Subgroups of Patients With Cancer With Different Symptom Experiences and Quality-of-Life Outcomes: A Cluster Analysis

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Purpose/Objectives: To identify subgroups of outpatients with cancer based on their experiences with the symptoms of fatigue, sleep disturbance, depression, and pain; to explore whether patients in the subgroups differed on selected demographic, disease, and treatment characteristics; and to determine whether patients in the subgroups differed on two important patient outcomes: functional status and quality of life (QOL).

Design: Descriptive, correlational study.

Setting: Four outpatient oncology practices in northern California.

Sample: 191 outpatients with cancer receiving active treatment.

Methods: Patients completed a demographic questionnaire, Karnofsky Performance Status scale, Lee Fatigue Scale, General Sleep Disturbance Scale, Center for Epidemiological Studies–Depression Scale, Multidimensional Quality-of-Life Scale–Cancer, and a numeric rating scale of worst pain intensity. Medical records were reviewed for disease and treatment information. Cluster analysis was used to identify patient subgroups based on patients' symptom experiences. Differences in demographic, disease, and treatment characteristics as well as in outcomes were evaluated using analysis of variance and chi square analysis.

Main Research Variables: Subgroup membership, fatigue, sleep disturbance, depression, pain, functional status, and QOL.

Findings: Four relatively distinct patient subgroups were identified based on patients' experiences with four highly prevalent and related symptoms.

Conclusions: The subgroup of patients who reported low levels of all four symptoms reported the best functional status and QOL.

Implications for Nursing: The findings from this study need to be replicated before definitive clinical practice recommendations can be made. Until that time, clinicians need to assess patients for the occurrence of multiple symptoms that may place them at increased risk for poorer outcomes.

Key Points . . .

- Fatigue, depression, sleep disturbance, and pain are common symptoms that can co-occur in outpatients with cancer who are receiving cancer treatment.
- Younger patients may be at greater risk for the co-occurrence of more severe levels of all four symptoms.
- Additional research is warranted to determine whether distinct subgroups of outpatients with cancer can be identified based on their experiences with the co-occurrence of fatigue, depression, sleep disturbance, and pain.

Epidemiologic studies have demonstrated that outpatients with cancer undergoing active treatment (Cleeland et al., 2000; Portenoy et al., 1994), as well as patients with advanced disease (Francoeur, 2005; Walsh, Donnelly, & Rybicki, 2000), report high prevalence rates for

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Digital Object identifier: 10.1188/06.ONF.E79-E89

a number of symptoms. In addition, clinical experience reinforces the fact that patients with cancer rarely present with a single symptom. Therefore, a need exists to evaluate the impact of multiple symptoms on patient outcomes.

In 2001, Dodd, Miaskowski, and Paul defined the concept of a symptom cluster as three or more concurrent symptoms (e.g., pain, anxiety, and depression) that are related to each other. In their study, the effect of the symptom cluster of pain, fatigue, and sleep insufficiency on functional status was evaluated in a sample of 93 outpatients with cancer who received three cycles of chemotherapy. Symptom severity was assessed prior to the first cycle of chemotherapy using single items from a quality-of-life (QOL) inventory (Padilla, Ferrell, Grant, & Rhiner, 1990). In addition, functional status was assessed before the first and at the end of the third cycle of chemotherapy using the Karnofsky Performance Status (KPS) scale (Karnofsky, Abelmann, Craver, & Burchenal, 1948). Using a two-stage, hierarchical multiple regression analysis, with the KPS score at the end of the third cycle as the dependent variable, the KPS score at baseline entered into step 1, and age and the symptom cluster entered into step 2, the model explained 48.4% of the variance in functional status. The findings were the first to suggest that a specific symptom cluster could influence the outcomes of patients undergoing cancer treatment.

Subsequent work by Given, Given, Azzouz, & Stommel (2001) demonstrated that the same symptom cluster (i.e., pain, fatigue, and insomnia) had a consistent and significant negative effect on functional status in a sample of 826 older adult patients with lung cancer. Of note, the effect of the symptom cluster on functional status was independent of type of cancer treatment, stage of disease, or comorbid conditions.

More recent studies have focused on identifying symptom clusters in patients newly diagnosed with lung cancer and determining whether the symptom clusters changed over time (Gift, Jablonski, Stommel, & Given, 2004; Gift, Stommel, Jablonski, & Given, 2003). In the studies, the occurrence and severity of 37 symptoms commonly experienced by patients with cancer were assessed. In the first study (Gift et al., 2004), using data from the baseline assessment, a factor analysis of the Physical Symptom Experience Scale determined that seven of the 37 symptoms (i.e., fatigue, nausea, weakness, appetite loss, weight loss, altered taste, and vomiting) formed a cluster. In the second study (Gift et al., 2003), the symptom cluster identified at diagnosis remained at three and six months, although the severity of the symptoms decreased over time.

At a National Institutes of Health state-of-the-science conference on symptom management, Miaskowski, Dodd, and Lee (2004) noted that research on symptom clusters is still in its infancy and that multiple approaches can be used to evaluate the effect of symptom clusters on patient outcomes. To date, one focus of symptom cluster research has been to cluster symptoms, usually through the administration of a comprehensive symptom inventory and subsequent factor analysis of the inventory (Gift et al., 2003, 2004).

An equally valuable approach for symptom cluster research would be to cluster patients based on the intensity of symptoms reported for an *a priori* identified symptom cluster, using the statistical technique of cluster analysis. The approach may allow for the identification of subgroups of patients who experience multiple symptoms with greater or lesser severity and who may be at risk for poorer outcomes. For example, cluster analysis has been used in research studies of chronic pain to characterize distinct subtypes of patients with a complex regional pain syndrome (Bruehl et al., 2002). In addition, cluster analysis has been used to identify subgroups of patients based on their ratings of pain intensity, depression, and functional status and to determine whether, for a specific migraine headache treatment, patients in different subgroups experienced different outcomes (Davis, Reeves, Graff-Radford, Hastie, & Naliboff, 2003). However, the approach has not been used to identify subgroups of patients with cancer based on their experiences with common symptoms.

Therefore, in the current study, the statistical procedure of cluster analysis was used to identify subgroups of outpatients with cancer receiving active treatment for their cancer based on their experiences with the symptoms of fatigue, sleep disturbance, depression, and pain. The symptoms were chosen because of their high prevalence rates in the oncology population (Cleeland et al., 2000; Portenoy et al., 1994) and because of the previously established inter-relationships among the symptoms (Miaskowski & Lee, 1999). In addition, based on the authors' previous research (Dodd et al., 2001) and the work of others (Given et al., 2001), the hypothesis was made that patients with higher levels of the symptoms would report poorer functional status and QOL. Therefore, the purposes of the present study were to determine whether subgroups of outpatients with cancer could be identified based on their ratings of the severity of fatigue, sleep disturbance, depression, and pain; whether patients in the subgroups differed on selected demographic, disease, and treatment characteristics; and whether patients in the subgroups differed on two important patient outcomes, functional status and QOL.

Methods

Participants and Settings

The descriptive, cross-sectional study used self-report questionnaires to obtain information from a convenience sample of outpatients with cancer who were adults (> 18 years of age); were able to read, write, and understand English; gave written, informed consent; had KPS scores of 50 or higher; and were receiving active treatment for cancer. Patients were recruited from four outpatient settings, including a university-based cancer center, a Veterans Affairs facility, and two community-based outpatient facilities.

A total of 310 patients were approached to participate in the study, and 206 consented to participate (refusal rate of 34%). The primary reasons for refusal were that a patient was too ill to participate (80%), too busy (15%), or not interested in the research study (5%). Of the 206 patients who enrolled in the study, 191 (93%) had complete data on all of the study measures required for the cluster analysis. No differences were found in any demographic (gender, ethnicity, living arrangements, and employment status) or disease or treatment characteristics (KPS score, diagnosis, presence of metastatic disease, hemoglobin, and hematocrit) between those with (n = 191) and without (n = 15) complete data, except for age, education, marital status, and current treatments. Patients with complete data, when compared with those with incomplete data, were significantly younger (60.1 $\pm$ 12.3 versus 68.9 $\pm$ 9.6 years, respectively; p = 0.008), had more years of education (15.5 $\pm$ 2.8 versus 13.9 $\pm$ 2.5 years, respectively; p = 0.03), were more likely to be married or partnered (60% versus 40%, respectively; p = 0.02), were more likely to be receiving radiation therapy (41% versus 6%,

respectively; p = 0.008), and were less likely to be receiving chemotherapy (57% versus 93%, respectively; p = 0.006). The study was approved by the Human Subjects Committee at the University of California, San Francisco, and at each of the study sites. All patients signed a written, informed consent.

Instruments

The study instruments included a **demographic questionnaire,** the **KPS** scale, the **Lee Fatigue Scale (LFS)** (Gay, Lee, & Lee, 2004; Lee, Hicks, & Nino-Murcia, 1991; Lee, Portillo, & Miramontes, 1999), the **General Sleep Disturbance Scale (GSDS)** (Dorsey, Lee, & Scharf, 2004; Humphreys, Lee, Neylan, & Marmar, 1999; Lee, 1992; Lee, Portillo, & Miramontes, 2001), the **Center for Epidemiological Studies–Depression Scale (CES-D)** (Carpenter et al., 1998; Sheehan, Fifield, Reisine, & Tennen, 1995), the **Multidimensional Quality-of-Life Scale–Cancer (MQOLS-CA)** (Ferrell, Wisdom, & Wenzl, 1989), and a **descriptive numeric rating scale** for worst pain intensity (Jensen, 2003). In addition, the patients' medical records were reviewed for disease and treatment information that included diagnosis, current cancer treatments, presence of metastatic disease, hemoglobin, and hematocrit.

The demographic questionnaire provided information on age, gender, marital status, educational background, ethnicity, and employment status. In addition, patients completed the KPS scale (Karnofsky et al., 1948).

A fatigue severity score was calculated as the mean of the 13 items in the fatigue subscale of the LFS and could range from 0–10, with higher scores indicating higher levels of fatigue severity. The LFS has been used to measure the severity of fatigue in healthy individuals (Gay et al., 2004; Lee et al., 1991) as well as in patients with cancer (Miaskowski & Lee, 1999) and HIV (Lee et al., 1999). The LFS was chosen as the fatigue measure for the current study because it is relatively short and easy to administer. In addition, it does not focus on cancer fatigue, which allows for comparisons between patients with cancer and other populations of interest, including family caregivers who also participated in the present study. The LFS has established validity and internal consistency reliability coefficients, and, in this sample, Cronbach's alpha for the LFS was 0.95.

The GSDS consists of 21 items that evaluate various aspects of sleep disturbance (quality and quantity of sleep, sleep onset latency, number of awakenings, excessive daytime sleepiness, and medication use). Each item was rated on a numeric rating scale that ranged from 0 (never) to 7 (every day), and the 21 items were summed to yield 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 HIV (Dorsey et al., 2004; Humphreys et al., 1999; Lee, 1992; Lee et al., 2001). In the current study, Cronbach's alpha for the GSDS was 0.82.

The MQOLS-CA consists of 33 items that measure four dimensions of QOL in patients with cancer (i.e., physical well-being, psychological well-being, social concerns, and symptoms) and uses a 0–10 numeric rating scale (Ferrell et al., 1989). A total QOL score, as well as subscale scores, were calculated, with higher scores indicating better QOL. In the present study, Cronbach's alpha for the MQOLS-CA was 0.92.

The CES-D consists of 20 items selected to represent the major symptoms in the clinical syndrome of depression. Scores can range from 0–60, with scores higher than 16 indicating the need for patients to seek clinical evaluation for major depression. The CES-D has well-established concurrent and construct validity (Carpenter et al., 1998; Sheehan et al., 1995). In the current study, Cronbach's alpha for the CES-D was 0.89.

Worst pain intensity was evaluated using a descriptive numeric rating scale that ranged from 0 (no pain) to 10 (excruciating pain). A descriptive numeric rating scale is a valid and reliable measure of pain intensity (Jensen, 2003).

Procedures

Patients were recruited from four outpatient settings; signed written, informed consents; and completed the study questionnaires in their homes. Within one week of recruitment, each patient returned the study questionnaires to the research office in a postage-paid envelope.

Statistical Analyses

Data were analyzed using Stata® version 8.0 (StataCorp LP, College Station, TX), SAS® version 9.1 (SAS Institute Inc., Cary, NC), and SPSS® version 12.0 (SPSS Inc., Chicago, IL). Descriptive statistics and frequency distributions were generated on the sample characteristics. Cluster analyses were completed using Stata and confirmed with SAS to identify subgroups of patients based on their responses on the symptom inventories. Scores from the LFS, GSDS, CES-D, and worst pain numeric rating scale 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 (Everitt, Landau, & Leese, 2001; Milligan & Cooper, 1985). 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 used as the clustering method (Everitt et al.; McQuitty, 1966). For the question at hand, this clustering method is preferable to the commonly used Ward's method because the authors had no reason to expect that the sizes of the 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 (Everitt et al.).

Cluster analyses yielding two, three, four, and five 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 number of clusters for the analysis (Milligan & Cooper, 1985; StataCorp, 2003). Milligan and Cooper identified these two stopping rules as the best among 30 stopping rules for recovering from two to five true clusters in a Monte Carlo simulation. A large Calinski and Harabaz pseudo-F statistic, combined with two measures from Duda and Hart (i.e., a large Je(2)/Je(1) index and its associated small pseudo–T-squared value), identified four as the most appropriate number of clusters for the data (Everitt et al., 2001; Milligan & Cooper; StataCorp).

One-way analyses of variance (ANOVAs) were used to determine whether significant differences existed among the four subgroups of patients in demographic, disease, and treatment characteristics; symptom scores; and outcome measures (i.e., functional status and QOL). Differences among the four patient 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 value

presented for each pairwise contrast has been adjusted so that a value of less than 0.05 indicates significance.

Results

Cluster Analysis

One hundred ninety-one 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 the separate two-, three-, and four-cluster solutions. Table 1 contains the symptom severity scores for the subgroups formed with each cluster solution.

As illustrated in Figure 1, when classifications based on the two-cluster solution were obtained, 85% of the sample was categorized as a "low to moderate on all symptoms" subgroup and 15% 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, and the "low to moderate on all symptoms" subgroup was divided into two groups. One subgroup of patients (35%) reported high levels of fatigue and low levels of pain, whereas the other subgroup (50%) reported low to moderate levels of all four symptoms. When classifications based on the four-cluster solution were obtained, the "high fatigue and low pain" and the "high on all symptoms" subgroups remained intact, and the "low to moderate on all symptoms" subgroup was divided into a subgroup (35%) that reported low levels of all four symptoms and a subgroup (15%) that reported low levels of fatigue and high levels of pain. The naming of the subgroups was based on analysis of the findings from the post hoc contrasts.

The standardized symptom scores for the four patient subgroups are shown in Figure 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), HIGH FATIGUE AND LOW PAIN (i.e., high levels of fatigue and low levels of pain), LOW FATIGUE AND HIGH PAIN (i.e., low levels of fatigue and high levels of pain), and ALL HIGH (i.e., high levels of all four symptoms).

Patient Subgroup Differences in Demographic, Disease, and Treatment Characteristics

Tables 2 and 3 summarize the demographic and disease and treatment characteristics for the total sample and for the four patient subgroups. No differences were found among the four subgroups in any of the demographic characteristics except age ($p = 0.04$) and marital status ($p = 0.007$). Patients in the ALL HIGH subgroup were significantly younger than patients in the ALL LOW subgroup ($p = 0.02$). A significantly smaller percentage of patients in the ALL HIGH subgroup were married or partnered compared to patients in the ALL LOW ($p = 0.0001$) or the LOW FATIGUE AND HIGH PAIN ($p = 0.04$) subgroups. No differences were found among the four subgroups in any 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. The comparison of each subgroup to the other three subgroups on the various symptoms is based on the results from the post hoc contrasts.

ALL LOW subgroup: Patients in the ALL LOW subgroup reported significantly lower fatigue (all $p \leq 0.002$) and sleep disturbance (all $p \leq 0.0001$) scores than the other three subgroups. No differences in depression scores were found between the ALL LOW and the LOW FATIGUE AND HIGH PAIN subgroups. No differences in worst pain intensity scores were

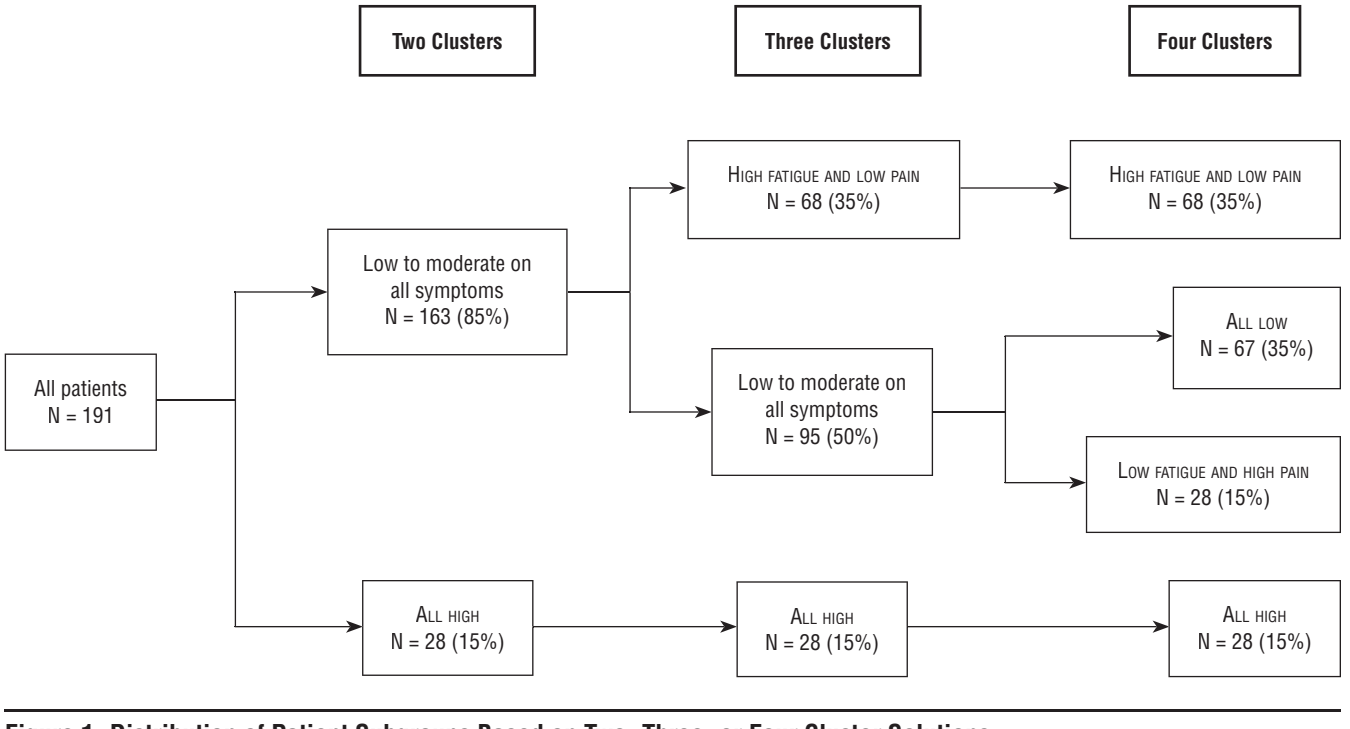


Figure 1. Distribution of Patient Subgroups Based on Two, Three, or Four Cluster Solutions

Table 1. Symptom Severity Scores for Subgroups Formed With Two, Three, and Four Cluster Solutions

	Two Cluster Solution			
	Low to Moderate on All Symptoms (N = 163, 85%)		All High (N = 28, 15%)	
Symptom Inventory	$\bar{X}$	SD	$\bar{X}$	SD
LFS score	3.3	2.2	5.9	1.3
GSDS total score	50.7	19.5	78.1	11.4
CES-D score	11.6	8.2	24.7	10.4
Worst pain intensity score	2.2	3.3	8.3	1.1

	Three Cluster Solution					
	High Fatigue and Low Pain (N = 68, 35%)		Low to Moderate on All Symptoms (N = 95, 50%)		All High[a] (N = 28, 15%)	
Symptom Inventory	$\bar{X}$	SD	$\bar{X}$	SD	$\bar{X}$	SD
LFS score	5.2	1.6	2.0	1.4	5.9	1.3
GSDS total score	63.4	16.4	41.6	16.3	78.1	11.4
CES-D score	15.4	8.7	8.8	6.7	24.7	10.4
Worst pain intensity score	1.0	1.9	3.1	3.7	8.3	1.1

	Four Cluster Solution							
	High Fatigue and Low Pain[a] (N = 68, 35%)		All Low (N = 67, 35%)		Low Fatigue and High Pain (N = 28, 15%)		All High[a] (N = 28, 15%)	
Symptom Inventory	$\bar{X}$	SD	$\bar{X}$	SD	$\bar{X}$	SD	$\bar{X}$	SD
LFS score	5.2	1.6	1.7	2.1	2.8	1.5	5.9	1.3
GSDS total score	63.4	16.4	37.3	14.6	51.9	15.8	78.1	11.4
CES-D score	15.4	8.7	8.1	6.4	10.5	7.1	24.7	10.4
Worst pain intensity score	1.0	1.9	0.9	1.8	8.3	1.0	8.3	1.1

N = 191

[a] The subgroup remained intact.

CES-D—Center for Epidemiological Studies–Depression Scale; GSDS—General Sleep Disturbance Scale; LFS—Lee Fatigue Scale

found between the ALL LOW and the HIGH FATIGUE AND LOW PAIN subgroups.

HIGH FATIGUE AND LOW PAIN subgroup: Patients in the HIGH FATIGUE AND LOW PAIN subgroup reported fatigue scores that were comparable to patients in the ALL HIGH subgroup but were significantly higher (both $p < 0.0001$) than patients in the ALL LOW or LOW FATIGUE AND HIGH PAIN subgroups. The subgroup had significantly higher sleep disturbance scores ($p \leq 0.005$) than the ALL LOW or LOW FATIGUE AND HIGH PAIN subgroups but significantly lower scores than the ALL HIGH subgroup ($p < 0.0001$). The exact same pattern was seen for the depression scores (all $p \leq 0.04$). In the subgroup, worst pain intensity scores were significantly lower than the LOW FATIGUE AND HIGH PAIN or ALL HIGH subgroups (both $p < 0.0001$).

LOW FATIGUE AND HIGH PAIN subgroup: Patients in the LOW FATIGUE AND HIGH PAIN subgroup had significantly lower fatigue scores than the HIGH FATIGUE AND LOW PAIN or the ALL HIGH subgroups (both $p \leq 0.002$) but had higher scores than the ALL LOW subgroup ($p < 0.0001$). Patients in the subgroup reported significantly less sleep disturbance than patients in the HIGH FATIGUE AND LOW PAIN and ALL HIGH subgroups (both $p \leq 0.005$) but had significantly more than the ALL LOW subgroup ($p < 0.0001$). No significant differences in depression scores were found between the ALL LOW and LOW FATIGUE AND HIGH PAIN subgroups. However, the subgroup's depression scores were significantly lower than the HIGH FATIGUE AND LOW PAIN or ALL HIGH subgroups (both $p \leq 0.04$). Worst pain intensity scores were comparable to the ALL HIGH subgroup but significantly higher than the ALL LOW or HIGH FATIGUE AND LOW PAIN subgroups (both $p < 0.0001$).

ALL HIGH subgroup: No differences in fatigue scores were found between the ALL HIGH and HIGH FATIGUE AND LOW PAIN subgroups. The ALL HIGH subgroup reported significantly higher fatigue scores than the ALL LOW or LOW FATIGUE AND HIGH PAIN subgroups (both $p < 0.0001$). The ALL HIGH subgroup reported significantly higher sleep disturbance and depression scores than the other three subgroups (all $p < 0.0001$). No differences in worst pain intensity scores were found between the ALL HIGH and LOW FATIGUE AND HIGH PAIN subgroups. However, worst pain intensity scores were significantly higher in the ALL HIGH subgroup compared to the ALL LOW or HIGH FATIGUE AND LOW PAIN subgroups (both $p < 0.0001$).

Differences in Each of the Symptom Severity Scores

This section describes differences in each of the symptom severity scores among the four patient subgroups. As shown in Table 4, significant differences were found in all four of the symptom severity scores among the four patient subgroups.

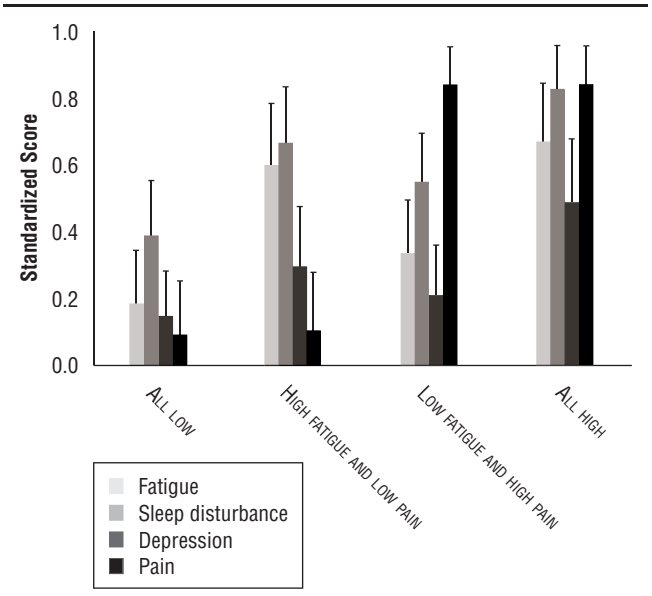


Figure 2. Standardized Symptom Severity Scores for the Four Patient Subgroups

Fatigue: Significant differences in fatigue severity scores were found among the four subgroups ($F [3, 187] = 95.7$; $p < 0.0001$). Patients in the ALL LOW subgroup reported significantly lower fatigue scores than the other three groups (all $p < 0.002$). Patients in the LOW FATIGUE AND HIGH PAIN subgroup reported significantly lower levels of fatigue than the HIGH FATIGUE AND LOW PAIN or ALL HIGH subgroups (both $p < 0.00001$). Patients in the HIGH FATIGUE AND LOW PAIN and ALL HIGH subgroups reported comparable levels of fatigue.

Sleep disturbance: Significant differences in general sleep disturbance total scores were found among the four subgroups ($F [3, 187] = 60.6$; $p < 0.0001$). Patients in the ALL LOW subgroup had significantly lower sleep disturbance scores than the other three groups (all $p \leq 0.0001$). Patients in the LOW FATIGUE AND HIGH PAIN subgroup had significantly lower sleep disturbance scores than the HIGH FATIGUE AND LOW PAIN or ALL HIGH subgroups (both $p \leq 0.005$). Patients in the ALL HIGH subgroup reported the highest levels of sleep disturbance compared to the other three groups (all $p \leq 0.005$).

Depressive symptoms: Significant differences in CES-D scores were found among the four subgroups ($F [3, 187] = 30.6$; $p < 0.0001$). Patients in the ALL LOW subgroup reported significantly lower levels of depressive symptoms than the HIGH FATIGUE AND LOW PAIN or ALL HIGH subgroups (both $p < 0.0001$). Patients in the LOW FATIGUE AND HIGH PAIN subgroup had levels of depressive symptoms that were comparable to patients in the ALL LOW subgroup but were significantly lower than patients in the HIGH FATIGUE AND LOW PAIN or ALL HIGH subgroups (both $p \leq 0.04$). Patients in the ALL HIGH subgroup reported the highest levels of depressive symptoms compared to the other three subgroups (all $p \leq 0.0001$).

Worst pain: Significant differences in worst pain intensity scores were found among the four subgroups ($F [3, 187] = 256.7$, $p < 0.0001$). Patients in the ALL LOW and HIGH FATIGUE AND LOW PAIN subgroups had significantly lower worst pain intensity scores than the LOW FATIGUE AND HIGH PAIN or ALL HIGH subgroups (all $p < 0.0001$). Patients in the ALL LOW and HIGH FATIGUE AND LOW PAIN subgroups reported comparable levels of worst pain. No differences in pain intensity scores were found between the LOW FATIGUE AND HIGH PAIN and ALL HIGH subgroups.

Differences in Patient Outcomes

Functional status: Figure 3 illustrates the KPS scores for the total sample (79.1 ± 14.3) and the four subgroups. One-way ANOVA demonstrated significant differences in KPS scores among the four subgroups ($F [3, 184] = 13.8$; $p < 0.0001$). Post hoc contrasts revealed that patients in the ALL LOW subgroup reported significantly higher KPS scores (86.8 ± 11.2) than the other three subgroups (all $p < 0.0001$). No differences in KPS scores were found among the other three subgroups.

Table 2. Demographic Characteristics for the Total Sample and Differences in Demographic Characteristics Among the Four Patient Subgroups

	Total Sample (N = 191)		ALL LOW: Subgroup 1 (n = 67, 35%)		HIGH FATIGUE AND LOW PAIN: Subgroup 2 (n = 68, 35%)		LOW FATIGUE AND HIGH PAIN: Subgroup 3 (n = 28, 15%)		ALL HIGH: Subgroup 4 (n = 28, 15%)		
Characteristic	$\bar{X}$	**SD**	$\bar{X}$	**SD**	$\bar{X}$	**SD**	$\bar{X}$	**SD**	$\bar{X}$	**SD**	**Test, Statistical Significance, and Post Hoc Contrasts[a]**
Age (years)	60.1	12.3	62.4	12.3	60.5	11.7	59.5	12.4	54.4	12.8	$F (3,185) = 2.9$; $p = 0.04$; $4 < 1$, $p = 0.02$
Education (years)	15.5	2.8	15.6	2.4	15.3	3.0	16.2	3.1	15.4	2.9	$F (3,185) = 0.7$; $p = 0.54$
Characteristic	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**Test, Statistical Significance, and Post Hoc Contrasts[a]**
Female	107	56	38	57	36	53	17	61	16	57	$\chi^2 = 0.5$; $p = 0.91$
Ethnicity: white	155	82	51	77	57	86	24	86	23	81	$\chi^2 = 24.6$; $p = 0.14$
Married or partnered	112	60	48	73	38	57	16	59	10	36	$\chi^2 = 31.9$; $p = 0.007$; $4 < 1$, $p < 0.001$ and $4 < 2$, $p = 0.04$
Live alone	53	29	14	22	24	32	5	18	13	46	$\chi^2 = 7.7$; $p = 0.052$
Work for pay	61	32	24	36	20	30	9	32	8	29	$\chi^2 = 0.9$; $p = 0.84$

[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.

Table 3. Disease and Treatment Characteristics for the Total Sample and Differences in Disease and Treatment Characteristics Among the Four Patient Subgroups

	Total Sample (N = 191)		All Low (n = 67, 35%)		High Fatigue and Low Pain (n = 68, 35%)		Low Fatigue and High Pain (n = 28, 15%)		All High (n = 28, 15%)		
Characteristic	$\bar{X}$	**SD**	$\bar{X}$	**SD**	$\bar{X}$	**SD**	$\bar{X}$	**SD**	$\bar{X}$	**SD**	**Test and Statistical Significance**
Hemoglobin	12.5	2.6	12.7	1.6	12.1	1.8	12.6	1.7	13.1	5.4	F = 1.1; p = 0.35
Hematocrit	36.9	4.9	37.8	4.3	36.3	5.2	37.6	3.9	35.4	6.0	F = 2.1; p = 0.09
Characteristic	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**Test and Statistical Significance**
Diagnosis											$\chi^2 = 34.0$; p = 0.08
Breast	52	27	20	30	17	25	9	32	6	21	
Prostate	27	14	13	19	10	15	3	11	1	4	
Lung	18	9	3	5	9	13	3	11	3	11	
Colon	10	5	5	8	1	2	2	7	2	7	
Head and neck	11	6	–	–	5	7	3	11	3	11	
Melanoma	1	1	1	2	–	–	–	–	–	–	
Non-Hodgkin lymphoma	14	7	2	3	8	12	4	14	–	–	
Ovarian	11	6	4	6	3	4	–	–	4	14	
Other	47	25	19	28	15	22	4	14	9	32	
Presence of metastatic disease	78	41	28	42	31	46	9	32	10	36	$\chi^2 = 2.0$; p = 0.57
Current treatment[a]											
Chemotherapy	109	57	56	84	42	63	11	39	20	71	$\chi^2 = 7.1$; p = 0.07
Radiation therapy	78	41	27	40	27	40	13	46	11	39	$\chi^2 = 0.4$; p = 0.94
Hormonal therapy	28	15	12	18	11	16	4	14	1	4	$\chi^2 = 3.5$; p = 0.33
Biotherapy	9	5	4	6	1	2	3	11	1	4	$\chi^2 = 4.1$; p = 0.25
Other	16	8	5	8	5	8	3	11	3	11	$\chi^2 = 0.5$; p = 0.91

[a] Some patients were receiving more than one cancer treatment.

Note. Because of rounding, not all percentages total 100.

Quality of life: Figure 4 illustrates the QOL scores for the total sample (5.8 ± 1.4) and for the four subgroups. One-way ANOVA demonstrated significant differences in QOL scores among the four subgroups (F [3, 177] = 36.1; p < 0.0001). Post hoc contrasts revealed that patients in the ALL LOW subgroup reported significantly higher QOL scores (6.7 ± 1.0) than those in the other three subgroups (all p ≤ 0.01). No differences in QOL scores were found between patients in the HIGH FATIGUE AND LOW PAIN (5.3 ± 1.2) and LOW FATIGUE AND HIGH PAIN (5.9 ± 1.1) subgroups. Patients in the ALL HIGH subgroup (4.3 ± 1.1) reported lower QOL scores than the other three subgroups (all p < 0.0001).

An analysis of the subscale scores of the MQOLS-CA found significant differences among the four patient subgroups in physical well-being (F [3, 182] = 46.3; p < 0.0001), psychological well-being (F [3, 179] = 24.9; p < 0.0001), and social well-being (F [3, 182] = 24.3; p < 0.0001). Post hoc contrasts revealed differences in subscale scores among the patient subgroups that were identical to the total QOL scores. No differences in spiritual well-being scores were found among the four patient subgroups.

Although the four subgroups did differ on age and marital status, the differences among the four subgroups in functional status and QOL, reported previously, were independent of the effects of age and marital status. The findings were confirmed by performing analyses of covariance in which age and marital status (as dichotomous variables) were treated as covariates and subgroup was the main between-subjects factor of interest for both of the outcome variables. Controlling for the possible confounding effects of age and marital status did not alter the subgroup differences in functional status and QOL reported previously.

Discussion

The present study is the first to attempt to identify subgroups of outpatients with cancer based on their experiences with four highly prevalent and related symptoms—fatigue, sleep disturbance, depressive symptoms, and pain—and to determine whether the subgroups differed on demographic, disease, and treatment characteristics as well as on two important patient outcomes: functional status and QOL. The cluster analysis procedure identified four relatively distinct subgroups of patients: those who reported low levels of all four symptoms (35%), those who reported high levels of all four symptoms (15%), those who reported high levels of fatigue and low levels of pain (35%), and those who reported low levels of fatigue and high levels of pain (15%).

Differences in Patient Outcomes

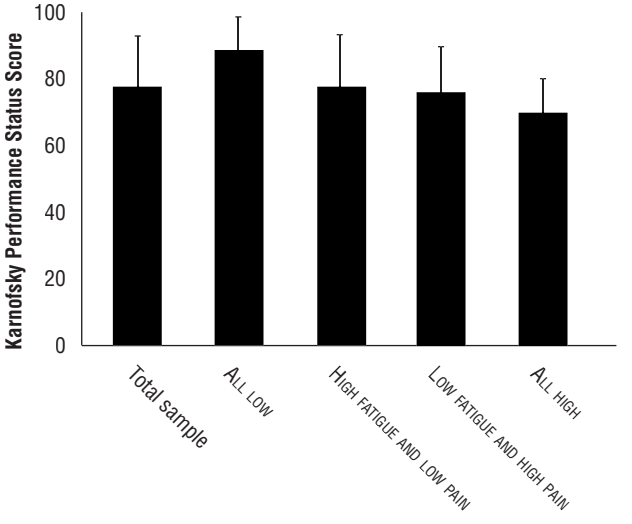
Of note, patients categorized in the ALL HIGH subgroup reported the lowest QOL scores (4.3 ± 1.1) compared to patients in the ALL LOW subgroup, who reported the highest QOL scores (6.7 ± 1.0), which represents a difference of 1.7 standard deviation units in QOL scores (calculated as d = [$\bar{X}$ score for group 1 – $\bar{X}$ score for group 2]/standard deviation of the

Table 4. Symptom Inventory Scores for the Total Sample and Differences in Fatigue, Sleep Disturbance, Depression, and Pain Scores

	Total Sample (N = 191)		All Low: Subgroup 1 (n = 67, 35%)		High Fatigue and Low Pain: Subgroup 2 (n = 68, 35%)		Low Fatigue and High Pain: Subgroup 3 (n = 28, 15%)		All High: Subgroup 4 (n = 28, 15%)		
Symptom Inventory	$\bar{X}$	SD	$\bar{X}$	SD	$\bar{X}$	SD	$\bar{X}$	SD	$\bar{X}$	SD	Test, Statistical Significance, and Post Hoc Contrasts[a]
Lee Fatigue Scale score	3.7	2.3	1.7	1.2	5.2	1.6	2.8	1.5	5.8	1.3	$F(3, 187) = 95.7$; $p < 0.0001$; 1 < 2, 3, and 4, all $p \leq 0.002$; 3 < 2 and 4, both $p < 0.0001$; 2 versus 4 is not significant.
General Sleep Disturbance Scale total score	54.7	20.9	37.3	14.6	63.4	16.4	51.9	15.8	78.1	11.4	$F(3, 187) = 60.6$; $p < 0.0001$; 1 < 2, 3, and 4, all $p < 0.0001$; 3 < 2 and 4, both $p < 0.005$; 2 < 4, $p < 0.0001$
Center for Epidemiological Studies–Depression Scale score	13.5	9.7	8.1	6.4	15.5	8.7	10.5	7.1	24.7	10.4	$F(3, 187) = 30.6$; $p < 0.0001$; 1 < 2 and 4, both $p < 0.0001$; 3 < 2 and 4, both $p \leq 0.04$; 2 < 4, $p < 0.0001$; 1 versus 3 is not significant.
Worst pain intensity score	3.1	3.8	0.9	1.8	1.0	1.9	8.3	1.0	8.3	1.1	$F(3, 187) = 259.7$; $p < 0.0001$; 1 < 3 and 4, both $p < 0.0001$; 2 < 3 and 4, both $p < 0.0001$; 1 versus 2 and 3 versus 4 are 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.

total sample). Based on previous reports in the QOL literature that minimally important differences in QOL scores are in the range of 0.2–0.5 standard deviation units (Guyatt, Osoba, Wu, Wyrwich, & Norman, 2002; Norman, Sloan, & Wyrwich, 2003; Osoba, Rodrigues, Myles, Zee, & Pater, 1998), the difference represents not only a statistically but also a clinically meaningful difference in QOL scores. Compared to the ALL LOW subgroup, patients in the HIGH FATIGUE AND LOW PAIN (5.3 ± 1.2) and LOW FATIGUE AND HIGH PAIN (5.9 ± 1.1) subgroups had differences in QOL scores that were statistically significant as well as clinically important (i.e., 1.0 and 0.6 standard deviation units, respectively).



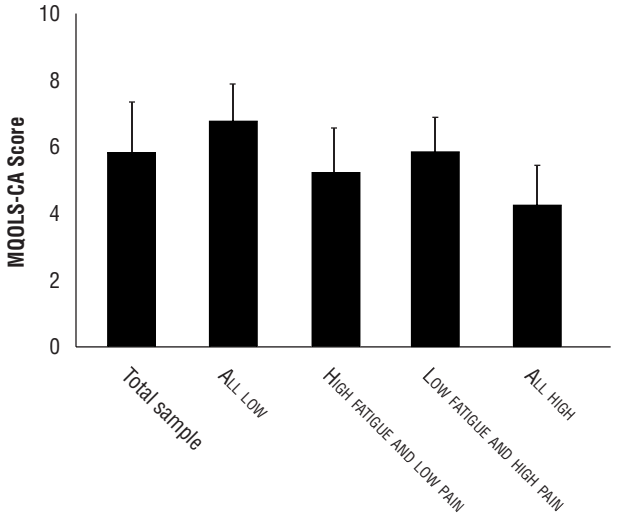
Note. Post hoc contrasts demonstrated that patients in the ALL LOW subgroup had significantly higher Karnofsky Performance Status scores than patients in the other three subgroups (all $p < 0.0001$).

Figure 3. Karnofsky Performance Status Scores for the Total Sample and Four Patient Subgroups

An evaluation of differences in functional status among the four groups found that patients in the ALL LOW subgroup had significantly higher KPS scores than those in the other three subgroups. The failure of the KPS to distinguish among the four patient subgroups suggests that more sensitive measures of functional status should be used in subsequent studies. Perhaps functional status measures that discriminate between activities of daily living and other aspects of physical functioning will provide more useful information regarding how different symptom experiences affect the functional status of outpatients with cancer.

Potential Mechanism to Explain the Patient Subgroups

As stated in the introduction, the identification of subgroups of patients who experience symptoms with greater or lesser severity may alert clinicians to patients who are at greater risk for poorer outcomes. Although the biologic basis for the different symptom experiences reported by the patients in the four subgroups remains to be elucidated, an emerging area of research may guide future studies of patients with different levels of symptom severity. Cleeland et al. (2003) noted a growing awareness that common biologic mechanisms, such as the release of cytokines, may underlie or contribute to the occurrence of multiple symptoms. The idea is exemplified by animal models of sickness behavior that have symptoms in common with those of patients with cancer. Sickness behavior refers to a constellation of physiologic and behavioral responses observed in animals after the administration of



MQOLS-CA—Multidimensional Quality-of-Life Scale–Cancer

Note. Post hoc contrasts demonstrated that patients in the ALL LOW subgroup had significantly higher MQOLS-CA scores than patients in the other three subgroups (all $p \leq 0.01$); patients in the HIGH FATIGUE AND LOW PAIN and LOW FATIGUE AND HIGH PAIN subgroups had comparable MQOLS-CA scores; and patients in the ALL HIGH subgroup had significantly lower MQOLS-CA scores than patients in the other three subgroups (all $p < 0.00001$).

Figure 4. Multidimensional Quality-of-Life Scale–Cancer Scores for the Total Sample and Four Patient Subgroups

inflammatory agents or pro-inflammatory cytokines (Kelley et al., 2003; Lee, Dantzer, et al., 2004; Payne, Piper, Rabinowitz, & Zimmerman, 2006; Watkins & Maier, 1999). Physiologic components of sickness behavior include fever, pain, and wasting. Behavioral components include decreased activity, cognitive impairment, somnolence, and decreased social interaction. The model of sickness behavior suggests that the symptoms of fatigue, sleep disturbance, depressive symptoms, and pain may share a common mechanism.

Further support for the idea comes from work by Francoeur (2005), who determined, in a sample of patients with cancer initiating palliative radiation, that variation in depressive affect could be attributed to different symptom clusters. However, data from the current study suggest that some aspects of sickness behavior may be manifested in different levels of intensity in outpatients with cancer. Future research will need to evaluate differences in cytokine levels among the four patient subgroups.

Additional Characteristics That Appear to Influence the Symptom Experience

The finding that age partially distinguished among the four patient subgroups is consistent with two other studies that used cluster analysis to identify subgroups of patients with cancer based on QOL scores (Nagel, Schmidt, Strauss, & Katenkamp, 2001) and psychosocial variables (Trask & Griffith, 2004). In the current study and in the study by Nagel et al., younger age was associated with more symptoms and poorer QOL. In contrast, in the study by Trask and Griffith, older age was associated with poorer physical health. Reasons for the differences may relate to the measures used to create the subgroups or to the patient populations that were evaluated.

The finding that marital status distinguished among the four subgroups in that patients with the lowest level of all four symptoms were more likely to be married or partnered than patients with high levels of all four symptoms may be related to perceived levels of social support. Several studies have shown that patients with cancer who perceived higher levels of social support reported lower levels of depressive symptoms (Hann et al., 2002; Kurtz, Kurtz, Stommel, Given, & Given, 2002; Simpson, Carlson, Beck, & Patten, 2002). Although social support was not measured directly in this study, marital status may have served as an indirect measure of social support. Findings from the current study suggest that the relationship observed between higher levels of perceived social support and lower levels of depression occurs with other symptoms as well. The hypothesis warrants investigation in future studies.

A surprising finding from the present study was that neither gender nor any clinical characteristic or treatment variable distinguished among the four subgroups. Possible explanations for the lack of significant differences in clinical or treatment characteristics are the relatively small sample sizes in each subgroup, the heterogeneous diagnoses of the patients, and the heterogeneity of the sample in terms of treatment trajectories. The explanation seems plausible because differences among the four subgroups approached significance for diagnosis ($p = 0.08$), chemotherapy administration ($p = 0.07$), and hematocrit ($p = 0.09$). The observations warrant additional investigation in homogeneous and heterogeneous populations of patients with cancer in terms of cancer diagnosis, stage of disease, intensity of the treatment regimen, and types of treatment regimens. Such studies may provide insights into whether the symptoms of fatigue, pain, sleep disturbance, and depression share a common biologic mechanism across cancer diagnoses and treatments. Equally plausible is the idea that diagnosis and treatment interactions (e.g., patients with breast cancer versus patients with prostate cancer who receive radiation therapy) occur and contribute to certain subgroups of patients experiencing symptoms with different levels of intensity.

An alternative explanation for the lack of disease and treatment effects is that the different subgroups of patients may harbor different determinants (e.g., genetic) for experiencing symptoms that are independent of demographic, disease, and treatment characteristics. Recent work in animal models of disease that display one or more of the symptoms in the current study (Belfer et al., 2004; Diatchenko et al., 2005; Landgraf & Wigger, 2003; Taheri, 2004) supports the concept that a portion of the variance in these measures is the result, at least in part, of genetic variation. If subsequent work, perhaps with gene expression profiling, reveals distinct subgroups of patients who are at increased risk for more severe symptoms, the finding may lead to a better understanding of the mechanisms that underlie related symptoms and provide new directions for the development of pharmacologic approaches for the management of single or multiple symptoms. Such studies are under way in the authors' laboratory.

Findings Related to Specific Symptoms

Of note, approximately 72% of the patients in this study reported moderate to high severity levels of one or more of the four symptoms. In addition, more than 50% of the patients reported moderate to severe levels of two or more symptoms. The finding confirms previous reports that outpatients with cancer undergoing active treatment (Cleeland et al., 2000;

Portenoy et al., 1994) or palliative care (Francoeur, 2005; Walsh et al., 2000) experience multiple symptoms that warrant interventions.

When each of the symptoms is considered separately, several findings are worth noting. Fatigue severity scores in the present sample ranged from mild (1–3) to severe (7–10) (ranges set by Mendoza et al., 1999). Note that patients reported comparable levels of fatigue with and without severe pain and that a subgroup of patients with severe pain reported low levels of fatigue. The finding of two distinct subgroups demonstrates that for some patients, fatigue and pain occur independent of each other. In addition, based on the findings from this cluster analysis, depressive symptoms and sleep disturbance appear to be more closely associated with fatigue than with pain. Additional research is warranted to better characterize the subgroups of patients in which high levels of pain are present without fatigue and vice versa. In addition, the relationships among these common symptoms need to be examined in more detail in homogeneous and heterogeneous groups of patients with cancer.

Approximately 30% of the patients in the present sample reported worst pain intensity scores in the severe range (i.e., ≥ 7) (range set by Serlin, Mendoza, Nakamura, Edwards, & Cleeland, 1995). The finding points to the continued undertreatment of chronic cancer pain in the outpatient setting. The majority of the patients in the present study reported moderate levels of sleep disturbance (i.e., ≥ 50). As noted by Lee, Cho, Miaskowski, and Dodd (2004), sleep disturbance has not been well studied in patients with cancer and warrants additional investigations. Finally, depressive symptoms were prevalent in the sample (34% of the patients had a cut-off score ≥ 16 on the CES-D), particularly in the HIGH FATIGUE AND LOW PAIN and ALL HIGH subgroups. Findings from the current study confirm previous reports that noted that depressive symptoms often are underdiagnosed and undertreated in outpatients with cancer (Jacobsen et al., 2005; Miaskowski, 2004; Potash & Breitbart, 2002).

Study Limitations

Several limitations of this study should be noted. Cluster analysis is an exploratory statistical procedure that requires investigators to label patient subgroups based on an examination of the variables of interest subsequent to the formation of the optimal number of subgroups. Therefore, the names of the subgroups and their characteristics may not be generalizable to all outpatient populations. The current sample is limited to primarily middle-aged, well-educated, Caucasian patients, which also limits the generalizabilty of the study findings. In addition, the primary reason for refusal to participate in the current study was being too ill. Therefore, the sample may underrepresent patients with more severe symptoms.

Implications for Future Research and Practice

Future research on the use of cluster analysis to identify subgroups of patients with different symptom experiences will need to determine whether more definitive subgroups can be categorized if more homogeneous (e.g., similar diagnoses, similar treatment regimens) or heterogeneous samples are used. Different samples of patients may be required to answer different types of research questions. For example, a disease-specific sample may be needed to determine which subgroups of patients are at particularly high risk for poorer outcomes. In contrast, heterogeneous patient samples may provide more useful information to determine whether certain subgroups of patients have a genetic predisposition for more severe symptom experiences, independent of type of cancer or cancer treatment.

Summary

This study focused on the evaluation of four symptoms that commonly co-occur in patients with cancer yet typically are examined independently. The finding of four relatively distinct subgroups of patients with different symptom experiences suggests that cluster analysis techniques may be useful to explore potential mechanisms for or genetic differences that influence symptom experiences. In addition, the use of this statistical strategy 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. The approach used in the current study is distinctly different from studies that use analytic strategies, such as factor analysis, to identify symptom clusters in patients with homogeneous or heterogeneous cancer diagnoses or similar or different treatment regimens. Considering that symptom cluster research is still in its infancy (Miaskowski et al., 2004), both approaches are likely to yield clinically useful insights that may lead to the development and testing of novel symptom management interventions.

The findings from this study warrant replication before definitive clinical practice recommendations are formulated. Until more detailed information is available on defined subgroups of patients with different symptom profiles, clinicians need to assess patients with cancer, particularly younger patients, for the highly prevalent and frequently occurring symptoms discussed in this article. Patients with high levels of all four symptoms may require multiple interventions to improve functional status and QOL.

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