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Symptom Cluster Analyses Based on Symptom Occurrence and Severity Ratings Among Pediatric Oncology Patients During Myelosuppressive Chemotherapy

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Abstract

Background—Symptom cluster research is an emerging field in symptom management. The ability to identify symptom clusters that are specific to pediatric oncology patients may lead to improved understanding of symptoms' underlying mechanisms among patients of all ages.

Objective—The purpose of this study, in a sample of children and adolescents with cancer who underwent a cycle of myelosuppressive chemotherapy, was to compare the number and types of symptom clusters identified using patients' ratings of symptom occurrence and symptom severity.

Interventions/Methods—Children and adolescents with cancer (10 to 18 years of age; N=131) completed the Memorial Symptom Assessment Scale 10–18 on the day they started a cycle of myelosuppressive chemotherapy, using a one week recall of experiences. Symptom data based on occurrence and severity ratings were examined using Exploratory Factor Analysis (EFA). The defined measurement model suggested by the best EFA model was then examined with a latent variable analysis.

Results—Three clusters were identified when symptom occurrence ratings were evaluated which were classified as a chemotherapy sequelae cluster, mood disturbance cluster, and a neuropsychological discomforts cluster. Analysis of symptom severity ratings yielded similar cluster configurations.

Conclusions—Cluster configurations remained relatively stable between symptom occurrence and severity ratings. The evaluation of patients at a common point in the chemotherapy cycle may have contributed to these findings.

Implications for Practice—Additional uniformity in symptom clusters investigations is needed to allow appropriate comparisons among studies. The dissemination of symptom clusters research methodology through publication and presentation may promote uniformity in this field.

Introduction

Children with cancer experience numerous physical and psychosocial sequelae related to their disease and treatment. Symptom research in pediatric oncology has focused on the prevalence and treatment of single symptoms rather than multiple concurrent symptoms.^{1, 2}

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However, in clinical practice symptoms do not occur in isolation. While seven studies have described multiple symptoms in pediatric oncology patients,³⁻⁹ most of these investigations reported simply occurrence rates and/or severity scores.

Symptom cluster research is an emerging field in symptom management which can shed important light to mechanisms and/or management of cancer-related symptoms. When interventions are directed to ameliorate a particular symptom within a cluster, other symptoms within the cluster may be relieved. Symptom clusters are defined as a group of three or more related symptoms that occur concurrently.¹⁰ While the identification of symptom clusters has become more common in studies of adult oncology patients, research on symptom clusters in children and adolescents with cancer is more limited. Symptom clusters can be evaluated based on a priori assumptions about the relationships among symptoms or by statistical analyses.^{11, 12} To our knowledge only two studies have been published in which clusters were identified statistically.^{5, 8}

Symptom Cluster Research in Pediatric Oncology

In one study,⁵ pediatric patients (N=144) were assessed during any phase of active treatment as well as after the completion of cancer therapy. Symptom distress ratings on the Memorial Symptom Assessment Scale 10–18 (MSAS 10–18) were analyzed using cluster analysis. Five clusters were identified: 1) symptoms related to sensory discomfort and body image; 2) symptoms related to circulatory and respiratory system malfunction; 3) fatigue, sleep disturbance, and depression; 4) body image and eating difficulties; 5) symptoms related to gastrointestinal irritations and pain.⁵ The theoretical connections among some of the symptoms within the clusters were not described in the manuscript and are difficult to interpret (e.g., the inclusion of diarrhea in the “symptoms related to sensory discomfort and body image cluster”). A more homogeneous sample of patients (e.g., patients during active treatment) or the use of occurrence or severity ratings rather than distress may have yielded a more meaningful and conceptually sound set of clusters.

In a second study,⁸ the M.D. Anderson Symptom Inventory (MDASI) was used to evaluate for symptom clusters among a heterogeneous sample of pediatric oncology patients. Two symptom clusters were identified using factor analysis based on the severity ratings from the MDASI: a gastrointestinal factor (i.e., nausea, vomiting, anorexia) and a general symptoms factor. When cluster analysis was done using MDASI symptom severity ratings, two clusters of symptoms with six components were identified (i.e., (1) nausea, vomiting, and anorexia; (2) shortness of breath and dry mouth; (3) disturbed sleep and mood-related symptoms (distress, sadness, fatigue, and drowsiness); (4) pain; and (5) numbness; and (6) memory). The cluster analysis results were similar to the factor analysis,⁸ but differed from the clusters identified by Yeh and colleagues.⁵

While lessons can be learned from studies of symptom clusters in adult oncology patients, independent analyses are warranted in pediatric oncology patients. The experiences of pediatric cancer patients are not like those of adults. Children's metabolism and other physiologic features differ considerably from those of adults.¹³ In addition, very distinct cancer diagnoses are found in children and adolescents.¹⁴ Even among cancers that are common in children as well as adults (e.g., leukemia), the therapies and outcomes for different age groups can be quite disparate.¹⁵ The study of health and illness in childhood is critical to the understanding of disease throughout the lifespan.¹⁶ The ability to identify symptom clusters that are specific to pediatric oncology patients may lead to improved understanding of symptoms' underlying mechanisms among patients of all ages. For example, differences in symptom occurrence rates and clusters between children and adults may shed light on potential epigenetic factors associated with these symptom clusters. This

type of exploration may ultimately lead to improvements in symptom management interventions.

Existing symptom cluster research is scant and conducted among small and heterogeneous groups of pediatric patients. Given that only two studies have used statistical processes to identify symptom clusters in pediatric oncology patients, the purpose of this study, in a sample of children and adolescents with cancer who underwent a cycle of myelosuppressive chemotherapy, was to compare the number and types of symptom clusters identified using patients' ratings of symptom occurrence and symptom severity.

Conceptual Framework

The University of California, San Francisco Symptom Management Theory (SMT)¹⁷ can be used to explain the relationships among the key components of the symptom experience, symptom management strategies and patient outcomes. This analysis focuses on the symptom experience, in particular patients' perceptions and evaluation of symptoms. The symptom management strategies component includes critical factors such as: who delivers the strategies, what strategies are delivered, when, where and how they are delivered. The patient outcomes component includes symptom status, quality of life, and functional status.¹⁷ According to the SMT, the symptom experience is evaluated within the context of three dimensions of nursing science (i.e., person, health and illness, environment). The person dimension includes demographic, psychological, sociological, physiological, and developmental factors. The health and illness dimension includes patients' current health status and degree of disease or injury as well as associated risk factors for these conditions. The environment dimension includes physical, social, and cultural factors.

Methods

Patients and Procedures

In this descriptive study, self-report questionnaires were administered to a convenience sample of children and adolescents with cancer (10 to 18 years of age) who were able to understand English or Spanish and gave consent/assent to participate. Participants were receiving chemotherapy either as their initial therapy or for relapsed or refractory disease; had received chemotherapy within the preceding 4 weeks; and were scheduled for additional myelosuppressive chemotherapy on the day of enrollment into the study.

For this study, myelosuppressive chemotherapy was defined as treatment that was expected to cause a significant drop in the absolute neutrophil count to less than 500 cells/ μ L, with subsequent blood count recovery expected to occur within three to four weeks. Among common cancer diagnoses, a standard chemotherapy regimen was targeted (e.g., enrolled patients with acute lymphoblastic leukemia during delayed intensification and patients with osteosarcoma during cisplatin courses). Patients were excluded if they were receiving concurrent radiation therapy. Patients were recruited from three pediatric oncology settings in the San Francisco Bay area.

A total of 144 patients were approached to participate and 131 provided consent or assent (response rate of 91%). The primary reason for refusal was that patients were not interested in completing questionnaires. The study was approved by the Human Subjects Committee at the University of California, San Francisco, and at each of the study sites. Patients' parents or guardians and patients who were 18 years of age signed written, informed consents. Patients aged 10 to 17 gave either written or verbal assent as per each institution's guidelines.

During the enrollment visit, children completed the MSAS 10–18.³ In addition, patients completed a modified version of the Karnofsky Performance Status (KPS) scale in laymen's terms,¹⁸ a demographic form, and a weekly data form to capture other data not uniformly included in the medical record (e.g., number of hospitalizations, fever). Patients were asked to respond to each question based on their experiences during the week prior to chemotherapy administration.

Patients received support from the research assistants to complete the study questionnaires as needed. The instruments were translated from English to Spanish using forward and backward translation procedures.¹⁹ Patients' medical records were reviewed for disease and treatment information. They received a gift card to compensate them for their time.

Instruments

The revised version of the MSAS 10–18 assesses 31 symptoms on three dimensions. If patients reported the occurrence of a symptom over the previous week, they rated the symptom's frequency within the past week (ranges from 1 [almost never] to 4 [almost always]); severity (ranges from 1 [slight] to 4 [very severe]); and distress (ranges from 0 [not at all] to 4 [very much]) using Likert scales. Data on the patients' occurrence and severity ratings are presented in this paper. Positive responses for occurrence of each symptom were summed to determine the total number of symptoms experienced by each patient. In a manner similar to previously published research,^{20, 21} if the patient indicated that they did not experience a symptom, a zero was used in the calculation of the symptom severity score in order to determine the mean symptom severity score for each symptom for the entire sample.

The MSAS 10–18 was chosen because it is a multidimensional inventory that evaluates 31 symptoms, yet can be completed in less than 15 minutes and has established validity and reliability.³

The KPS scale was used to assess patients' functional status. KPS scores can range from 0 (dead) to 100 (normal function) in 10 point increments.¹⁸ The KPS has well established validity and reliability in adults^{22, 23} and has been used in pediatric studies.^{8, 24–26}

Data Analysis

Occurrence (i.e., the presence of a symptom) was examined as a dichotomous variable (i.e., present or absent) using Mplus 6.0.²⁷ The estimator employed was Weighted Least Squares estimation with a Mean and Variance adjusted chi-square statistic (WLSMV) because the items were categorical. This estimator was found to perform better with categorical and ordinal variables than several other estimators, including maximum likelihood.^{28, 29} In addition, it recovers the true factor structure better with confirmatory factor analysis (CFA) of categorical and ordinal items than maximum likelihood.³⁰ The following analyses were conducted using symptom occurrence rates and then repeated using patients' symptom severity ratings.

Exploratory Factor Analysis

Five of the 31 symptom items on the MSAS (i.e., problems with urination, shortness of breath, itching, problems swallowing, swelling) were excluded from the analysis because less than 25% of the respondents reported experiencing these symptoms.

First exploratory factor analysis (EFA) was done, using GEOMIN oblique rotation and six factor solutions were evaluated.^{27, 31} GEOMIN is the recommended method of rotation by Muthén and Muthén³² and is the Mplus default method of rotation beginning in Mplus

Version 6 for EFA.³³ It is also recommended as the best method for rotation in EFA by Browne³¹ and Yates.³⁴ Identification of a plausible factor structure was based on an evaluation of three types of fit indices for latent variable models (i.e., absolute fit, fit adjusting for model parsimony, and comparative or incremental fit).³⁵ A combination of the Chi-square test of model fit (i.e., expected to be non-significant; a measure of absolute fit), the comparative fit index (i.e., [CFI] with a desired value >0.95; a measure of comparative fit),^{36, 37} and the root mean square error of approximation (i.e., [RMSEA] with desired values of <0.06 or for close fit of < 0.05; a measure that adjusts for model parsimony)^{36, 38, 39} were reviewed. Additional requirements for a plausible factor structure were that the factor had three or more items with acceptable loadings, and that the combination of the contents of the items made conceptual and clinical sense.^{40, 41} In addition, factor solutions were obtained with unweighted least squares (ULS) as the estimator, to discover whether this approach would produce a clearer factor solution than WLSMV, because the sample was relatively small, and the items were categorical.²⁹ Finally, the analyses were carried out with VARIMAX orthogonal rotation, using both ULS and WLSMV as estimators to determine if an orthogonal rotation produced a clearer factor solution. The models obtained using WLSMV and GEOMIN oblique rotation provided the clearest solutions. A primary goal of the analysis was to obtain clear factor solutions after rotation, with items loading strongly on only one factor, and each factor defined by at least three items with loadings greater than 0.30 in absolute value. Although the oblique rotation method allows the factors to be correlated, this goal of “simple structure” for interpreting the factors is still desirable. The EFA solutions using ULS as the estimator, and using VARIMAX orthogonal rotation with either WLSMV or ULS as the estimators, did not achieve factor solutions that fit the data as well according to the fit indices, and/or they did not provide “simple structure” solutions that were superior to the WLSMV estimation with GEOMIN oblique rotation.

The criterion for assigning symptoms to factors was a rotated loading of ≥ 0.3 in absolute value.⁴⁰ As noted, an oblique method of rotation was employed to improve factor interpretation, because the latent variables represented by these factors were expected to be correlated. Therefore, items that “cross-loaded” on more than one factor were retained for further analysis if their loadings were above the 0.30 criterion.

Latent Variable Analysis

Following examination of the EFA solutions, the defined measurement model suggested by the best EFA model was examined with a latent variable analysis. This procedure is similar to an EFA on data from one sample followed by a CFA on data from a second or hold-out sample.^{42–44} However, because a second sample with which to evaluate the factor structure was not available, and because the sample size was not large enough to use a hold-out sample for this analysis, the evaluation of this measurement model is purely an extension of the EFA, carried out to further evaluate model fit based on the symptom sets. Sample sizes for relatively uncomplicated structural equation models, of which a measurement model such as the CFA models we presented is a simple case, usually require 200 or more observations to obtain reliable estimates.^{45, 46} This number may not be sufficient for non-normal data such as dichotomies and ordinal items when using estimation methods such as maximum likelihood or generalized least squares.

For this model, WLSMV was used as the estimator due to the small sample and because dichotomous items were examined. The loadings listed for the exploratory measurement model are unstandardized regression coefficients and provide information about the unique association of each symptom to the latent factor, relative to the first symptom on the list. Higher loadings indicate stronger unique associations of particular symptoms to the latent variables.

Results

Demographic and Clinical Characteristics

The demographic and clinical characteristics of the patients (n=131) are summarized in Table 1. The majority of the children were male (57.3%), a member of a racial/ethnic minority (i.e., patients with self-reported race/ethnicity other than non-Hispanic white) (63.4%), with a mean age of 14.8 years, and an average KPS score of 82.1. Children were diagnosed with a wide range of cancers and 25.9% were receiving treatment for a relapse or disease progression. Patients' mean time since diagnosis was 12.8 months. A few patients had experienced late relapses which contributed to a standard deviation of 25.8 months. The median time since diagnosis was 3.3 months. Most treatment was delivered in the inpatient setting (70%).

Symptom Characteristics

Patients experienced a mean of 11.6 symptoms (SD=5.6) in the prior week. As shown in Table 2, across the 31 symptoms, the mean severity score was 0.76 (SD=0.45) and mean distress score was 0.62 (SD=0.51) (possible ranges 0 to 4). The five most common symptoms were: lack of energy (75.6%), hair loss (74.6%), pain (62.6%), nausea (53.1%), and feeling drowsy (53.1%).

Symptom Clusters Based on Symptom Occurrence Rates

For patients' reports of symptom occurrence, a three factor solution provided the best fit. For the EFA, all three fit indices were within the prespecified parameters ($\chi^2 = 276.547$, $P = 0.12$, CFI = 0.958, RMSEA = 0.028). As expected, the measurement model produced similar fit indices ($\chi^2 = 288.793$, $P = 0.22$, CFI = 0.972, RMSEA = 0.022). No evidence of miss-assigned items or correlated residuals was detected from an evaluation of the modification indices (no MI ≥ 10).²⁷ Moderate to strong correlations among the latent factors (0.39 to 0.70) confirmed our expectation that the oblique rotation for the EFA was necessary. In addition, all items fit conceptually within each factor, so that no items were eliminated due to lack of clinical relevance to other symptoms in the cluster.

Each factor was named based on the constellation of symptoms within the factor (i.e., chemotherapy sequelae cluster, mood disturbance cluster, neuropsychological discomforts cluster). The symptoms included in each cluster are listed in Tables 3 through 5. One symptom (i.e., numbness or tingling in hands or feet) did not load on any factor. Three symptoms (i.e., pain, insomnia, feeling irritable) "cross-loaded" on two factors. Models were examined with these symptoms assigned to both factors and to each factor alone. The best fitting solution was one in which pain and insomnia were assigned to the neuropsychological discomforts cluster and feeling irritable was assigned to two factors (i.e., mood disturbance and neuropsychological discomforts clusters) in the exploratory measurement model. The decision to assign the cross-loading items to only one factor, or to allow them to load on two factors, was made by evaluating their contributions to the factors, the model fit indices described in the paper, and an evaluation of the modification indices for the items. The fit was superior for the model reported, compared to models where they were assigned to only one factor, and the modification indices for the items that were allowed to cross-load were not significant (which indicated support for the assignment to two factors). In other words, the cross-loading items provided statistically significant contributions to each factor they were assigned to, and there was evidence that assigning them to two factors made the model fit better than if they were assigned to only one factor.

All loadings for the three factors were significant and in the theoretically and clinically meaningful direction. Cronbach α coefficients based on occurrence data were 0.76, 0.65, and

0.68 for the chemotherapy sequelae cluster, mood disturbance cluster, and neuropsychological discomforts cluster, respectively. Nunnally and Bernstein⁴⁷ view α internal consistency coefficients of 0.70 or higher as sufficient for instruments used in the early stages of research.

Most of the symptoms had similar contributions to the chemotherapy sequelae cluster. However, sweating, constipation, headache, and cough made relatively weak contributions to this factor. Feeling irritable made the weakest contribution to the mood disturbance cluster. Feeling irritable, altered self-perception and skin changes made the weakest contributions to the neuropsychological discomforts cluster.

Symptom Clusters Based on Symptom Severity Ratings

For symptom severity ratings, a three factor solution provided the best fit using EFA. Although the fit indices were not all within the desired ranges for the EFA solution ($\chi^2 = 322.724$, $P < 0.01$, CFI = 0.924, RMSEA = 0.047), the exploratory measurement model achieved a better fit with all indices in the recommended ranges ($\chi^2 = 215.856$, $P = 0.06$, CFI = 0.966, RMSEA = 0.036).

Cronbach α coefficients for the three clusters based on severity data were 0.76, 0.65, and 0.72 for the chemotherapy sequelae cluster, mood disturbance cluster, and neuropsychological discomforts cluster, respectively.

Sweating and constipation made the weakest contributions to the chemotherapy sequelae cluster for the analyses based on symptom severity. The weakest contributor to the mood disturbance cluster was feeling irritable. The weakest contributors to the neuropsychological discomforts cluster were feeling irritable, hair loss, headache, and skin changes.

Comparison of the Factor Structures Based on Symptom Occurrence Rates and Severity Ratings

As shown in Tables 3 through 5, the constellation of symptoms in each of the clusters were nearly identical when the occurrence and severity data were compared. Based on the findings from the exploratory measurement models, 8 of 13 symptoms in the chemotherapy sequelae cluster; 4 of 5 symptoms in the mood disturbance cluster; and 7 of 8 symptoms in the neuropsychological discomforts cluster were identical when the factors were determined using occurrence rates or severity ratings. When the analysis was based on symptom severity ratings, three additional symptoms (i.e., lack of energy, headache, hair loss) loaded on this factor. The strength of the symptoms' contributions to a particular cluster was similar between the symptom occurrence and severity analyses.

Discussion

This study is the first to compare the number and types of symptom clusters identified using pediatric oncology patients' ratings of symptom occurrence and severity. The groupings of symptoms identified in the EFA analyses are clinically meaningful and were confirmed in the latent variable analysis. With the exception of cough and sweating, the symptoms in the chemotherapy sequelae cluster are among the most common physical symptoms associated with chemotherapy administration. The mood disturbance cluster was limited to psychosocial symptoms. Most of the symptoms in the neuropsychological discomforts cluster (i.e., all except hair loss, altered self-perception, and skin changes) are associated with the sickness behavior syndrome that is observed following the administration of pro-inflammatory cytokines.^{48–50}

These findings have direct implications for clinical care. In this study, 8 symptoms clustered in the chemotherapy sequelae cluster in the analyses based on symptom severity (11 symptoms when analyses were based on symptom occurrence). The complexity of this configuration may be perplexing to clinicians and researchers. However, the symptoms made variable contributions to this cluster, as noted by the estimates for the exploratory measurement model. Notably, nausea and vomiting made the strongest contributions to this cluster, and may be particularly important targets for nurses when planning symptom management interventions in the clinical setting or designing intervention research. Additionally, nurses may direct interventions towards the symptom in a cluster which is most amenable to treatment, with the potential of concurrent treatment of symptoms in the cluster which are more difficult to treat. For example, strategies to ameliorate worry (e.g., provision of clear and accurate anticipatory guidance) may be effective in decreasing feelings of sadness. In the SMT, this approach addresses the “what” query of the symptom management component. Nurses in the clinical setting may be best poised to identify patterns in symptom management that warrant further evaluation by researchers. In addition, considering the constellation of symptoms in the neuropsychological discomforts cluster, further investigation of the potential association of cancer-related symptoms with cytokines or other biologic mechanisms is warranted. Such investigation may ultimately lead to discoveries of new pharmacologic therapies for these untoward effects.

Direct comparisons across pediatric and adult studies are difficult because different symptom inventories were used, and the total number of symptoms varies across instruments. Symptom inventories may evaluate as few as 8 to 10 symptoms (e.g., the M.D. Anderson Symptom Inventory,⁵¹ the Symptom Distress Scale⁵²). The MSAS 10–18 with 31 symptoms was used for this study to maximize the cluster configurations. However, constellations of symptoms within a cluster are likely to differ if a symptom inventory with only 8 items versus 31 items is used to evaluate for symptom clusters.

In addition, comparisons across studies are difficult when patients are enrolled at different points in their treatment trajectories (e.g., on or off therapy) and at different points within a treatment cycle (e.g., at the start of a chemotherapy cycle or at blood count nadir). All patients in this study were enrolled at the start of a myelosuppressive chemotherapy regimen to minimize variability. No similar trials (i.e., investigations of symptom clusters exclusively among patients receiving chemotherapy) were noted in the pediatric oncology literature. Considering the early stage of these investigations in pediatric oncology, the lack of comparable studies among children with cancer is not surprising. With this in mind, one might look to the symptom clusters literature in adult oncology for lessons learned. However, despite the publication of a large number of symptom clusters studies among adult cancer patients, only three studies were found in which chemotherapy was uniformly administered.^{53–55} These studies show few similarities in their symptom cluster configurations. These disparities may be expected as none of these studies structured data collection around a common point in patients’ chemotherapy cycles, with recall periods up to one month.

Differences in the choice of symptom dimension used in the statistical analysis (e.g., occurrence, severity, distress) have the potential to affect study results. In this study, notable similarities were found between the symptom clusters identified based on symptom occurrence and severity ratings. The most striking commonalities were found in the mood disturbance cluster and is congruent with previous studies.^{56, 57} For example, Kim and colleagues reported similarities in occurrence and severity symptom cluster analyses among breast and prostate cancer patients during radiotherapy.⁵⁶ In a study by Suwisith and colleagues,⁵⁷ the symptom clusters based on severity ratings were quite similar to those based on distress ratings among women receiving chemotherapy for breast cancer.

Comparisons between data sets based on occurrence and severity may not be ideal. However, symptom clusters research is an emerging field, and at times researchers must rely on such comparisons across symptom dimensions if studies with analyses based on similar dimensions are not available.

Finally, numerous statistical analyses have been utilized in prior studies. Consensus on the most robust statistical analysis to use to evaluate for symptom clusters has not been reached. However, Skerman recommends the use of EFA or hierarchical cluster analysis when researchers' goals are to identify unknown groupings of symptoms from an array of symptoms and the use of confirmatory factor analysis to validate hypothesized clusters of symptoms.¹¹

Despite the difficulties in comparing studies based on disparate methodologies as outlined above, variations on the common symptom cluster of fatigue, sleep disturbance, pain and depression are noted in the studies with the most similar patient populations (i.e., children or adolescents with cancer,^{5, 8} and adults receiving cancer chemotherapy^{53–55}). In our study, we noted an association between pain, feeling drowsy, insomnia (in the analysis based on symptom occurrence only), and lack of energy (in the analysis based on symptom severity only). Feelings of sadness clustered with other psychological symptoms (i.e., with feeling nervous, worry, feeling irritable). Among the pediatric studies, both Tseng and colleagues⁸ and Yeh and colleagues⁵ reported an association between fatigue, sadness (or psychological distress), and disturbed sleep, while pain clustered with taste changes⁵ or grouped as a single symptom.⁸ Aprile and colleagues⁵³ reported an association of pain and fatigue among adults with cancer, while depression clustered with anxiety. These researchers based symptom occurrence on medical record review. Sleep disturbance and insomnia were not included in the cluster configuration, as they were rarely abstracted from patients' charts (but likely were significant issues for hospitalized patients). Skerman and colleagues⁵⁴ reported the association of sleep, fatigue, and pain. However, no psychosocial variables were evaluated in this study. Thus the relationship of depression to other variables cannot be determined. Yamagishi and colleagues⁵⁵ reported the association of fatigue and sleep, while pain clustered with dyspnea and numbness and psychological distress was grouped as a single item. None of these studies reported the complete constellation of fatigue, sleep disturbance, pain and depression. The inconsistencies in the clustering of depression or feelings of sadness are not surprising when one considers the extreme variability in the inclusion of psychosocial variables among the groups of symptoms being evaluated in these studies. Feelings of sadness or depression was one of numerous psychosocial variables included in some studies,^{5, 53} was listed as "psychological distress" in others,^{8, 55} and was not evaluated in another.⁵⁴ In addition, psychological symptoms have many different connotations which vary considerably based on the verbiage chosen for particular symptom checklists. Likewise, the clustering of pain varied among these studies. The heterogeneity in the types of pain experienced during cancer treatment (e.g., procedure-related pain, chronic, disease-related pain) may contribute to these findings. Nevertheless, the overall consistency of the clustering of fatigue, sleep disturbance, pain and depression emphasizes the importance of addressing these symptoms in clinical practice and in additional research. When conducting symptom cluster research it is critical to include these four symptoms and a wide range of additional psychosocial symptoms in order to best delineate the relationships among a large number of variables.

According to the SMT, multiple perceptions of the symptom experience must be considered (e.g., the perception of the patient and that of the clinician), with the potential for discordant evaluations. These incongruences can lead to difficulties in symptom management.⁵⁸ The patients' perspective is considered to be the gold standard. However, in pediatrics, parental concerns are often brought to the foreground and may be in conflict with patients' reports. In

this investigation the adolescent patients' perspectives were analyzed. Future analyses could compare symptom cluster constellations based on parental report to those based on patients' reports to gain insight into factors that influence the effectiveness of symptom interventions.

Limitations of this study include the relatively small sample size and the use of a very heterogeneous sample with regards to cancer diagnoses, the chemotherapy agents used, and the time elapsed since the patients' diagnoses. The chemotherapy sequelae cluster may have a very different configuration (e.g., fewer symptoms than the 8 symptoms noted in the current investigation) if a symptom inventory was administered to a more homogeneous sample in terms of cancer diagnosis, chemotherapy regimen, and/or treatment cycle. In addition, this study was a cross-sectional analysis during a single chemotherapy cycle. Therefore, changes in symptom clusters over time were not evaluated. The KPS was used to measure patients' functional status. Although this scale was used in pediatric oncology research, psychometric evaluation of the measure in pediatric studies has not been published. Finally, a one week recall period was used to evaluate symptoms. Anecdotally, some patients reported difficulties in recalling and/or summarizing events during the past week due to the variable nature of the symptoms.

Despite these limitations, to our knowledge this study is the first to evaluate symptom clusters based on a standardized time point in relation to chemotherapy administration. The nature of symptom patterns following myelosuppressive cancer chemotherapy adds credence to our conceptual approach of evaluating patients at similar points in their chemotherapy schedules. With significant variability in analytic approaches to symptom clusters research, a state of the science summit for key researchers to debate these issues and make recommendations may promote uniformity in forthcoming investigations.

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Table 1

Demographic and Clinical Characteristics (N= 131)

Characteristics	Results
Age (years)	
Mean (SD)	14.8 (2.5)
Range	10–18
Median	15.3
Time Since Diagnosis (months)	
Mean (SD)	12.9 (25.8)
Median	3.3
Karnofsky Performance Status	
Mean (SD)	82.1 (18.3)
Range	30–100
Median	90
Gender	
Male	75 (57.3%) ^a
Female	56 (42.7%)
Ethnicity	
Non-Hispanic White	36.6%
Hispanic White	36.6%
Mixed Race	13.0%
Asian/Pacific Islander	8.4%
Black	3.1%
Native American	1.5%
Diagnoses	
Acute lymphoblastic leukemia	34 (26%)
Osteosarcoma	16 (12.2%)
Ewing sarcoma	13 (9.9%)
Central nervous system tumors	12 (9.2%)
Non-Hodgkin lymphoma	11 (8.4%)

Characteristics	Results
Hodgkin disease	11 (8.4%)
Rhabdomyosarcoma	7 (5.3%)
Acute myeloid leukemia	5 (3.8%)
Other solid tumors	16 (12.2%)
Other leukemia	6 (4.6%)
Number of Relapses	
0	97 (74.1%)
1	28 (21.4%)
≥ 2	6 (4.5%)

^aValue given are number (%)

Table 2

Occurrence and Severity Ratings for Symptoms

Symptom	Occurrence (%)	Mean Severity (SD)
Lack of energy	75.6	1.4 (1.1)
Hair loss	74.6	2.2 (1.6)
Pain	62.6	1.3 (1.2)
Nausea	53.1	1.0 (1.1)
Feeling drowsy	53.1	1.0 (1.1)
Feeling irritable	48.8	1.0 (1.2)
Weight loss	48.5	0.9 (1.1)
Worrying	47.6	0.8 (1.0)
Headache	46.9	0.9 (1.1)
Feelings sad	46.0	0.8 (1.1)
Lack of appetite	45.2	1.1 (1.3)
Insomnia	43.4	1.0 (1.3)
Change in the way food tastes	42.3	0.9 (1.3)
Feeling nervous	38.5	0.6 (0.9)
"I don't look like myself" (Altered self- perception)	37.2	0.8 (1.3)
Dry mouth	36.2	0.6 (1.1)
Lack of concentration	35.9	0.6 (0.8)
Numbness/Tingling in hands/feet	35.7	0.7 (1.0)
Sweating	35.7	0.6 (0.9)
Skin changes	31.0	0.6 (1.0)
Cough	30.8	0.5 (0.8)
Constipation	30.2	0.6 (1.0)
Diarrhea	30.2	0.6 (1.0)
Mouth sores	28.7	0.6 (1.1)
Vomiting	28.6	0.6 (1.1)
Dizziness	26.4	0.4 (0.8)
Itching	21.6	0.3 (0.8)
Dyspnea	16.7	0.3 (0.8)
Difficulty swallowing	16.3	0.4 (0.9)

Symptom	Occurrence (%)	Mean Severity (SD)
Swelling of arms/legs	10.1	0.2 (0.7)
Problems with urination	5.4	0.1 (0.4)

Table 3
Factor Loadings for the Chemotherapy Sequelae Cluster Based on Occurrence and Severity Data

Symptom	Occurrence		Severity	
	EFA Loadings	Exploratory Measurement Model Estimates	EFA Loadings	Exploratory Measurement Model Estimates
Lack of energy	0.646	1.000		
Cough	0.633	0.543		
Dry mouth	0.606	0.646	0.526	1.000
Nausea	0.748	0.970	0.711	1.561
Vomiting	0.947	1.030	0.915	1.780
Diarrhea	0.471	0.620	0.428	1.017
Sweating	0.527	0.410	0.357	0.669
Lack of appetite	0.500	0.733	0.559	1.508
Headache	0.362	0.553		
Mouth sores	0.504	0.717		
Weight loss	0.518	0.712	0.483	1.091
Hair loss	0.415	0.675		
Constipation	0.580	0.422	0.504	0.697

Abbreviations: EFA=Exploratory Factor Analysis

Table 4
Factor Loadings for the Mood Disturbance Cluster Based on Occurrence and Severity Data

Symptom	Occurrence		Severity	
	EFA Loadings	Exploratory Measurement Model Estimates	EFA Loadings	Exploratory Measurement Model Estimates
Lack of concentration	0.341	1.000		
Feeling nervous	0.545	1.293	0.550	1.000
Feeling of sadness	0.566	1.506	0.551	1.032
Worry	0.999	1.635	0.941	1.179
Feeling irritable	0.598	0.833	0.499	0.579

Abbreviations: EFA=Exploratory Factor Analysis

Table 5
Factor Loadings for the Neuropsychological Discomforts Cluster Based on Occurrence and Severity Data

Symptom	Occurrence			Severity		
	EFA Loadings	Exploratory Measurement Model Estimates	EFA Loadings	Exploratory Measurement Model Estimates	EFA Loadings	Exploratory Measurement Model Estimates
Pain	0.429	0.963	0.537	1.000		
Feeling drowsy	0.436	1.000	0.331	1.003		
Insomnia	0.302	0.797				
Feeling irritable	0.613	0.629	0.407	0.562		
Taste changes	0.479	1.006	0.401	1.160		
Altered self-perception	0.384	0.642	0.436	0.833		
Skin changes	0.504	0.588	0.678	0.797		
Dizziness	0.391	0.943	0.424	0.942		
Lack of energy			0.735	1.328		
Headache			0.350	0.773		
Hair loss			0.364	0.734		

Abbreviations: EFA=Exploratory Factor Analysis