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Exploring the differential experience of breast cancer treatment-related symptoms: a cluster analytic approach

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Abstract
Introduction Cancer patients experience multiple concurrent symptoms. This exploratory analysis assessed symptom burden among patients undergoing chemotherapy for breast cancer to identify distinct subgroups of patients who experience differential symptom burden and assessed whether the patient subgroups were associated with deleterious quality of life (QOL) outcomes.
Materials and methods Women (N=133) with stage I and II breast cancer undergoing adjuvant chemotherapy after primary surgery were evaluated at baseline and at the end of chemotherapy using the Memorial Symptom Assessment Scale (MSAS) and the SF-36 QOL questionnaire. Post treatment MSAS symptoms were included in hierarchical cluster analysis. Two patient subgroups were identified that corresponded to a high-symptom prevalence group and a low-symptom group.
Results and discussion No marked, statistically significant differences were found between groups on demographic, symptoms, QOL, or treatment variables at baseline. Patients in the high-symptom cluster were more likely to have stage I disease ($p<0.05$). The two groups of patients showed significant differences in end-of-treatment symptoms and QOL scores ($p<0.05$). The high-symptom burden group was more likely to report greater symptom prevalence and poorer QOL.
Conclusions Future research needs to examine why these differences occur despite similarities in treatment and how symptom burden can be reduced for the high-symptom prevalence group.

Keywords Breast cancer · Cluster analysis · Symptom clusters · Symptom management · Quality of life

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Introduction

Advances in the early detection and treatment of cancer have produced significant reductions in cancer-related mortality. Unfortunately, these gains in survival and disease control are associated with a marked burden of symptoms as insights into the management of disease- and treatment-related symptoms have lagged behind. To that end, psychometric symptom assessment instruments have been developed [1–3] to help detect these symptoms and guide symptom management. Previous studies have shown that cancer patients experience multiple concurrent symptoms that may be characterized as symptom clusters [3–10]. In addition, studies have shown that the number or intensity of symptoms reported by patients is correlated with their perception of quality of life (QOL) [3–8]. Thus, previous research has focused on identifying distinct subgroups of patients [11–16] who report similar outcomes, and more recently, on clusters of related or similar symptoms (symptom clusters) [3–10, 17].

Recently, the National Institutes of Health convened a State-of-the-Science Conference titled, "Symptom Management in Cancer: Pain, Depression and Fatigue" [17, 18]. The focus of the conference was on examining the current state of the knowledge regarding the management of pain, depression, and fatigue in individuals with cancer and identifying directions for future research. One of the key questions the conference examined was how to identify individuals who are at simultaneous risk for cancer-related pain, depression, and fatigue. Consistent with this goal, we explored the question of whether subgroups of patients who experience a distinctly different burden of treatment-related symptoms could be identified at the end of chemotherapy in a homogeneous sample of stage I and II breast cancer patients.

A review of the literature shows that efforts to identify subgroups of patients at risk for poor functional outcomes began over two decades ago [19–23] with chronic pain patients. More recently, several studies have used cluster analysis with cancer patients to identify subgroups of patients who differ in coping [11–13, 15], quality of life [14, 15], and symptoms [15] using published psychometric instruments. A study by Hack and Degner [13] identified three patient subgroups among stage I and stage II breast cancer patients using the Coping Responses Inventory, but did not generate subgroups based on symptoms or examine whether the patient subgroups differed on QOL outcomes. Nagel et al. [14] performed cluster analysis using the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ) Breast Module (BR) and identified four patient subgroups that differed on perceived intrusiveness of disease and treatment, view toward future, age, body image and sexual activity, reported pain, and other QOL domains. Patient subgroups were not generated based on patient-reported symptoms. However, the authors concluded that, based on the symptom profiles observed in the patient subgroups after their treatment for breast cancer, patients reporting higher levels of intrusiveness from cancer treatment would benefit more from medical intervention and rehabilitation programs, whereas those reporting more psychological issues could benefit more from psychological support [14].

Trask and Griffith [15] used a combination of coping, anxiety, and health functioning measures to identify groups of melanoma patients who differ on coping, psychological well-being, and QOL functioning, and examined whether these differences correspond to differences in the course of distress and health. Four patient subgroups were identified: psychologically unhealthy, physically unhealthy, combined psychologically and physically unhealthy, and healthy. These clusters differed on the General Severity Index of the Brief Symptom Inventory and the General Health scale of the SF-36 at each of four assessment intervals over a 9-month period. The combined and psychologically unhealthy subgroups had greater levels of distress, whereas the combined and physically unhealthy subgroups had poorer overall health.

More recently, a cluster analysis of patients with different types of cancers identified four relatively distinct subgroups of patients based on differential experiences on four highly prevalent and related symptoms—fatigue, sleep disturbance, depression, and pain [16]. These four symptoms were measured by psychometrically validated scales including the Lee Fatigue Scale, General Sleep Disturbance Scale, Center for Epidemiological Studies—Depression Scale, and a numeric rating scale of worst pain intensity. The four subgroups of patients were: all low levels of symptoms (n=67, 35%), low fatigue and high pain (n=28, 15%), high fatigue and low pain (n=68, 35%), and all high levels of symptoms (n=28, 15%). The authors [16] also explored whether the patient groups differed on selected demographic, disease, and treatment characteristics and on functional status (Karnofsky Performance Status Scale) and QOL (Multidimensional Quality-of-Life Scale—Cancer). Overall, patients in the "all low" group reported the best functional status and QOL. This study demonstrated that distinct patient subgroups were identified based on patients' self-reported experiences with four highly prevalent and related symptoms.

To date, no published studies utilizing cluster analysis based on a comprehensive list of self-reported symptoms have identified distinct subgroups of patients that differ on symptom experience and QOL in a homogeneous (same diagnosis, similar stage of disease, and similar treatment) sample of patients undergoing chemotherapy treatment. Use of a comprehensive symptom assessment measure captures the broad scope of symptom prevalence and burden, whereas a homogeneous sample of patients with the same diagnosis and similar treatment provides an opportunity to examine individual patient variability in symptom burden while holding diagnosis and treatment constant. Toward this end, we assessed patterns of symptom burden among patients undergoing chemotherapy for stage I and II breast cancer to: (1) identify distinct patient subgroups based on symptoms and (2) evaluate whether patient subgroups were associated with deleterious QOL outcomes and specific demographic, disease, and treatment variables. Despite the apparent homogeneity of the sample (same disease type, similar stage, and similar treatment), it was hypothesized that, based on previous literature, patient subgroups with distinctly differing burden of treatment-related symptom experience could be identified. It was also hypothesized that these subgroups would be associated with differences in QOL. Finally, the study examined whether differences between subgroups were related to differences on demographic characteristics (e.g., age, marital status, education,

income, and employment) or disease and treatment characteristics (e.g., tumor stage, surgery type, and chemotherapy regimen). Based on the mixed results in the literature with some studies showing no association [13] and others showing differences between patient subgroups [15, 16], this objective was considered exploratory.

Materials and methods

Patients

The research was conducted as part of a larger Institutional Review Board (IRB) approved longitudinal study to investigate the course and correlates of fatigue [24]. Patients were recruited from two oncology practices at university-based institutions, and provided informed consent before participating in the primary study. For the current study, a total of 179 women with stage I or II breast cancer who received adjuvant chemotherapy after primary breast surgery were identified in the database of the larger ongoing study. The patients were evaluated before initiating chemotherapy and at the last scheduled chemotherapy infusion for symptoms using the Memorial Symptom Assessment Scale (MSAS) and for quality of life (QOL) using the Medical Outcomes Survey (MOS) 36-Item Short-Form (SF-36). Forty-one women did not have MSAS data, and thus, were excluded from the cluster analysis. Information was also available from patients on demographic characteristics (age, race, education, marital status, and household income) and from medical charts on disease and treatment characteristics (stage of disease, primary surgery type, and chemotherapy regimen). Among 138 patients included in the cluster analysis, 5 women were excluded from further analysis because of significant missing demographic or clinical data, resulting in an evaluable sample of 133 women. No statistically significant differences were found in demographic, clinical, and QOL between patients missing MSAS data (n=41) and evaluable patients (n=133).

Symptom and quality of life measures

The MSAS is a validated patient-rated instrument comprised of 32 highly prevalent physical and psychological symptoms [25, 26]. If a symptom was present during the past week, patients rate symptom frequency, severity, and distress for 24 physical symptom items; the remaining 8 psychological symptom items are rated only for severity and distress. Instrument reliability and validity in cancer patients has been demonstrated [3, 25, 26]. The current study used an adapted version of the MSAS consisting of 26 items rated for prevalence (present or absent). Based on our collective clinical experience with the study population, we adapted the original MSAS by rewording some items, dropping items that were felt to be less relevant, and adding new items considered to be salient to breast cancer patients. For example, we replaced “lack of energy” with “fatigue” and used one item “emotional upset” in the adapted version to replace four items: “feeling nervous, worrying, feeling sad, and feeling irritable”. Similarly, the original item “problems with sexual interest or activity” was replaced with two specific symptoms (vaginal dryness and heavy menstrual flow) believed to be more salient to this population. Items that were dropped altogether included cough, dry mouth, shortness of breath, feeling bloated, problems with urination, swelling of arms and legs, and I don't feel like myself. The adapted MSAS included four new items: chills, hot flashes, heartburn, and muscle weakness. The presentation and administration formats were consistent with the original approach focusing on prevalence (yes or no), then severity and distress for each symptom experienced. The adapted 26-item MSAS yielded an internal consistency reliability coefficient (Cronbach) alpha of 0.79 based on pretreatment prevalence data.

The MOS SF-36, consisting of 36 items that assess 8 health concepts: (1) limitations in physical functioning because of health problems; (2) limitations in social functioning because of physical or emotional problems; (3) role limitations because of physical health problems (role physical); (4) bodily pain; (5) general mental health (psychological distress and well-being); (6) role limitations because of emotional problems (role emotional); (7) vitality (energy and fatigue); and (8) general health perceptions. Considerable evidence was found for the reliability of the SF-36 and for construct validity in terms of distinguishing between groups with expected health differences [27–31]. In the current study, the scores for each of the eight health dimensions on the SF-36 questionnaire and the two component scores (physical and mental health) were used as outcome measures.

Determining patient subgroups

To determine whether distinct subgroups of patients experiencing differing levels of symptom burden were present, we modeled our cluster analysis on the work by Miaskowski et al. [16] and employed a hierarchical cluster analysis with squared Euclidean distances used in the proximities matrix and weighted average linkage used as the clustering method [32]. These analyses were applied to symptom the presence or absence from the MSAS measured at the end of chemotherapy treatment. To determine the number of clusters represented in our data, we varied the number of groups/clusters to be extracted from two to five to determine the cluster structure that best

fit the data and provided the most parsimonious interpretation of groups. For the final clustering solution, we examined the cubic clustering criterion (CCC) [33] and pseudo *F* statistic (PSF), both of which are produced in SAS. We examined the clusters that were extracted, ranging from two to five, for possible inflection points, which are indicative of appropriate cluster groupings of the data. In addition, we examined the PSF values with large values suggesting a good stopping point for the cluster solution. After the cluster analysis, we examined potential differences between the patient subgroups on MSAS symptoms at baseline and at the end of chemotherapy. In addition, we examined the differences between the clusters on demographic and clinical characteristics, and on QOL indicators measured at the end of treatment.

Results

Overall, patients were predominantly white (89%), married (75%), and had greater than high school education (72%). Less than one-half (44%) of the patients were employed but the majority (68%) reported annual household incomes ≥$40,000. Patient age ranged from 29 to 71 years with a median age of 52 years (mean=51, standard deviation (SD)= 9.4). The median chemotherapy duration was 85 days (mean= 102, SD=63 days). Fifty-three percent were post menopausal. The majority had stage II disease (73%), had unilateral lumpectomy as their primary surgery (89%), had lymph node dissection (85%), and received doxorubicin-based chemotherapy (83%), perhaps reflecting the practices of a university-based setting. The mean quality of life scores at pretreatment baseline were 45 and 50 for the SF-36 Physical Component and Mental Health Component Scales, respectively.

Cluster analysis

Before examining the presence of distinct patient subgroups, we examined the prevalence of the MSAS symptoms at the end of treatment. Rather than using the symptom intensity score, it was felt that the prevalence scores allow a better characterization of the variability in both the individual symptoms and overall symptom burden. The results indicated that three symptoms had very low or high base rates including heavy menstrual flow (4%), vomiting (9%), and fatigue (94%). These symptoms were eliminated from the cluster analysis due to the limited variability, and the remaining 23 symptoms were selected for inclusion in the analysis. That is, because either a very small proportion or a very large proportion of the sample endorsed these items, they were of limited value in terms of our attempt to differentiate patients on the basis of symptom prevalence.

In the hierarchical cluster analysis, two, three, four, and five patient cluster solutions were extracted. The results from the CCC and the PSF indicated that a two-cluster solution provided the best representation of the data. Moreover, the three- to five-cluster solutions resulted in groups that contained a small number of patients. For example, cluster 3 in the three-cluster solution was comprised of only 11 patients who were largely indistinguishable in their symptom prevalence relative to patients in clusters 1 and 2. Similarly, the four-cluster solution further divided the 11 patients into a seven-patient and a four-patient cluster. As a result, the two-cluster solution provided the best description of the data and was chosen because of the CCC and PSF statistics, and because it provided better group separation and more parsimonious interpretation. This solution yielded a high-symptom burden patient subgroup (n=45) and a low-symptom burden patient subgroup (n=88).

Table 1 displays the symptom prevalence for the two-cluster solution for symptoms at the end of chemotherapy and those symptoms at pretreatment. The results from chi-square analysis indicated that significant ($p<0.05$) differences were observed between the high- and low-symptom burden groups on 19 of the 26 MSAS symptoms after chemotherapy; in all cases, the high-symptom burden group had a greater prevalence compared to the low-symptom burden group. To ensure that these differences in symptom prevalence did not reflect preexisting differences between the groups, we examined prevalence rates between the groups at pretreatment. The results indicated that only five significant ($p<0.05$) differences were present between the groups. Thus, the differences described in this study appear to primarily reflect the differences at the end of chemotherapy rather than the preexisting differences between patient subgroups.

Demographic and clinical characteristics of patient clusters

Table 2 summarizes the demographic and clinical (disease, treatment, and pretreatment quality of life) characteristics of patients by subgroup (patient cluster) membership. Patients who were categorized in the high-symptom prevalence group were significantly more likely to have stage I disease than patients in the low-symptom prevalence group (41% vs 19%) (p=0.015). No other statistically significant differences in demographic and clinical variables were evident, suggesting that the patients in the two groups were similar before the initiation of chemotherapy.

Quality of life outcomes

Finally, we examined the relation of patient subgroups with QOL scores as measured by the SF-36. Two sample t tests showed no statistically significant (p=0.08) group differ-

Table 1 MSAS symptom prevalence for the total sample and clusters from baseline and at the end of treatment

Symptom	At the end of treatment	At the end of treatment		Pretreatment	
	Total sample N=133	High burden n=45	Low burden n=88	High burden n=45	Low burden n=88
Chills	35	62	21***	30	22
Vomiting[a]	9	18	4*	15	9
Fatigue[a]	94	100	91	85	66*
Hair loss	63	82	53**	10	4
Emotional upset	44	73	30***	65	50
Change in taste	63	87	52***	20	20
Weight gain	36	33	35	15	6
Pain	46	76	31***	60	38*
Muscle weakness	57	80	46***	25	22
Change in appetite	50	73	39***	33	30
Diarrhea	22	40	13***	15	13
Sleep problems	65	82	56**	63	48
Nausea	33	71	14***	28	23
Numbness and tingling	43	53	36	33	23
Drowsiness	56	76	46**	53	39
Mouth sores	32	51	23**	18	2**
Night sweats	43	51	53	28	27
Heartburn	37	58	28**	23	20
Problems with concentration	51	87	34***	50	35
Heavy menstrual flow[a]	4	0	4	5	5
Hot flashes	54	58	52	44	27
Vaginal dryness	35	51	28*	31	8**
Lightheadedness/dizziness	30	62	14***	45	24*
Difficulty swallowing	14	27	8**	5	0
Constipation	34	47	26*	30	17
Skin irritation	25	33	21	15	11

[a] Symptom not included in the cluster analysis.
*p<0.05, **p<0.01, ***p<0.001 based on chi-square tests.

ences in pretreatment QOL as shown in Table 2 for the physical and mental component scores. To examine whether there were significant differences in quality of life outcomes at the end of treatment, we applied ANCOVA to each item, covarying for QOL values from baseline. The results indicated that there were significant differences between the two subgroups of patients in the end of treatment QOL outcomes (see Table 3). Patients in the high-symptom prevalence subgroup had significantly (p<0.001) poorer scores compared to patients in the low-symptom prevalence group on both the Physical and Mental Component Summary Scales. Significant (p<0.001) end of treatment group differences were also seen on all eight SF-36 subscales. The greatest magnitude of difference between the two subgroups, based on Cohen's [34] effect size d, which describes group differences in terms of standard deviation units, was seen on the bodily pain (d=0.74), social functioning (d=0.87), and vitality (d=0.80) subscales. However, even the smallest group difference on general health (d=0.54) corresponded to a medium-sized effect according to Cohen's conventions [34]. The large end of treatment differences in mean QOL measures between the two patient groups suggest a distinct differential impact of chemotherapy treatment on QOL and functioning.

Discussion

The results of this study demonstrate that two distinctly different subgroups of patients with stage I and stage II breast cancer can be identified using a cluster analysis applied to self-reported symptom data. These patient subgroups, characterized as "high-symptom burden" and "low-symptom burden", differed in symptom prevalence and QOL outcomes. For example, a statistically significant greater proportion of patients in the high-symptom burden group reported chills (62%), emotional upset (73%), and problems with concentration (87%) compared to the low-symptom burden cluster (21%, 30%, and 34%, respectively). In addition, the two patient subgroups in this study differed in the expected direction on all QOL measures at the end of chemotherapy treatment. Specifically, the high-

Table 2 Patient characteristics and pretreatment quality of life assessments (N=133) by patient subgroup (cluster) membership

	High-symptom burden (n=45)	Low-symptom burden (n=88)	p value	All patients
	Number (%)	Number (%)		Number (%)
Age			NS	
Mean (SD)	51.5 (9.8)	51.4 (9.3)		51.4 (9.4)
Median (range)	52.0 (29–69)	51.8 (33–71)		51.9 (29–71)
Race			NS	
White	40 (91)	78 (87)		118 (89)
Other	4 (9)	10 (13)		14 (11)
Education			NS	
High school or less	12 (27)	25 (29)		37 (28)
Some college	15 (34)	23 (26)		38 (29)
College degree or higher	17 (39)	39 (45)		56 (43)
Marital status			NS	
Married	32 (73)	67 (76)		99 (75)
Other	12 (27)	21 (24)		33 (25)
Employment			NS	
Employed (full/part-time)	17 (39)	40 (46)		57 (44)
Other	27 (61)	47 (54)		74 (56)
Household income			NS	
<$40,000	15 (35)	24 (30)		39 (32)
>$40,000	28 (65)	56 (70)		84 (68)
Menopausal status			NS	
Post menopausal	24 (56)	45 (52)		69 (53)
Pre/perimenopausal	19 (44)	42 (48)		61 (47)
Stage of disease			0.0147	
Stage I	18 (41)	17 (19)		35 (27)
Stage II	26 (59)	71 (81)		97 (73)
Surgery type			NS	
Unilateral lumpectomy alone	41 (91)	78 (89)		119 (89)
Mastectomy or lumpectomy plus mastectomy	4 (9)	10 (11)		14 (11)
Lymph node dissection			NS	
Yes	41 (91)	70 (82)		111 (85)
No	4 (9)	15 (18)		19 (15)
Chemo regimen 1[a]			NS	
Doxirubicin-based	33 (80)	65 (84)		98 (83)
No doxirubicin	8 (20)	12 (16)		20 (17)
Chemo regimen 2[a]			NS	
Taxane-based	12 (27)	26 (30)		38 (29)
No taxane	33 (73)	62 (70)		95 (71)
Chemotherapy duration (days)			NS	
Mean (SD)	105 (46)	101 (42)		102 (43)
Median (range)	85 (49–235)	83 (42–204)		83 (42–235)
Pretreatment SF-36 quality of life	Mean (SD)	Mean (SD)		Mean (SD)
Physical component scale	42.9 (8.7)	45.9 (9.2)	0.081	44.9 (9.1)
Mental component scale	47.2 (10.4)	50.9 (10.4)	0.0828	49.8 (10.5)

p values based on group comparisons by chi-square tests for categorical variables and two sample t tests for continuous variables.
[a] These categories are not mutually exclusive; some patients received a combination of both classes of drugs.
NS: not statistically significant (p>0.05), *SD*: standard deviation

symptom burden group was associated with poorer QOL in all SF-36 domain and component scores compared to the low-symptom burden group. These findings suggest that greater symptom burden is associated with greater deleterious effects on the quality of life. End of treatment differences in QOL measures between the two patient groups suggest a distinct differential impact of chemotherapy treatment on QOL and functioning. It is worth noting that the greatest magnitude of differences in mean QOL scores between the two groups of patients at the end of treatment was seen on the bodily pain, role physical, and social functioning subscales.

Table 3 End of treatment comparisons of mean quality of life scores (N=133) by patient subgroup (cluster) membership

	High-symptom burden (n=45)	Low-symptom burden (n=88)	p value
SF-36 scores	Mean (SD)	Mean (SD)	
General health	63.5 (14.6)	71.6 (14.1)	0.003
Bodily pain	61.3 (23.9)	79.0 (22.6)	<0.001
Role physical	15.1 (38.8)	47.8 (36.7)	<0.001
Physical functioning	54.8 (20.0)	66.9 (19.2)	0.001
Vitality	29.5 (22.3)	47.8 (21.3)	<0.001
Social functioning	51.3 (25.8)	74.1 (24.7)	<0.001
Role emotional	46.9 (39.7)	77.9 (37.9)	<0.001
Mental health	70.1 (14.6)	80.7 (13.9)	<0.001
Physical component scale	39.9 (8.0)	42.9 (7.7)	<0.001
Mental component scale	42.9 (8.9)	51.2 (8.5)	<0.001

Comparisons-based ANCOVA with baseline QOL scores as covariates. Means and SDs are covariate adjusted values.
SD: standard deviations

The current study is the first to identify distinct patient subgroups based on symptoms in a homogeneous (same diagnosis, early stage disease, and similar treatment) sample of cancer patients. The identification of patient subgroups that experience differential symptom burden and deleterious QOL outcomes is most beneficial if the findings can guide treatment/management of disease- or treatment-related symptoms through interventions tailored to individuals in each group. This indeed has been the goal of cluster analyses in chronic pain patients [19, 22, 23] and cancer patients [12–16].

Taken together, the study findings corroborate published literature using cluster analysis in chronic pain patients [19–23] and cancer patients [11, 12, 14–16] and support our hypothesis that distinct patient subgroups can be identified based on differential treatment-related symptom experience in a homogeneous sample of breast cancer patients. In addition, the differences in QOL support our hypothesis that the clusters would be associated with differential treatment-related impact on QOL [13–16].

Regarding our exploratory aim, we found no differences between clusters on demographic, disease, or treatment characteristics with the exception of tumor stage. A recent study [16] found no relationship between group membership and education, employment status, race/ethnicity, tumor type/site, presence of metastatic disease, hemoglobin level, or treatment type. The study [16] did find that patients in the "all low" group were older than patients in the "all high" group. These authors also reported that being married was associated with lower symptom burden. A study by Trask and Grifffith [15] found differences between groups on age and gender, but no differences with regard to education, employment, or marital status. These authors [15] reported that individuals in the physically unhealthy group were significantly older than those in either the psychologically unhealthy or the healthy group. It is not clear whether the observed age differences [15, 16] are consistently replicable in other settings such as the current study using end of treatment symptom experience to derive distinct patient subgroups. Thus, in the light of the fact that there have been inconsistency in the reporting of differences on demographic [15] characteristics, it is not surprising that we found no differences on age, race, education, marital status, employment, or household income. It is important to note that our sample was drawn from tertiary level academic cancer centers and may differ from the typical patient treated in a community-based clinical practice.

Our findings regarding differences between patient subgroups on tumor stage are surprising in terms of both the direction and magnitude of differences. Although there were equal numbers of women with stage I disease in both clusters, the proportion of women with stage II disease was higher (81%) in the low-symptom burden group compared to 59% in the higher-symptom burden group. The greater representation (81%) of stage II patients in the low-symptom subgroup is particularly surprising given the fact that there were no differences between groups on baseline pretreatment symptoms, surgery type, or chemotherapy regimen. In contrast, Trask and Griffith [15] who also utilized a cluster analysis in patients with stage I and II breast cancer found no differences between groups on stage of disease. Future research on patient-reported symptom burden should examine whether a disease stage difference is replicable or solely an artifact of this study.

The current study differs in approach and methodology from other studies that focused on symptom clusters. Rather than using factor or cluster analysis to group "similar" or "related" symptoms (factors) [5–7, 9, 10, 17, 35], the current study utilized cluster analysis to identify patient subgroups (distinct, mutually exclusive subgroups) that were defined by a similar symptom experience [12–15, 19, 22, 23]. Given that symptom cluster research is still in its

infancy in oncology [17], it is likely that both approaches may contribute unique insights to symptom burden analysis and possibly inform development of more effective symptom intervention approaches.

Taken together, the current findings suggest that cluster analysis is a useful method for identifying patient subgroups with distinctly different burdens of symptoms in a homogeneous sample of patients with the same diagnosis, early stage disease, and similar treatment. The patient subgroups did not differ markedly at pretreatment baseline with regard to symptoms and QOL, suggesting that the observed end of treatment differences in symptom burden may be attributed to chemotherapy treatment effects. However, subgroups of patients identified using symptom data could benefit from interventions to reduce symptom burden if identified early and if symptom burden is correlated with factors amenable to intervention. Thus, further research is needed to identify subgroups early and to identify factors amenable to intervention. For example, future research could include social support or coping measures to determine if the observed cluster (subgroup) differences are associated with differences in support or coping styles. In addition, future studies could include biological markers to determine if differences in patient-reported symptom and QOL experience are mediated by individual differences in genetic vulnerability to specific types of symptoms or more severe symptom and QOL outcomes experience [36]. If identified factors are amenable to change before, during, or after the course of treatment, then the deleterious impact on QOL maybe reduced or eliminated.

Conclusions

This study is the first to describe the use of a cluster analytic approach to derive patient subgroups based on a comprehensive symptom assessment measure (MSAS) in a homogeneous sample of cancer patients. Findings revealed a subgroup of patients who experience a high-symptom burden at the end of chemotherapy treatment that has deleterious effects on QOL and another subgroup of patients that report low-symptom burden. The findings from this study warrant replication with larger and more diverse samples of patients so that definitive clinical and practice implications can be proposed. Given the comprehensive symptom burden identified in this study, it is conceivable that patients with high-symptom burden may require multiple or more intensive interventions to improve both functional and QOL outcomes. Future research is also needed to examine why the patient differences occur despite similarities in diagnosis and treatment, and determine how symptom burden can be reduced in distinct subgroups of patients.

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