Original Article

The Symptom Experience of Oncology Outpatients Has a Different Impact on Quality-of-Life Outcomes

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Abstract

The aims of this replication study were to determine if subgroups of oncology outpatients receiving active treatment could be identified based on their experience with the symptoms of fatigue, sleep disturbance, depression, and pain; whether patients in these subgroups differed on selected demographic, disease, and treatment characteristics; and if patients in these subgroups differed on functional status and quality of life (QOL). A convenience sample of 228 oncology outpatients was recruited from seven outpatient settings in Israel. Patients completed a demographic questionnaire, a Karnofsky Performance Status score, the Multidimensional Quality of Life Scale—Cancer, the Lee Fatigue Scale, the General Sleep Disturbance Scale, the Center for Epidemiological Studies—Depression Scale, and a numeric rating scale of worst pain intensity. Cluster analysis was used to identify the patient subgroups based on their symptom experience. Four relatively distinct patient subgroups were identified based on their experiences with the above symptoms (i.e., low levels of all four symptoms (32.9%), low levels of pain and high levels of fatigue (18.0%), high levels of pain and moderate levels of fatigue (42.5%), and high levels of all four symptoms (6.6%). No differences were found among the four subgroups on any demographic, disease, or treatment characteristics. The subgroup of patients who reported high levels of all four symptoms reported the worst functional status and poorest QOL. In conclusion, differences

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in the symptom experience of oncology outpatients suggest that patients may harbor different phenotypic characteristics (e.g., environmental or physiologic) or genetic determinants for experiencing symptoms that are independent of demographic, disease, and treatment characteristics. J Pain Symptom Manage 2008;35:162–170. *© 2008 U.S. Cancer Pain Relief Committee. Published by Elsevier Inc. All rights reserved.*

Key Words
Cluster analysis, depressive symptoms, fatigue, functional status, pain, quality of life, sleep disturbances, symptom clusters

Introduction

Pain, fatigue, and depression are complex affective, sensory, and cognitive phenomena.[1] All of these symptoms, as well as sleep disturbances, are common in oncology patients who are receiving cancer treatment.[1–3] In addition, recent studies suggest that these symptoms can co-occur in oncology patients.[4–10] Therefore, a need exists to evaluate the impact of multiple symptoms on patient outcomes. In a recent study that used cluster analysis, Miaskowski et al.[11] identified four subgroups of oncology outpatients based on their different experiences with pain, fatigue, sleep disturbance, and depression. Of note, the subgroup of patients who reported low levels of all four symptoms reported the best functional status and quality of life (QOL) compared to a subgroup with high levels of all four symptoms.

Miaskowski et al.[11] stated that because these findings were so novel they would need to be replicated before definitive conclusions could be made about these patient subgroups. Therefore, the primary purpose of the present study was to replicate and elaborate on these findings with a sample of oncology outpatients from a different geographic location. In this study, we used hierarchical cluster analysis to identify subgroups of oncology outpatients receiving active treatment for their cancer, based on their experience with the same four symptoms. Specifically, the aims of this study were: to determine if subgroups of oncology outpatients could be identified based on their ratings of the severity of fatigue, sleep disturbance, depression, and pain; to determine if patients in these subgroups differed on selected demographic, disease, and treatment characteristics; and to determine if the patients in these subgroups differed on two important patient outcomes (i.e., functional status and QOL).

Patients and Methods

Participants and Settings

This descriptive, cross-sectional study used self-report questionnaires to obtain information from a convenience sample of oncology outpatients who were adults (>18 years of age); were able to read, write, and understand Hebrew; gave written informed consent; had a Karnofsky Performance Status (KPS) score of ≥50; and were receiving active treatment for their cancer. Patients were recruited from seven outpatient settings in Israel. The questionnaires, method for data collection, and statistical analysis procedures were identical to those used by Miaskowski et al. [11] and are abbreviated here.

A total of 228 patients had complete data on all of the study measures required for the cluster analysis. The study was approved by the Human Subjects Committee at each of the study sites.

Instruments

The study instruments included the following:

1. Demographic Questionnaire that provided information on age, gender, marital status, educational background, and employment status. In addition, the patient's medical record was reviewed for disease and treatment information, which included diagnosis, current cancer treatments, and presence of metastatic disease.

2. The 18-item Lee Fatigue Scale (LFS) uses a 0–10 numeric rating scale (NRS) format to assess fatigue and energy. A fatigue severity score was calculated as the mean of the 13 items in the fatigue subscale and could range from 0 to 10, with higher scores indicating higher levels of fatigue severity. The LFS has been used to measure fatigue in healthy individuals,[12,13] as well as in patients with cancer[4] and HIV disease.[14] The LFS has established validity and internal consistency reliability coefficients.[12–14] In this sample, the Cronbach's α for the LFS was 0.93.
3. The General Sleep Disturbance Scale (GSDS)[15–18] consists of 21 items that evaluate various aspects of sleep disturbance (i.e., quality and quantity of sleep, sleep onset latency, number of awakenings, excessive daytime sleepiness, medication use). Each item was rated on an NRS that ranged from 0 (never) to 7 (every day), and the 21 items were summed and yielded a total score that could range from 0 (no disturbance) to 147 (extreme disturbance). The GSDS has well-established validity and reliability in shift workers, pregnant women, and patients with cancer and HIV disease.[4,19–22] In this study, the Cronbach's α for the GSDS was 0.80.
4. The Center for Epidemiologic Studies-Depression Scale (CES-D)[19,20] consists of 20 items selected to represent the major symptoms in the clinical syndrome of depression. Patients were asked to rate a series of statements on a 0 (rarely or none of the time) to 3 (most or all of the time) scale for how frequently the symptoms were experienced in the past week. Scores can range from 0 to 60, with scores greater than 16 indicating the need for patients to seek a clinical evaluation for major depression. The CES-D has well-established concurrent and construct validity.[19,20] In this study, the Cronbach's α for the CES-D was 0.87.
5. A descriptive NRS that ranged from 0 (no pain) to 10 (excruciating pain) was used to evaluate worst pain intensity. A descriptive NRS is a valid and reliable measure of pain intensity.[21]
6. The Multidimensional Quality of Life Scale—Cancer (MQOLS-CA)[23] consists of 33 items that measure four dimensions of QOL in cancer patients (i.e., physical well-being, psychological well-being, social concerns, and symptoms). Patients responded to each item on the QOL Inventory using a 0–10 NRS. A total QOL score was calculated, with higher scores indicating a better QOL. In this study, the Cronbach's α reliability for the MQOLS-CA was 0.89.

All of the instruments were translated into Hebrew using the forward and backward procedure.[24]

Methods

Patients were recruited in the outpatient settings, signed a written informed consent, and completed the study questionnaires either while waiting to receive their treatment or at home and returned it to the research nurse at the next clinic visit.

Statistical Analyses

Data were analyzed using Stata® Version 9.0 and SPSS™ Version 14.0. Descriptive statistics and frequency distributions were generated on the sample characteristics. Hierarchical cluster analyses were done, using Stata®, to identify subgroups of patients based on their responses to the symptom inventories. Scores from each of the symptom questionnaires were standardized on their ranges and then used in the cluster analysis to "equalize" the influence of variables with different scale lengths on the cluster solution.[25,26] To determine the number of subgroups of patients, an agglomerative hierarchical cluster analysis was performed, with squared Euclidean distances used in the proximities matrix and weighted average linkage (also known as WPGMA) used as the clustering method.[25,27] For our question, this clustering method is preferable to the commonly used Ward's method, because there was no reason to expect that the sizes of our patient subgroups would be similar. Ward's method is known to produce spherical clusters, forcing them toward subgroups of similar sizes, and the method is sensitive to outliers.[27]

Cluster analyses yielding 2, 3, 4, and 5 clusters were obtained on the symptom data. The Calinski and Harabasz pseudo-F stopping rule index and the Duda and Hart Je(2)/Je(1) index were used jointly to select the final number of clusters for our analysis.[26,28] Milligan and Cooper[26] identified these two stopping rules as the "best" among 30 stopping rules for recovering from two to five "true" clusters in a Monte Carlo study. A large Calinski and Harabaz pseudo-F statistic, combined with two measures from Duda and Hart (a large Je(2)/Je(1) index and its associated small pseudo-T-squared value) identified four clusters in these data as the most appropriate number of clusters (see Fig. 1).[25,26,28]

One-way analyses of variance (ANOVAs) were used to determine if there were significant differences among the four subgroups of patients on demographic, disease, and treatment characteristics, symptom scores, and outcome measures (i.e., functional status and QOL). Differences among the four subgroups were considered statistically significant at the $P < 0.05$ level. Post hoc contrasts were done using the Bonferroni procedure to control the overall family alpha level of the six possible pairwise contrasts at 0.05. The *P*-values presented for each pairwise contrast have been adjusted so that values of less than 0.05 indicate significance.

Results

Cluster Analysis Results

Two hundred twenty-eight patients, who provided complete data on all four of the symptom inventories, were entered into the cluster analysis. Figure 1 provides the breakdown of the patient subgroups following 2, 3, and 4 cluster solutions. When classifications based on the two-cluster solution were obtained, 93.4% of the sample was categorized as a "low to moderate on all symptoms" subgroup and 6.6% as a "high on all symptoms" subgroup. When classifications based on the three-cluster solution were obtained, the "high on all symptoms" subgroup remained intact, whereas the "low to moderate on all symptoms" subgroup was divided into two groups. One subgroup of patients (42.5%) reported high levels of pain and moderate levels of fatigue and the other subgroup (50.9%) reported low-to-moderate levels of all four symptoms. When classifications based on the four cluster solution were obtained, the "high pain and moderate fatigue" and the "high on all symptoms" subgroups remained intact, whereas the "low to moderate on all symptoms" subgroup was divided into a subgroup (32.9%) that reported low levels of all four symptoms and a subgroup (18.0%) that reported low levels of pain and high levels of fatigue. The naming of the subgroups was based on analysis of the findings from the post hoc contrasts presented below.

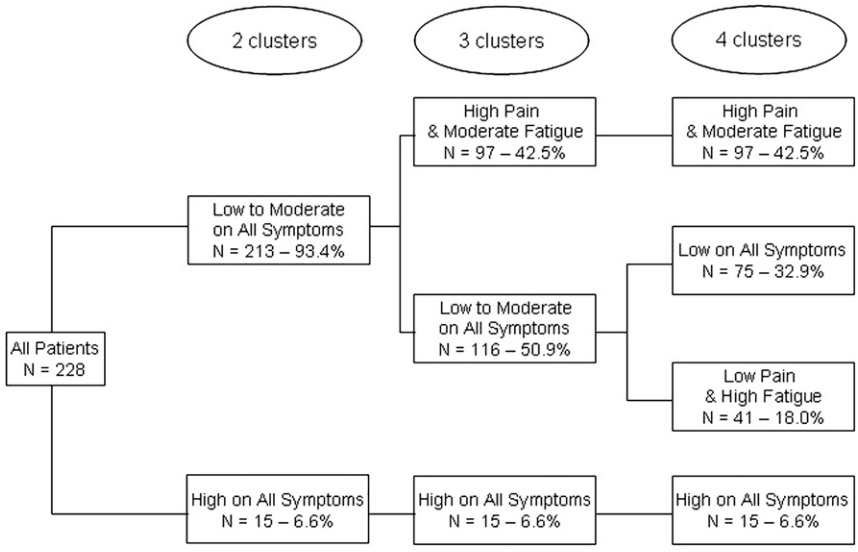

Fig. 1. Distribution of patient subgroups based on 2, 3, or 4 cluster solutions.

The standardized symptom scores for the four patient subgroups are shown in Fig. 2. For the remainder of this article, the patient subgroups will be referred to as ALL LOW (i.e., low levels of all four symptoms), LOW PAIN and HIGH FATIGUE (i.e., low levels of pain and high levels of the fatigue), HIGH PAIN and MODERATE FATIGUE (i.e., high levels of pain and moderate levels fatigue), and ALL HIGH (i.e., high levels of all four symptoms).

Differences in Demographic, Disease, and Treatment Characteristics. Table 1 summarizes the demographic, disease and treatment characteristics for the total sample. No differences were found among the four subgroups on any of the demographic, disease, or treatment characteristics.

Patient Subgroup Differences in Symptom Severity Scores. This section describes differences in fatigue, sleep disturbance, depression, and pain scores for each patient subgroup compared to the other three subgroups. As shown in Table 2, significant differences were found in all four of the symptom severity scores among the four subgroups of patients. The comparison of each subgroup to the other three subgroups on the various symptoms is based on the results of the post hoc contrasts.

ALL LOW Subgroup. Patients in this subgroup reported significantly lower fatigue (all $P \leq 0.001$), sleep disturbance (all $P \leq 0.0001$), and depression scores ($P \leq 0.005$) than the patients in the other three subgroups. No differences in worst pain intensity scores were found between the ALL LOW and the LOW PAIN and HIGH FATIGUE subgroups.

LOW PAIN and HIGH FATIGUE Subgroup. Patients in this subgroup had significantly higher fatigue scores compared to patients in the ALL LOW and HIGH PAIN and MODERATE FATIGUE subgroups, but significantly lower than the ALL HIGH subgroup (all $P \leq 0.001$). This subgroup had significantly higher sleep disturbance scores ($P \leq 0.0001$) than the ALL LOW subgroup. As for depression, this subgroup had a significantly lower score than the ALL HIGH subgroup but a significantly higher score than the other two subgroups. Worst pain intensity scores were significantly lower in this subgroup than in the HIGH PAIN and MODERATE FATIGUE and the ALL HIGH subgroups (both $P < 0.0001$).

HIGH PAIN and MODERATE FATIGUE Subgroup. Patients in this subgroup had significantly lower fatigue scores than the LOW PAIN and HIGH FATIGUE and the ALL HIGH subgroups, but higher than the ALL LOW subgroup (all $P \leq 0.001$). Patients in this subgroup reported significantly less sleep

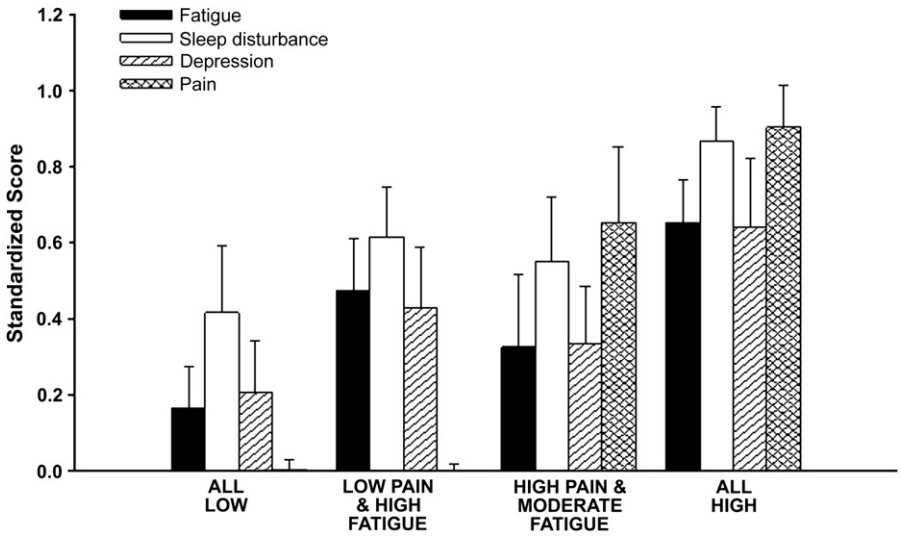

Fig. 2. Standardized symptom severity scores for the four patient subgroups. All values are expressed as means ± SDs.

Table 1
Demographic Characteristics for the Total Sample ($n = 228$)

Characteristic	Mean ± SD
Age (years)	53.9 ± 12.7
Number of chronic conditions	3.3 ± 2.2
	%
Female	69.8
Education	
Primary school	5.7
High school	24.1
Junior college or vocational school	23.2
College or graduate school	46.1
Married/partnered	84.9
Lives alone	10.0
Working for pay	50.4
Diagnosis	
Breast	37.6
Colon	14.2
Ovarian	9.2
Lung	8.3
Non-Hodgkin's lymphoma	6.9
Prostate	3.2
Hodgkin's disease	2.3
Malignant melanoma	1.4
Head and neck	0.5
Other	16.5
Presence of metastatic disease	25.0
Current treatment	
Chemotherapy	86.2
Radiation therapy	0.9
Hormonal therapy	2.2
Other	10.7

disturbance than patients in the ALL HIGH subgroup ($P \leq 0.0001$) but significantly more than the ALL LOW subgroup ($P < 0.0001$). This subgroup's depression scores were significantly lower (both $P \leq 0.005$) than the LOW PAIN and HIGH FATIGUE and the ALL HIGH subgroups. Worst pain intensity scores in this subgroup were significantly lower than in the ALL HIGH subgroup ($P < 0.0001$), but significantly higher than in the ALL LOW and the LOW PAIN and HIGH FATIGUE subgroups (both $P < 0.0001$).

ALL HIGH Subgroup. This subgroup reported significantly higher fatigue, sleep disturbance, depression, and worst pain intensity scores than the other three subgroups (all $P \leq 0.001$).

Differences in Patient Outcomes. Functional Status. Figure 3 illustrates the KPS scores for the total sample and for the four subgroups.

Table 2
Symptom Inventory Scores for the Total Sample and Differences in Fatigue, Sleep Disturbance, Depression, and Pain Scores Among the Four Patient Subgroups

Symptom Inventory	TOTAL SAMPLE; $n = 228$	ALL LOW Subgroup 1; $n = 75$, 32.9.0%	LOW PAIN and HIGH FATIGUE Subgroup 2; $n = 41$, 18.0%	HIGH PAIN and MODERATE FATIGUE Subgroup 3; $n = 97$, 42.5%	ALL HIGH Subgroup 4; $n = 15$, 6.6%	Test, Statistical Significance, and Post hoc Contrasts[a]
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	
Lee Fatigue Scale score	3.2 (2.0)	1.6 (1.0)	4.7 (1.3)	3.2 (1.8)	6.4 (1.1)	$F(3,224) = 64.2$; $P < 0.0001$ $1 < 3 < 2 < 4$ all $P \leq 0.001$
General Sleep Disturbance Total score	51.2 (18.5)	39.7 (16.4)	58.4 (12.5)	52.3 (15.9)	82.1 (8.6)	$F(3,224) = 38.6$; $P < 0.0001$ $1 < 3$,&4, all $P < 0.0001$ 2 and $3 < 4$, $P < 0.0001$ 2 versus 3 is not significant
Center for Epidemiological Studies—Depression Scale score	16.9 (9.6)	10.5 (7.0)	22.0 (8.1)	17.2 (7.6)	32.9 (9.1)	$F(3,224) = 45.7$; $P < 0.0001$ $1 < 3 < 2 < 4$, all $P \leq 0.005$
Worst pain intensity score	3.4 (3.7)	0.04 (0.3)	0.02 (0.1)	6.5 (2.0)	9.1 (1.1)	$F(3,224) = 510.5$; $P < 0.0001$ $1 < 3$ and 4, both $P < 0.0001$ $2 < 3 < 4$, both $P < 0.0001$ 1 versus 2 is not significant

[a]The *P*value presented for each pairwise post hoc contrast has been adjusted so that a value of less than 0.05 indicates significance.

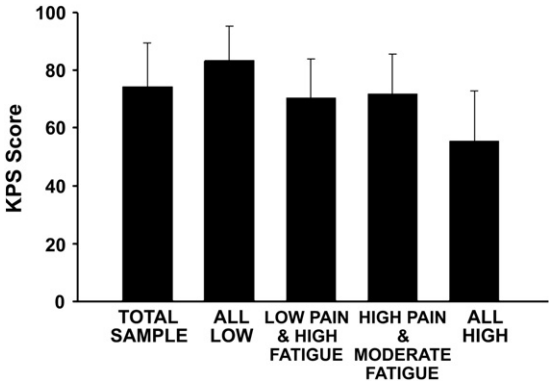

Fig. 3. Karnofsky Performance Status (KPS) scores for the total sample and four patient subgroups. All values are expressed as means ± SDs. Post hoc contrasts demonstrated that patients in the ALL HIGH subgroup had significantly lower KPS scores than patients in the other three subgroups (all $P < 0.002$).

One-way ANOVA demonstrated significant differences in KPS scores among the four subgroups ($F(3,218) = 22.9$, $P < 0.0001$). Patients in the ALL LOW subgroup reported significantly higher KPS scores than the other three subgroups (all $P < 0.0001$). Patients in the ALL HIGH subgroup reported significantly lower KPS scores than the other three subgroups (all $P < 0.002$).

Quality of Life. Figure 4 illustrates the QOL scores for the total sample and for the four subgroups. One-way ANOVA demonstrated

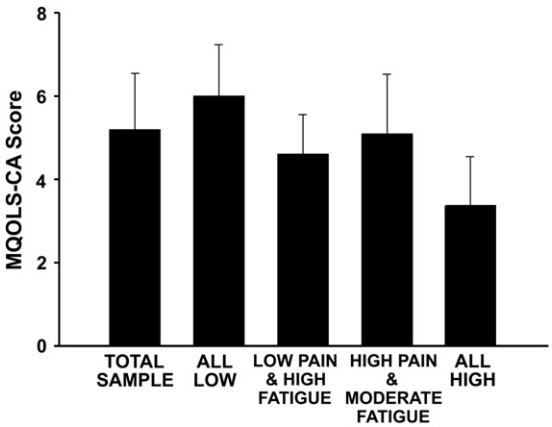

Fig. 4. Multidimensional Quality of Life Scale-Cancer (MQOLS-CA) scores for the total sample and four patient subgroups. All values are expressed as means ± SDs. Post hoc contrasts demonstrated that patients in the ALL HIGH subgroup had significantly lower MQOLS-CA scores than the patients in the other three subgroups (all $P < 0.00001$).

significant differences in QOL scores among the four subgroups ($F(3,220) = 28.5$, $P < 0.0001$). Patients in the ALL LOW subgroup reported significantly higher QOL scores than the other three subgroups (all $P \leq 0.0001$). Patients in the ALL HIGH subgroup reported significantly lower QOL scores than the other three subgroups (all $P < 0.003$).

Discussion

This replication study, which used the same symptom and outcome questionnaires and the same methods as Miaskowski et al.,[11] confirmed that four different subgroups of oncology outpatients could be identified based on their experiences with four highly prevalent symptoms. Importantly, this study confirmed that the symptom experiences of these patients had different effects on their functional status and QOL and were not dependent on any disease or treatment characteristics.

In addition, the findings of differences in functional status and QOL based on different symptom experiences were not only statistically significant but also clinically significant. In this study, patients categorized in the ALL HIGH subgroup reported the lowest KPS scores (55.4 ± 17.6) compared to patients in the ALL LOW subgroup who reported the highest KPS scores (83.3 ± 11.8), which represents a difference of 1.8 SD units. In addition, patients categorized in the ALL HIGH subgroup reported the lowest QOL scores (3.4 ± 1.2) compared to patients in the ALL LOW subgroup who reported the highest QOL scores (6.0 ± 1.2), which represents a difference of 2.0 SD units. Based on previous reports in the QOL literature that minimally important differences in QOL scores are in the range of 0.2−0.5 SD units,[29−31] these differences represent, not only statistically, but *clinically meaningful* differences in two important patient outcomes.

Comparisons of the findings from this study with those of Miaskowski et al.[11] demonstrate that the four patient subgroups, identified through cluster analysis, were almost identical. Both studies found two distinct subgroups of patients who reported low and high levels of all four symptoms and one subgroup that reported low levels of pain and high levels of

fatigue. The only subgroup that had slightly different characteristics was the HIGH PAIN and MODERATE FATIGUE subgroup, which in the study of Miaskowski et al.[11] was characterized as HIGH PAIN and LOW FATIGUE. This difference may be attributed to small differences in age, gender distribution, diagnosis, and cancer treatments between the two studies.

In agreement with Miaskowski et al.,[11] in this study neither gender nor any of the disease or treatment characteristics were distinguished among the four subgroups. However, unlike the former study, age and marital status did not differentiate among the four subgroups. It is not readily apparent why these differences were found and they warrant investigation in future studies.

Based on the findings from these two studies, additional research is needed to determine the potential mechanisms that may contribute to the different symptom experiences associated with these four subgroups of patients. The ALL LOW and ALL HIGH subgroups may offer the optimal populations to determine if these patients harbor different risk factors (e.g., genetic) for experiencing these four symptoms that are independent of demographic, disease, and treatment characteristics. One potential mechanism for this cluster of symptoms (i.e., pain, fatigue, sleep disturbance, depression) is the syndrome of "sickness behavior" that was recently identified in rodents.[32–34] One can hypothesize that certain subgroups of patients are predisposed to experience higher levels of these four symptoms than other patients. It is interesting to note that the ALL HIGH subgroup was a relatively small portion of both study samples (i.e., 6.6% and 15.0%). Subsequent studies need to focus on the identification of phenotypic characteristics (e.g., environmental, physiologic) and perhaps genetic characteristics that place patients at increased risk for experiencing more severe symptoms.

The findings of four relatively distinct subgroups of patients with different symptom experiences suggest that cluster analysis techniques may be useful to explore potential mechanisms that influence symptom experiences. In addition, the use of this statistical methodology may help to identify low, moderate, and high-risk groups of patients who may warrant different types, different doses, or more targeted symptom management interventions. These findings point to a significant need to evaluate the existence of multiple symptoms among cancer patients, which may possibly facilitate the design of individually tailored symptom management plans to improve outcomes. Patients with high levels of all four symptoms may require multiple interventions to improve functional status and QOL.

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