpoint groups for both scores ($p < .001$; Low > Moderate > High).

Table 1 –

Results of the Cutpoint Analyses for Total Number of Symptoms Using the Total Score for the Multidimensional Quality of Life Scale – Patient Version

Cutpoints for number of symptoms per group	Rank	Analysis of variance F statistic
Low = 0 to 5, Medium = 6 to 13, High = 14 to 38	18	197.815
Low = 0 to 5, Medium = 6 to 14, High = 15 to 38	19	197.534
Low = 0 to 5, Medium = 6 to 15, High = 16 to 38	8	210.517
Low = 0 to 5, Medium = 6 to 16, High = 17 to 38	22	188.657
Low = 0 to 5, Medium = 6 to 17, High = 18 to 38	24	184.676
Low = 0 to 6, Medium = 7 to 13, High = 14 to 38	21	193.317
Low = 0 to 6, Medium = 7 to 14, High = 15 to 38	20	194.047
Low = 0 to 6, Medium = 7 to 15, High = 16 to 38	10	207.636
Low = 0 to 6, Medium = 7 to 16, High = 17 to 38	23	187.381
Low = 0 to 6, Medium = 7 to 17, High = 18 to 38	25	184.429
Low = 0 to 7, Medium = 8 to 13, High = 14 to 38	16	201.293
Low = 0 to 7, Medium = 8 to 14, High = 15 to 38	12	205.294
Low = 0 to 7, Medium = 8 to 15, High = 16 to 38	3	221.201
Low = 0 to 7, Medium = 8 to 16, High = 17 to 38	13	204.429
Low = 0 to 7, Medium = 8 to 17, High = 18 to 38	15	203.966
Low = 0 to 8, Medium = 9 to 13, High = 14 to 38	14	204.026
Low = 0 to 8, Medium = 9 to 14, High = 15 to 38	9	210.284
Low = 0 to 8, Medium = 9 to 15, High = 16 to 38	**1**	**227.548**
Low = 0 to 8, Medium = 9 to 16, High = 17 to 38	6	213.664
Low = 0 to 8, Medium = 9 to 17, High = 18 to 38	5	215.059
Low = 0 to 9, Medium = 10 to 13, High = 14 to 38	17	199.491
Low = 0 to 9, Medium = 10 to 14, High = 15 to 38	11	207.018
Low = 0 to 9, Medium = 10 to 15, High = 16 to 38	2	224.746
Low = 0 to 9, Medium = 10 to 16, High = 17 to 38	7	213.167
Low = 0 to 9, Medium = 10 to 17, High = 18 to 38	4	215.839

Table 2 –

Differences in Demographic and Clinical Characteristics Among the Patients Based on Cutpoints for Total Number of Symptoms

Characteristic	Low (1) 0 to 8 symptoms 25.3% (n=336)	Moderate (2) 9 to 15 symptoms 36.3% (n=482)	High (3) 16 to 38 symptoms 38.4% (n=511)	Statistics
	Mean (SD)	Mean (SD)	Mean (SD)	
Age (years)	60.4 (11.3)	57.2 (12.4)	55.3 (12.5)	F=18.08, p<.001 1 > 2 > 3
Education (years)	16.2 (3.2)	16.6 (3.0)	15.8 (2.9)	F=8.61, p<.001 2 > 3
Body mass index (kg/m^2)	25.9 (5.3)	26.1 (5.3)	26.5 (6.2)	F=1.28, p=.278
Alcohol Use Disorders Identification Test score	3.1 (2.3)	2.9 (2.3)	2.9 (2.8)	F=0.67, p=.512
Karnofsky Performance Status score	86.6 (10.6)	81.2 (11.8)	74.6 (11.8)	F=108.79, p<.001 1 > 2 > 3
Number of comorbid conditions	2.1 (1.3)	2.3 (1.3)	2.7 (1.5)	F=24.12, p<.001 1 and 2 < 3
Self-administered Comorbidity Questionnaire score	4.6 (2.6)	5.2 (2.9)	6.4 (3.6)	F=37.06, p<.001 1 < 2 < 3
Time since diagnosis (years)	1.8 (3.2)	2.2 (4.3)	1.9 (3.9)	KW=1.42, p=.493
Time since diagnosis (years, median)	0.43	0.42	0.42	
Number of prior cancer treatments	1.5 (1.5)	1.7 (1.5)	1.6 (1.5)	F=0.58, p=.559
Number of metastatic sites including lymph node involvement[a]	1.3 (1.2)	1.3 (1.2)	1.2 (1.3)	F=2.27, p=.104
Number of metastatic sites excluding lymph node involvement	0.8 (1.0)	0.8 (1.1)	0.7 (1.1)	F=1.08, p=.339
MAX2 score	0.16 (0.08)	0.17 (0.08)	0.18 (0.08)	F=6.24, p=.002 1 and 2 < 3
	% (n)	% (n)	% (n)	
Gender (% female)	66.4 (223)	75.7 (364)	87.3 (446)	X^2=53.24, p<.001 1 < 2 < 3
Self-reported ethnicity				KW=5.52, p=.479
White	71.6 (237)	68.7 (327)	69.9 (353)	
Asian or Pacific Islander	13.6 (45)	13.0 (62)	10.7 (54)	
Black	6.6 (22)	7.8 (37)	7.1 (36)	
Hispanic, Mixed, or Other	8.2 (27)	10.5 (50)	12.3 (62)	

Characteristic	Low (1) 0 to 8 symptoms 25.3% (n=336)	Moderate (2) 9 to 15 symptoms 36.3% (n=482)	High (3) 16 to 38 symptoms 38.4% (n=511)	Statistics
	Mean (SD)	Mean (SD)	Mean (SD)	
Married or partnered (% yes)	67.9 (226)	67.4 (318)	59.2 (299)	X^2=9.50, p=.009 1 and 2 > 3
Lives alone (% yes)	20.4 (68)	19.3 (91)	24.5 (124)	X^2=4.30, p=.117
Currently employed (% yes)	41.1 (136)	38.3 (183)	28.3 (143)	X^2=17.72, p<.001 1 and 2 > 3
Annual household income				
Less than $30,000 [+]	14.4 (41)	14.9 (66)	24.3 (112)	KW=26.66, p<.0001 1 and 2 > 3
$30,000 to $70,000	19.6 (56)	19.6 (87)	23.6 (109)	
$70,000 to $100,000	16.5 (47)	17.3 (77)	16.3 (75)	
Greater than $100,000	49.5 (141)	48.2 (214)	35.8 (165)	
Child care responsibilities (% yes)	18.2 (60)	21.7 (103)	24.8 (123)	X^2=5.01, p=.082
Elder care responsibilities (% yes)	4.2 (13)	9.5 (41)	8.9 (41)	X^2=8.14, p=.017 1 < 2 and 3
Past or current history of smoking (% yes)	31.6 (105)	36.9 (175)	36.3 (182)	X^2=2.71, p=.259
Exercise on a regular basis (% yes)	73.6 (245)	72.9 (347)	67.2 (330)	X^2=5.32, p=.070
Specific comorbid conditions				
Heart disease	5.7 (19)	6.2 (30)	5.5 (28)	X^2=0.27, p=.875
High blood pressure	32.1 (108)	30.1 (145)	29.7 (152)	X^2=0.60, p=.739
Lung disease	10.4 (35)	11.4 (55)	11.7 (60)	X^2=0.37, p=.832
Diabetes	9.5 (32)	8.7 (42)	9.2 (47)	X^2=0.17, p=.920
Ulcer or stomach disease	3.0 (10)	4.8 (23)	6.1 (31)	X^2=4.23, p=.121
Kidney disease	0.9 (3)	1.7 (8)	1.6 (8)	X^2=0.94, p=.627
Liver disease	6.5 (22)	6.4 (31)	6.5 (33)	X^2=0.01, p=.998
Anemia or blood disease	8.0 (27)	10.0 (48)	17.4 (89)	X^2=20.46, p<.001 1 and 2 < 3
Depression	7.7 (26)	12.9 (62)	32.7 (167)	X^2=100.84, p<.001 1 and 2 < 3
Osteoarthritis	10.7 (36)	10.6 (51)	14.9 (76)	X^2=5.25, p=.072

Characteristic	Low (1) 0 to 8 symptoms 25.3% (n=336)	Moderate (2) 9 to 15 symptoms 36.3% (n=482)	High (3) 16 to 38 symptoms 38.4% (n=511)	Statistics
	Mean (SD)	Mean (SD)	Mean (SD)	
Back pain	14.0 (47)	22.8 (110)	36.4 (186)	X^2=56.70, p<.001 1 < 2 < 3
Rheumatoid arthritis	3.3 (11)	2.5 (12)	3.9 (20)	X^2=1.61, p=.447
Cancer diagnosis				X^2=19.60, p=.003 1 < 3 1 > 2 and 3
Breast cancer	33.3 (112)	40.7 (196)	44.2 (226)	
Gastrointestinal cancer	38.4 (129)	29.3 (141)	26.8 (137)	
Gynecological cancer	14.9 (50)	17.8 (86)	19.0 (97)	NS
Lung cancer	13.4 (45)	12.2 (59)	10.0 (51)	NS
Prior cancer treatment				X^2=2.47, p=.872
No prior treatment	26.1 (85)	23.8 (112)	25.4 (126)	
Only surgery, CTX, or RT	41.1 (134)	42.6 (200)	42.1 (209)	
Surgery and CTX, or surgery and RT, or CTX and RT	21.5 (70)	20.2 (95)	18.5 (92)	
Surgery and CTX and RT	11.3 (37)	13.4 (63)	13.9 (69)	
Metastatic sites				X^2=13.25, p=.039 1 < 3
No metastasis	26.1 (86)	31.0 (148)	37.5 (189)	
Only lymph node metastasis	23.9 (79)	21.8 (104)	21.0 (106)	NS
Only metastatic disease in other sites	22.1 (73)	22.4 (107)	19.4 (98)	NS
Metastatic disease in lymph nodes and other sites	27.9 (92)	24.7 (118)	22.0 (111)	NS
Receipt of targeted therapy				X^2=5.06, p=.080
No	65.3 (216)	72.4 (343)	71.0 (353)	
Yes	34.7 (115)	27.6 (131)	29.0 (144)	
Cycle length				KW=1.33, p=.514
14-day cycle	42.9 (144)	40.1 (193)	43.4 (221)	
21-day cycle	50.3 (169)	52.0 (250)	49.5 (252)	
28-day cycle	6.8 (23)	7.9 (38)	7.1 (36)	
Emetogenicity of the CTX regimen				KW=0.58, p=.750
Minimal/low	16.4 (55)	21.0 (101)	20.2 (103)	
Moderate	68.5 (230)	59.1 (285)	58.0 (295)	

Characteristic	Low (1) 0 to 8 symptoms 25.3% (n=336)	Moderate (2) 9 to 15 symptoms 36.3% (n=482)	High (3) 16 to 38 symptoms 38.4% (n=511)	Statistics
	Mean (SD)	Mean (SD)	Mean (SD)	
High	15.2 (51)	19.9 (96)	21.8 (111)	
Antiemetic regimen				X^2=19.08, p=.004
None	9.7 (32)	6.7 (31)	5.8 (29)	NS
Steroid alone or serotonin receptor antagonist alone	19.3 (64)	22.2 (103)	19.6 (98)	NS
Serotonin receptor antagonist and steroid	53.2 (176)	46.5 (216)	45.2 (226)	NS
NK-1 receptor antagonist and two other antiemetics	17.8 (59)	24.7 (115)	29.4 (147)	1 < 3

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

[+]Reference group

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

Table 3 –

Differences in the Rank Order of Symptom Occurrence Rates Among the Cutpoint Groups for Total Number of Symptoms*

Rank	Low (1) 0 to 8 symptoms 25.3% (n=336)		Moderate (2) 9 to 15 symptoms 36.3% (n=482)		High (3) 16 to 38 symptoms 38.4% (n=511)	
	Symptom	Occurrence	Symptom	Occurrence	Symptom	Occurrence
1	Lack of energy	53.0	Lack of energy	89.0	Lack of energy	97.7
2	Difficulty sleeping	39.3	Difficulty sleeping	70.1	Difficulty sleeping	87.7
3	Numbness/tingling in hands/feet	31.3	Pain	58.7	Feeling drowsy	85.1
4	Hair loss	30.7	Feeling drowsy	58.3	Pain	82.2
5	Pain	29.8	Hair loss	50.4	Worrying	79.3
6	Feeling drowsy	25.3	Numbness/tingling in hands/feet	50.2	Difficulty concentrating	78.5
7	Change in way food tastes	24.1	Worrying	47.5	Nausea	75.0
8	Dry mouth	19.6	Difficulty concentrating	47.1	Hair loss	74.8
9	Difficulty concentrating	18.5	Change in way food tastes	45.0	Feeling sad	74.2
10	Nausea	18.2	Dry mouth	41.3	Feeling irritable	70.8
11	Constipation	17.6	Feeling sad	40.2	Change in way food tastes	70.1
12	Worrying	17.3	Nausea	38.8	Numbness/tingling in hands/feet	67.9
13	Cough	16.4	Constipation	37.8	Dry mouth	66.1
14	Hot flashes	13.7	Lack of appetite	37.6	Constipation	65.9
15	Feeling sad	11.6	Feeling irritable	34.2	Lack of appetite	64.4
16	Lack of appetite	11.6	“I don’t look like myself”	30.5	Feeling nervous	64.0
17	Weight gain	11.3	Feeling nervous	30.3	“I don’t look like myself”	62.6
18	“I don’t look like myself”	10.7	Changes in skin	29.9	Changes in skin	59.9
19	Increased appetite	9.8	Cough	27.6	Feeling bloated	56.2
20	Diarrhea	9.8	Hot flashes	27.4	Dizziness	52.8
21	Feeling nervous	9.5	Feeling bloated	26.8	Sweats	51.5
22	Sweats	9.5	Dizziness	26.8	Problems with sexual interest or activity	48.9
23	Weight loss	9.5	Diarrhea	25.6	Cough	47.9
24	Changes in skin	9.5	Sweats	24.9	Hot flashes	47.9

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Rank	Low (1) 0 to 8 symptoms 25.3% (n=336)		Moderate (2) 9 to 15 symptoms 36.3% (n=482)		High (3) 16 to 38 symptoms 38.4% (n=511)	
	Symptom	Occurrence	Symptom	Occurrence	Symptom	Occurrence
25	Itching	8.9	Problems with sexual interest or activity	24.7	Shortness of breath	46.6
26	Problems with sexual interest or activity	8.3	Weight gain	23.2	Diarrhea	46.0
27	Feeling bloated	7.1	Increased appetite	22.6	Abdominal cramps	41.9
28	Mouth sores	6.8	Itching	22.0	Weight loss	39.9
29	Feeling irritable	6.5	Weight loss	20.5	Increased appetite	39.5
30	Shortness of breath	6.0	Shortness of breath	20.5	Itching	38.0
31	Swelling of arms or legs	5.7	Mouth sores	16.0	Weight gain	36.6
32	Dizziness	5.1	Abdominal cramps	14.9	Difficulty breathing	36.0
33	Difficulty breathing	4.5	Difficulty breathing	13.7	Mouth sores	34.8
34	Chest tightness	4.2	Swelling of arms or legs	12.0	Chest tightness	33.9
35	Abdominal cramps	3.9	Chest tightness	10.4	Difficulty swallowing	27.0
36	Problems with urination	3.6	Problems with urination	9.8	Problems with urination	25.0
37	Difficulty swallowing	3.3	Vomiting	9.8	Swelling of arms or legs	22.9
38	Vomiting	3.3	Difficulty swallowing	7.1	Vomiting	20.7
Total Number of Symptoms (Mean (SD))						
	5.4 (2.2)		12.2 (2.0)		21.2 (4.8)	

Abbreviation: SD = standard deviation

*For all of the symptoms, differences in occurrence rates among the three groups were significantly different (all p <.05). Post hoc contrasts followed the expected pattern (Low < Moderate < High).

Table 4 –

Differences in Stress and Resilience Measures Among the Patients Based on Cutpoints for Total Number of Symptoms

Measures[a]	Low (1) 0 to 8 symptoms 25.3% (n=336)	Moderate (2) 9 to 15 symptoms 36.3% (n=482)	High (3) 16 to 38 symptoms 38.4% (n=511)	Statistics
	Mean (SD)	Mean (SD)	Mean (SD)	
PSS total score	14.0 (6.7)	18.0 (7.6)	21.9 (8.0)	F=108.90, p<.001 1 < 2 < 3
IES-R total score (≥24)	12.4 (9.8)	17.7 (11.9)	23.9 (14.0)	F=87.18, p<.001 1 < 2 < 3
IES-R intrusion	0.6 (0.5)	0.9 (0.7)	1.2 (0.7)	F=81.28, p<.001 1 < 2 < 3
IES-R avoidance	0.8 (0.6)	0.9 (0.6)	1.1 (0.7)	F=27.92, p<.001 1 < 2 < 3
IES-R hyperarousal	0.3 (0.4)	0.6 (0.6)	0.9 (0.7)	F=106.31, p<.001 1 < 2 < 3
LSC-R total score (range 0–30)	4.7 (3.0)	6.1 (3.8)	7.0 (4.2)	F=29.48, p<.001 1 < 2 < 3
LSC-R affected sum (range 0–150)	8.0 (7.4)	11.4 (9.8)	15.0 (12.6)	F=37.24, p<.001 1 < 2 < 3
LSC-R PTSD sum (range 0–21)	2.0 (2.2)	3.1 (2.9)	3.9 (3.3)	F=30.62, p<.001 1 < 2 < 3
CDRS total score (range 0–40; normative score = 31.8))	31.7 (6.1)	30.3 (6.2)	28.9 (6.5)	F=19.36, p<.001 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