Symptom Clustering in Older Taiwanese Children With Cancer

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Purpose/Objectives: To derive symptom clusters occurring in a large group of older pediatric patients with cancer in Taiwan and to examine whether each cluster differed based on gender, type of cancer and disease, pain, and functional status.

Design: Descriptive, correlational study.

Setting: Pediatric oncology inpatient unit and outpatient clinics in Taiwan.

Sample: 144 pediatric patients with cancer, aged 10–18 years.

Methods: Subjects completed the Memorial Symptom Assessment Scale 10–18, the Play Performance Scale for Children, and a demographic questionnaire. Medical records provided disease and treatment data. Cluster analysis techniques were used to identify the symptoms that clustered together by demographic characteristics, as well as disease, pain, and functional status.

Main Research Variables: Symptom cluster, pain status, and functional status.

Findings: Five clusters were identified from the statistical analysis. The symptoms that clustered together were somewhat surprising, and some can be explained by cultural differences. Patients with pain reported statistically significant higher distress in all five clusters.

Conclusions: Five symptom clusters are identified in older Taiwanese children with cancer. The way and possible rationale of how these symptoms clustered together is discussed.

Implications for Nursing: This is the first study that used a statistical procedure to derive symptom clusters experienced by pediatric oncology patients. Knowledge from this study can provide a starting point to investigate the stability of symptom clusters with different states of disease, different populations, and over various periods of time.

The prevalence of symptoms experienced by pediatric patients with cancer has been increasingly documented since the late 1990s (Goldman, Hewitt, Collins, Childs, & Hain, 2006; Hockenberry & Hooke, 2007). The ultimate goal of cancer treatment for pediatric patients with cancer is cure; thus, researchers and clinicians may have been more willing to overlook the symptoms that this population has experienced. Researchers have shown that children with cancer, like adults, also suffer from an array of symptoms during cancer treatment (Collins et al., 2000; Hockenberry & Hooke; Yeh, 2001) or during their terminal phase (Jalmsell, Kreicbergs, Onelov, Steineck, & Henter, 2006). Severe symptom distress may delay scheduled treatments, the effectiveness of treatment protocols, and the rehabilitation process.

When discussing symptom distress in children with cancer, studies have focused primarily on individual symptoms. For example, a comprehensive literature review that examined symptom management using traditional and complementary medicine in children with cancer (Ladas, Post-White, Hawks, & Taromina, 2006) showed that most studies focused only on a single symptom that was associated with a specific research question, such as procedure-related pain (Zeltzer et al., 2002), nausea or vomiting (Reindl et al., 2006), fatigue (Iwasaki, 2005), mucositis (Aquino et al., 2005), and anxiety or insomnia (Francis & Dempster, 2002). In clinical practice, patients undergoing cancer treatment seldom present with a single symptom but usually suffer from multiple symptoms simultaneously. Studies related to symptom management in adults has focused on symptom clusters, a construct in oncology nursing theory (Dodd, Miaskowski, & Lee, 2004) that is still in its infancy because of a lack of consensus about a definitive definition or a shared biologic mechanism (Miaskowski & Aouizerat, 2007). To date, only one study has discussed the symptom cluster of fatigue, sleep, and pain in pediatric patients with cancer (Hockenberry & Hooke, 2007). In addition, no empirical studies have provided evidence or foundational knowledge of the symptom clusters experienced by children with cancer; therefore, this new area should be explored and knowledge developed for management.

The purpose of this study was to develop knowledge on which to build a theoretical framework of symptom clusters among children who have cancer. The specific aim of this study was to use an analytic procedure to derive symptom clusters occurring in pediatric patients with cancer. The research questions were as follows.

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Quick Facts: Taiwan

Geography and economy: Taiwan is a relatively small island country in Asia that, as of June 2007, had a total population of about 23 million people. Because of the free economic environment and limited natural resources, Taiwan has transformed from a labor-intensive agricultural economy to a technology- and capital-intensive industrial economy.

Healthcare system: The Taiwan government has implemented a National Health Insurance (NHI) program that was established in 1994 and provides universal medical care to all of the citizens in Taiwan. Medical expenses for children who are diagnosed with cancer are covered by NHI for a very small co-pay.

Childhood cancer: Cancer is the leading cause of death in Taiwan. Childhood cancer is the second-leading cause of death for children aged 1–14 years (17% of total deaths for children aged 1–14 years). Each year, 500–600 children are newly diagnosed with cancer.

Bibliography

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- Do clusters of symptoms exist in older Taiwanese children with cancer?
- Are significant correlations present among each cluster and gender, type of cancer, disease status (on and off treatment), pain status, and functional status of symptoms that cluster together for children with cancer?

Literature Review

Dodd et al. (2004) defined a symptom cluster as "symptoms [that] need to be both related to one another and occurring concurrently" (p. 76); in addition, three or more concurrent symptoms have to relate to each other (Dodd, Miaskowski, & Paul, 2001). The concept of a symptom cluster recently has received attention in the adult oncology literature. In an integrated literature review on symptom cluster studies, Barsevick (2007) found that more than 30 studies were published since the late 1990s, but none of the studies focused on children with cancer. However, the definition of symptom cluster has faced its challenges in adult oncology, such as whether to include two, three, or more symptoms within a cluster and the meaning of "related to each other" (Miaskowski, 2006); how to assess a symptom cluster (subjective or objective criteria) (Barsevick); and determination of whether a shared biologic mechanism for symptom clusters must exist (Miaskowski & Aouizerat, 2007). Kim, McGuire, Tulman, and Barsevick (2005) revised the definition of symptom cluster as "consisting of two or more symptoms that are related to each other and that occur together" (p. 278). This was based on their literature review and concept analysis of cancer symptoms from different disciplines, including psychology or psychiatry, general medicine, and nursing. Researchers to date have suggested that symptoms within a cluster should have a stronger relationship than symptoms across clusters. However, no one has defined the criteria for strong relationships within a cluster.

Cleeland et al. (2003) suggested that some evidence exists for a biologic origin of symptom clusters. In research using sick animal models, they suggested that cytokines may be the common factor underlying the biologic mechanism in occurrences of physiologic symptoms (e.g., fever, pain, wasting) and behavioral symptoms (e.g., decreased activity, cognitive impairment, somnolence, decreased social interaction) (Cleeland et al.; Miaskowski, 2006). However, Dodd et al. (2004) suggested that symptoms within a cluster may not necessarily share the same biologic etiology.

Pain, fatigue, and sleep disturbance are suggested to be common in all pediatric patients with cancer (Hockenberry & Hooke, 2007), but these symptoms may not share a common etiology. For example, pain may be caused by cancer or a treatment or procedure, fatigue may result from treatment side effects, and sleep disturbances may develop because of chemotherapy or anxiety. Miaskowski and Aouizerat (2007) published a thorough review on the state of the knowledge about whether a common biologic link is present among clustering symptoms. They concluded that no definitive proof exists, but some interesting evidence indicates a biologic basis for symptoms that cluster together. Miaskowski and Aouizerat recommended that more studies be conducted to further elucidate the biologic basis.

Symptom assessment and management play a very important role in the clinical care of patients with cancer. To eliminate or minimize distressing symptoms, pharmaceutical interventions may be needed. When multiple symptoms are treated individually with pharmaceuticals, several issues must be considered. First, polypharmacy may occur because the symptoms in one cluster may have a mutual etiology or share a common mechanism thus causing the symptoms to cluster together (e.g., vomiting and nausea) (Miaskowski, Dodd, & Lee, 2004). Second, with a more holistic view, pharmaceuticals could target the wrong symptoms because within one symptom cluster, some physical symptom distress (fatigue) may result from psychological distress (depression) and vice versa (Hockenberry & Hooke, 2007). Moreover, within one symptom cluster, one symptom may be a side effect of the treatment (constipation) for another symptom (pain, the use of opioids), thus causing the symptoms to cluster with each other.

Polypharmacy may increase symptoms even further. If healthcare professionals can identify the symptoms that occur in clusters, they may be able to direct their management to reduce the use of polypharmacy, which may reduce systemic toxicities. When healthcare providers only assess a number of single symptoms or a selected group of symptoms, assessment can provide meaningful information; however, a number of symptoms or a selected group of symptoms may not be sufficient to assess a patient's actual clinical symptoms. A comprehensive and broad-spectrum assessment of physical and psychological symptoms may be more useful not only for research purposes, but also for clinical practice when caring for patients with cancer.

Tools, scales, and instruments designed for the assessment of symptoms range from single-question tools to complex multisymptom measures. Symptoms are subject to individual perception; therefore, an assessment should rely on patient self-report (Dodd, Janson, et al., 2001). In clinical research with all patients, the burden of completing assessment questionnaires is a major concern, particularly with pediatric patients with cancer. For this population, some measurement tools are available to assess a single symptom

such as pain, nausea or vomiting, nutrition, mucositis, or fatigue (Hockenberry, 2004). Multiple-symptom assessment tools for use among pediatric patients with cancer include the Therapy-Related Symptom Checklist (TRSC) (Williams, Schmideskamp, Ridder, & Williams, 2006), the Memorial Symptom Assessment Scale 10–18 (MSAS 10–18) (Collins et al., 2000), the MSAS 7–12 (Collins et al., 2002), a checklist of symptoms for the palliative phase (Theunissen et al., 2007), and qualitative descriptions of symptoms (Hedstrom, Haglund, Skolin, & von Essen, 2003).

Well-validated symptom assessment tools are very limited for children with cancer, but two instruments are available. The TRSC Child version (TRSC-C) (23 items) was adapted from the TRSC, which was developed for adult patients with cancer, and is used as a checklist by a parent or caregiver to monitor the severity of the child's symptoms during cancer treatments (Williams et al., 2006). The evidence of psychometric properties for the TRSC-C is extremely limited by the small sample size (N = 11 parents or caregivers) (Williams et al.). The MSAS is a well-validated multidimensional symptom assessment instrument that captures patient-rated severity, frequency, and distress associated with 32 highly prevalent symptoms (Portenoy et al., 1994). The MSAS 10–18 has been modified and used in adolescents with cancer (Collins et al., 2000), and a brief version for younger children (MSAS 7–12) has been designed and tested as well (Collins et al., 2002). Using the MSAS 10–18, Collins et al. (2000) found that the most prevalent symptoms reported by children with cancer were lack of energy, pain, drowsiness, nausea, cough, lack of appetite, and psychological symptoms (i.e., worrying or feeling sad, nervous, or irritable).

The studies previously cited have provided some foundational knowledge of symptom distress in children with cancer. Because of the limited empirical evidence about symptom clusters, statistical techniques such as cluster analysis can be used to identify clusters of symptoms based on patient self-reports. Cluster analysis is an exploratory statistical procedure that mathematically groups symptoms into factors that tend to occur together, with each cluster being unique and identified as only one of several symptom clusters in a particular data set (Johnson & Wichern, 1992). This approach seems reasonable and valuable for identifying patient self-rated symptom distress into symptom clusters.

Collins et al. (2000) reported that although the subscale scores of the MSAS 10–18 (including physical symptoms, psychological symptoms, and a global distress index) demonstrated large variability in symptom distress, they still were able to identify that patients who received chemotherapy reported high distress. However, the categorization of items within a subscale is based on a previously established study using factor analysis with varimax rotation in an adult population (Portenoy et al., 1994) and without any consideration of the co-occurrence of symptoms in pediatric patients with cancer.

The validity of the MSAS 7–12 was part of the validation study of the MSAS 10–18. A simplified version of the MSAS 10–18, the MSAS 7–12 is an eight-item measure selected from the most prevalent symptoms of physical and psychological distress revealed by the MSAS 10–18. It now is being used to assess symptom distress among younger children with cancer (Collins et al., 2002). The MSAS 7–12 was administered to 149 pediatric inpatients and outpatients aged 7–12 years from the United Kingdom and Australia (Collins et al., 2002). Reliability and validity show that young children with cancer can provide evidence of symptom distress. However, by selecting only the eight items that were most prevalent in older children using the MSAS 10–18, the authors limited the assessment of other symptoms.

The first theoretical framework for the symptom cluster of pain, sleep, and fatigue in children and adolescents with cancer was proposed by Hockenberry and Hooke (2007) based on 10 years of research. The framework highlights the antecedents (person, environment, and disease factors) and consequences (physical performance and behavior changes) of symptom experiences. Personal factors in the framework include gender, family, culture, ethnicity, age, and developmental stage; environmental factors include hospitalization, distance to the hospital, frequency of treatments, and school attendance; and disease factors include the type of cancer, stage of cancer, time since diagnosis, length of treatment, and type of chemotherapy received. To date, this is the only theoretical framework that might support symptom clusters. Although it is very useful, its broad theory is not specific to system clustering.

Methods

Subjects

The current study was part of a longitudinal study to identify and test a model of the coping patterns of children with cancer and their parents. For the purpose of this analysis, only the baseline data of children aged 10–18 years and one of their parents were used to describe the prevalence of symptoms. Subjects were eligible for the study if they had been diagnosed with cancer, their cancer was not complicated by another chronic illness, they were chronologically and cognitively aged 10–18 years, they spoke Chinese, their health was stable enough for them to participate in the study, and they wanted to do so. Subjects were recruited from a children's hospital in northern Taiwan. Among the 155 patients aged 10–18 years who were approached, 9 declined participation because of scheduling conflicts and 2 did not return the survey. In total, 144 patients and one parents each were recruited for data analysis. The response rate was 93%.

Measures

The MSAS originally was developed to capture patient-rated frequency, severity, and distress associated with 32 highly prevalent multidimensional symptoms for adults with cancer (Portenoy et al., 1994). Collins et al. (2000) revised the instrument for use among children. They removed two items from the MSAS, one related to sexual functioning and the other to bloatedness. The **MSAS 10–18** is a patient-rated instrument used to assess patients' experiences during the previous week. The first of its two parts measures occurrence of each symptom and has a yes-or-no format, whereas the second part consists of Likert-type scales of three dimensions—frequency, severity, and distress. Frequency and severity are rated on a separate four-point Likert scale from 1 (almost never) to 4 (almost always). Distress is scored as 1 (not at all) to 4 (very much). All 30 symptoms are assessed on severity and distress; frequency is assessed only for 22 symptoms because eight of the items are not frequency related (e.g., hair loss).

During the data collection, the subjects reported that the subscales of frequency, severity, and distress looked similar.

Portenoy et al. (1994) suggested that distress alone was the most informative single dimension when considering the patient burden of completing a questionnaire. Thus, for the purpose of the present study, only occurrence and distress were used. Collins et al. (2000) reported that the instrument had good reliability using Cronbach's alpha coefficient and that the convergent and discriminant validity were demonstrated by significant correlations with other instruments. The MSAS 10–18 was translated from English to Chinese by two bilingual PhD-prepared nursing faculty members and back translated by two different bilingual PhD-prepared nursing faculty members independently for this study. The original version and back-translation version were compared word by word to ascertain that the items matched the intent of the original instrument (Behling & Law, 2000). The research team discussed each of the few discrepancies, and the best translation was accepted. Then, the final version of the Chinese MSAS 10–18 was pilot tested with five Chinese-speaking adolescents with cancer to determine their understanding of each item. The Cronbach's alpha coefficient was 0.87 for the distress scale in this study.

The **Play Performance Scale for Children (PPSC)** was developed by Lansky, List, Lansky, Cohen, and Sinks (1985) to measure performance status on the basis of role and personal functioning and to reflect a child's ability to engage in age-appropriate play activities. Parents were asked to rate their children's activity level as it related to illness or treatment on a single scale ranging from 0 (unresponsive) to 10 (fully active). The psychometric properties of the scale have been reported as adequate (Lansky, List, Lansky, Ritter-Sterr, & Miller, 1987; Yeh & Hung, 2003).

Patient characteristics (e.g., age, gender) and disease information (e.g., diagnosis, duration since first diagnosed, treatment information [treatment protocol used and medication used]) were collected from hospital records (see Table 1). Demographic data about patients' parents and households also were collected from both parents (see Table 2).

Table 1. Demographic Characteristics From Hospital Records

Characteristic	n	%
Age (years)		
10–12	26	18
≥ 12	118	82
$\bar{X}$ (SD) = 14.2 (2.2)	–	–
Range = 10.0–18.9	–	–
Months since initial diagnosis		
$\bar{X}$ (SD) = 21.2 (27.0)	–	–
Range = 0.0–160.3	–	–
Gender		
Male	84	58
Female	60	42
Type of disease		
Leukemia	75	52
Lymphoma	26	18
Solid tumor	43	30
Illness stage		
Newly diagnosed	32	22
Remission on treatment	67	47
Relapsed on treatment	9	6
Completed treatment	36	25

N = 144

Table 2. Demographic Characteristics of Fathers and Mothers

	Fathers (N = 144)			Mothers (N = 144)		
Characteristic	$\bar{X}$	SD	Range	$\bar{X}$	SD	Range
Age (years)	45	5	32–63	42	5	30–54
Characteristic	n		%	n		%
Education[a]						
Primary school or less	5		4	6		4
Junior high school	38		28	36		25
High school	43		31	66		46
College or beyond	51		37	35		25
Religion[a]						
Folk beliefs	9		7	10		7
Buddhist	47		35	60		43
Taoist	39		29	37		26
None	33		25	30		21
Other	5		4	4		3
Socioeconomic status[a]						
Highest	1		1	–		–
Moderately high	22		16	10		7
Medium	48		36	38		27
Moderately low	39		29	46		32
Lowest	24		18	49		34

[a] Some data are missing.

Procedures

In addition to the required institutional review board approval, the hospital's established procedures for protecting confidentiality were strictly followed. Parents of eligible children were approached by trained RN data collectors. The parents received verbal and written explanations of the study and procedures and were asked about their willingness to participate along with their sick children. After parental consent and patient assent were obtained, participants were given questionnaire packets. Most families returned the packets during their stay at the hospital or clinic. If the questionnaire was not returned before the patient or parent left the hospital, a prestamped envelope was provided for subjects to mail the questionnaire. Follow-up phone calls (as many as two) were made if the data had not arrived by the end of the next week. Of 144 patients, only 6 patients and their parents returned their questionnaires by mail. Questionnaires not returned after two phone calls were counted as lost. All information on the questionnaires that could identify participants was removed immediately on receipt of the packet, and all materials were stored in a locked office.

Data Analysis

All of the missing items within a scale for any subject were imputed using the mean of the nonmissing items as long as at least 75% of the items were completed. Cluster analysis was used to classify symptoms that occurred in a number of patients with similar frequencies. An agglomerative hierarchical method was used, which considers each symptom as a cluster size of one; it then joins similar clusters together until all clusters are merged into a single cluster. A cluster of symptoms is defined by identification of groups of patients who experienced similar clusters or combinations of dis-

tressing symptoms. Ward's method with Euclidean distance as the similarity measure was used to establish the number of clusters (beginning with each symptom), and then two clusters separated by the shortest average distance are joined until finally a single large cluster exists that includes all of the symptoms. The pseudo-F stopping rule index and cubic clustering criterion (CCC) were used jointly to select the number of clusters for the analysis. Four, five, and six clusters were obtained from the data based on the results of heterogeneity between clusters (R^2). A relatively large pseudo-F statistic value of 83.01 resulted (Calinski & Harabasz, 1974) and met the CCC of 10.54 (Sarle, 1983), indicating five as the most appropriate number of clusters for the data.

After the cluster factors were identified, pooled t tests were used to compare the cluster factors with two groups, such as gender (male or female), treatment status (on or off), pain status (pain or no pain), and functional status (good or poor). Multiple comparisons were conducted using analysis of variance to identify tumor type, which had three groups. All of the data were entered into SPSS® 13.0 (SPSS Inc.) twice, and data were compared to ensure accuracy. Data analyses were performed using SAS software version 9.1.3 (SAS Institute).

Findings

Participant Characteristics

In this study, 144 children with cancer and one of their parents participated. Of the patients, 84 were male and 60 were female; 32 were newly diagnosed, 67 were in remission but continuing on treatment, 9 had relapsed and were on treatment, and 36 had completed treatment. The mean age of the patients was 14.2 years (range = 10–18.9, SD = 2.2 years). The mean duration of their illness since diagnosis for the on-treatment group was 21.2 months (range = 0–160, SD = 27 months). The types of cancer included leukemia (n = 75, 52%), lymphoma (n = 26, 18%), and other solid tumors (n = 43, 30%). The average number of children including the patients per household was 2.68 (range = 1–5, SD = 0.78). The mean age of the mothers was 41.9 (range = 30–54, SD = 4.6 years), and the mean age of the fathers was 45 (range = 32–63, SD = 5.0 years). Most of the parents had at least a high school education. More than 80% of families reported their socioeconomic status as low to medium.

Symptom Clusters

The prevalence of symptoms and distribution of prevalence scores experienced by patients are presented in Table 3. Five clusters identified from the cluster analysis reached the best resolution (pseudo-F = 83.01 and CCC = 10.54) and, therefore, were chosen as the final cluster categories (see Figure 1). The symptoms within each of the five clusters that resulted from the analysis follow in descending order of overall prevalence (see Table 4).

- **Cluster 1:** symptoms related to internal concerns of sensory discomfort and body image (7 items)—dry mouth, itching, diarrhea or loose bowel movement, numbness or tingling or pins-and-needles feeling in hands or feet, changes in skin, feeling nervous, and do not look like myself
- **Cluster 2:** symptoms related to circulatory and respiratory system malfunction (5 items)—shortness of breath, dizziness, swelling of arms or legs, cough, and problems with urination
- **Cluster 3:** fatigue, sleep disturbance, and depression (eight items)—difficulty concentrating or paying attention, difficulty sleeping, lack of energy, feeling drowsy, feeling sad, worrying, feeling irritable, and sweating
- **Cluster 4:** body image (external concern) and eating difficulties (5 items)—weight loss, hair loss, mouth sores, constipation, and difficulty swallowing
- **Cluster 5:** symptoms related to gastrointestinal irritations and pain (5 items)—nausea, vomiting, lack of appetite, pain, and change in the way food tastes

Sensitivity of Clusters

Table 5 lists the relationships among clusters and other demographic characteristics, including disease status, pain, and functional status. The mean scores of each cluster were computed using the sum of the symptoms identified within a cluster. Gender differences were only identified as statistically significant in cluster 5 (side effects related to gastrointestinal irritations and pain), indicating that boys reported statistically higher distress in this cluster than girls ($p < 0.05$). Patients with leukemia experienced more symptom distress in cluster 3 (fatigue, sleep disturbance, and depression) than patients with solid tumors or lymphoma. Patients with pain reported statistically higher distress in all five clusters. To compare

Table 3. Symptom Prevalence and Distress for Pediatric Patients With Cancer

Symptom	Prevalence (%)	Distress[a] (%)
Lack of concentration	41	3
Pain	41	19
Lack of energy	52	15
Cough	31	9
Feeling nervous	10	–
Dry mouth	42	2
Nausea	42	23
Feeling drowsy	47	7
Numbness or tingling in the hands or feet	27	5
Insomnia	31	16
Problems with urination	11	6
Dyspnea	15	5
Diarrhea	34	6
Feeling sad	22	10
Sweating	46	5
Worrying	46	2
Itching	32	10
Lack of appetite	50	15
Dizziness	28	8
Difficulty swallowing	12	31
Feeling irritable	30	9
Vomiting	35	18
Mouth sores	17	28
Change in the way food tastes	28	13
Weight loss	37	11
Hair loss	35	2
Constipation	25	14
Swelling of the arms or legs	16	13
I do not look like myself.	28	20
Skin changes	27	8

N = 144

[a] Percentage who answered quite a bit to very much

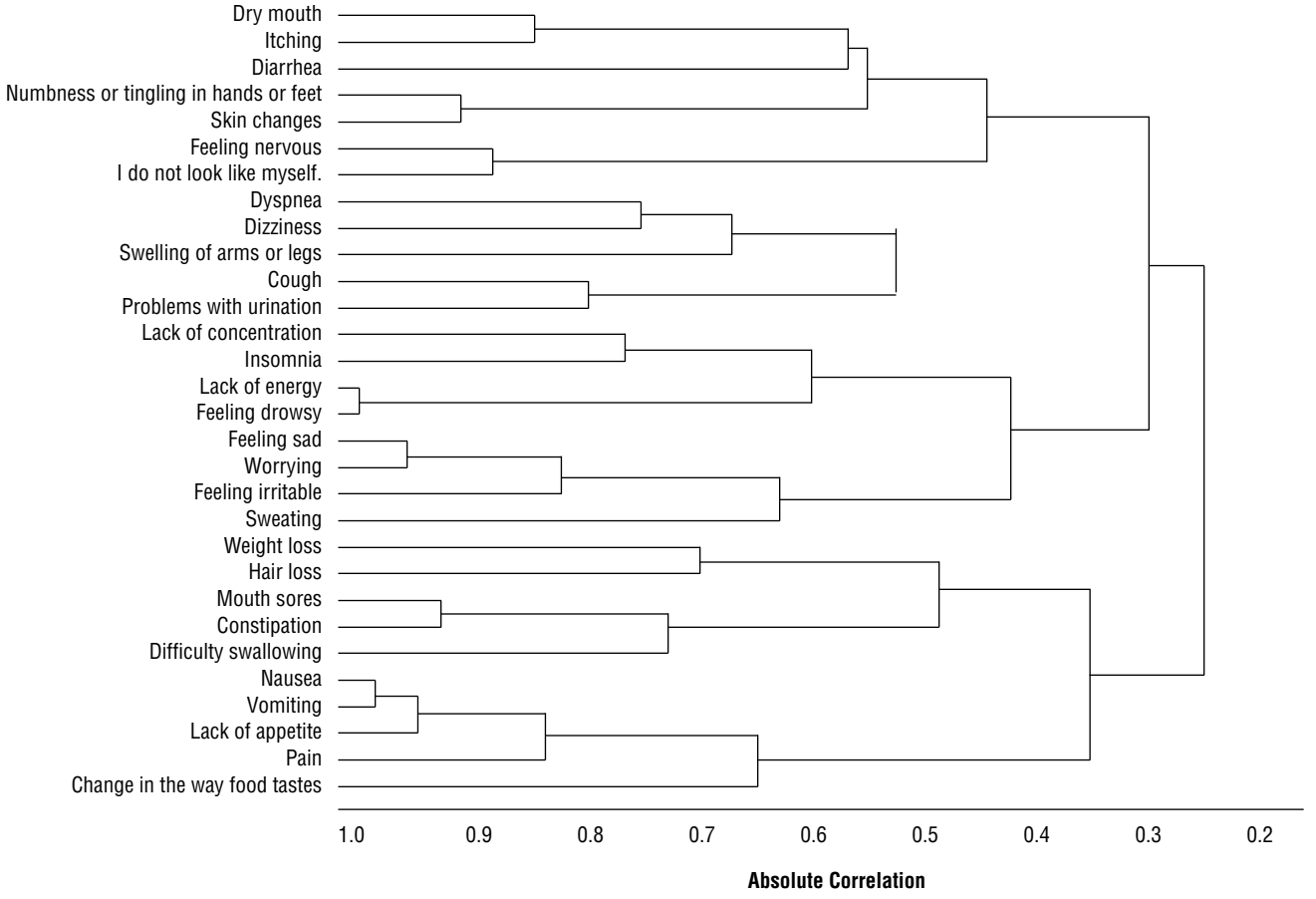

Figure 1. Cluster Tree of Cancer Symptoms for Older Taiwanese Children With Cancer Using Ward's Method

the patients' functional status with the cluster factor, play performance scores were dichotomized into two categories: Category 1 (score 0–7) was considered poor functioning, and catagory 2 (score 8–10) was considered good functioning. Patients with good function reported more side effects related to gastrointestinal irritations and pain (cluster 5, $p < 0.059$); otherwise, functional status was not related to the other clusters.

Discussion

The present study was the first to use an analytic procedure to derive symptom clusters from the self-reported data of pediatric patients with cancer. The concept of symptom clustering is in its infancy (Miaskowski, 2006). Cluster analysis can be used to examine symptoms that patients experience simultaneously. The identification of symptoms that clustered together in older Taiwanese children with cancer in this study may affect clinical symptom assessment and management (e.g., pharmacotherapy) for patients who experience symptoms related to the disease itself or to treatment side effects. For example, symptoms that tend to occur together may be lessened or avoided as a group. Although this study used a new method of examining the grouping of symptoms in pediatric patients with cancer, it is in its early stages; thus, the study results must be viewed with caution. Specifically, the cross-sectional nature of the data collection, especially the presence of only one data point, the heterogeneity of the stage of illness, and the variation of illness duration, should be considered. The stability of the cluster also needs to be examined in a longitudinal study. In addition, the statistical method used in this study was cluster analysis. The decision about the number of clusters for the final solution was based on researcher's judgment, with a variety of indexes to reference but with no consensus criteria at this point.

The current study included all of the symptoms reported by patients, and the data were analyzed with the statistical method of cluster analysis. Different from a previous study that analyzed only symptoms with a prevalence rate higher than 15% (Walsh & Rybicki, 2006), this study entered all of the symptoms for clustering. That strategy avoids the exclusion of symptoms that have lower prevalence (e.g., difficulty swallowing) but still may have some correlations with other symptoms that are more prevalent (e.g., weight loss). This method of including all symptoms is supported by a recent comprehensive literature review that indicated that neither a definitive nor common agreement of how to select symptoms for cluster evaluation has been derived (Barsevick, 2007). Thus, all of the symptoms should be included when clustering the symptoms experienced by patients. Different from exploratory factor analysis, cluster analysis also includes all of the symptoms in the analysis. To date, definitive conclusions regarding the symptoms included in a cluster are still uncertain (Miaskowski & Aouizerat, 2007).

The classification of clustering symptoms should meet the criteria of face validity before it can be linked to clinical relevance. In this study, consistent with Walsh and Rybicki (2006), the clustering of symptoms related to gastrointestinal irritations and pain is not surprising because of the use of opioids, which met the criteria of face validity. The clustering of gastrointestinal irritation and pain can be explained by the medications used to treat pain. According to the research, 33%–66% of patients who take opioids may develop nausea and vomiting (Aparasu, McCoy, Weber, Mair, & Parasuraman, 1999; Moulin et al., 1996). However, pain and constipation were not clustered together in the present study. Constipation is included in cluster 4 along with weight loss, mouth sores, swallowing difficulty, and hair loss. That cluster has face validity because patients with swallowing difficulty may suffer from constipation because of limited fiber intake. Further study is needed to examine the relationship between pain and constipation.

The items that grouped together in cluster 3 (fatigue, sleep disturbance, and depression) are partially consistent with the literature about adults with cancer (Chen & Tseng, 2006; Cleeland et al., 2003) and pediatric oncology literature (Hockenberry & Hooke, 2007). According to the definition of fatigue, it not only includes a physical basis but also psychological issues (Hockenberry-Eaton & Hinds, 2000). However, pain is not within the cluster for reasons unknown. One speculation of the discrepancy between the study finding and the literature may be explained by a Chinese medicine philosophy that is popular in Taiwan. In Taiwanese culture, when a person is sick, the most common description of one's sickness is "there is no *yuan qi* (vitality)." When a person does not feel well or is sick, Chinese food therapy, a practice of healing using natural foods, is very popular in Taiwanese culture. Cluster 3 has face validity from Chinese culture with the emphasis on food. Taiwanese children with cancer who suffer from pain may experience a lack of appetite because of the side effects of their cancer treatment.

The remaining three clusters also have face validity according to the items that clustered together. Validity of all five clusters in the current study also is demonstrated by pain status (patients with pain reported higher distress than patients without pain). Functional status approached significance in relation to cluster 5. Patients with good functional status reported more distress in cluster 5 than patients with poor functional status, which was unexpected. As mentioned in the methods section, the PPSC was used to measure functional status in the present study and was a good measure in previous studies (Lansky et al., 1985; Yeh & Hung, 2003); however, patients with good play performance reporting higher distress is questionable. That disagreement may be explained by the PPSC being reported by parent proxy rather than the patient. Parent-child proxy had more agreement in objective measures (e.g., physical functioning) than subjective measures (psychological functioning) (Chang & Yeh, 2005). Symptom assessments in the present study included items to assess psychological symptoms, so the validity of PPSC proxy report should be interpreted with caution. Future studies need to examine the validity of the PPSC to determine whether it is a good measure of functional status for pediatric patients with cancer.

Clusters identified in the present study may be important for clinical symptom assessment. Walsh and Rybicki (2006) suggested that symptoms within a cluster can be assessed as predictors (e.g., the management of a specific symptom), and then another symptom can serve as an outcome measure. For example, the specific symptom management such as relief of nausea should be assessed, followed by lack of appetite as an outcome variable. Such clusters still need further study to determine what kind of symptoms they constitute (Miaskowski & Aouizerat, 2007).

Table 4. Symptom Clusters Summary Experienced by Older Taiwanese Children With Cancer

Cluster	Symptoms Included
1. Symptoms related to sensory discomfort and body image (internal concerns)	Dry mouth Itching Diarrhea or loose bowel movement Numbness or tingling or pins-and-needles feeling in the hands or feet Changes in skin Feeling of being nervous I do not look like myself.
2. Symptoms related to circulatory and respiratory system malfunction	Shortness of breath Dizziness Swelling of arms or legs Cough Problems with urination
3. Fatigue, sleep disturbance, and depression	Difficulty concentrating or paying attention Difficulty sleeping Lack of energy Feeling of being drowsy Feelings of sadness Worrying Feeling of being irritable Sweating
4. Body image (external concern) and eating difficulties	Weight loss Hair loss Mouth sores Constipation or feeling uncomfortable because bowel movements are less frequent Difficulty swallowing
5. Symptoms related to gastrointestinal irritations and pain	Nausea Vomiting Lack of appetite Pain Changes in the way of food tastes

Implications for Research and Practice

Study of symptom clustering is in its early stage because of several unsolved issues including the number of symptoms and what kind of symptoms can or should be within one cluster, the relationships within and between clusters, and whether a single symptom or multidimensional scale should be used in data collection. This is the first study that used a statistical procedure to derive symptom clusters experienced by pediatric patients. Knowledge developed in this study can provide a starting point for investigation into the stability of clusters with different disease stages, different populations, and over time. Empirical studies are needed to establish the validity of symptom clusters with other outcome variables such as quality of life and func-

Table 5. Descriptive Characteristics and Differences of Five Symptom Clusters for Gender, Disease and Treatment Characteristics, Pain Status, and Functional Status

	Cluster 1			Cluster 2			Cluster 3			Cluster 4			Cluster 5		
Group Variable	$\bar{X}$	SD	t	$\bar{X}$	SD	t	$\bar{X}$	SD	t	$\bar{X}$	SD	t	$\bar{X}$	SD	t
Gender			−0.18			0.87			0.20			1.18			2.12*
Boy (n = 84)	8.98	1.86		6.08	1.35		11.18	2.52		6.37	1.42		7.21	1.80	
Girl (n = 60)	9.03	1.85		5.90	1.10		11.10	2.15		6.12	1.15		6.62	1.57	
Tumor type[a]			–			–			–			–			–
Leukemia (n = 75)	9.24	1.99		6.13	1.35		11.61	2.37		6.43	1.46		7.11	1.74	
Lymphoma (n = 26)	8.73	1.80		5.81	1.13		10.50	2.55		5.96	1.11		6.42	1.68	
Solid tumor (n = 43)	8.74	1.85		5.91	1.13		10.72	2.12		6.16	1.13		7.05	1.70	
Treatment			1.67			1.43			−0.51			3.23**			3.92***
On (n = 108)	9.15	1.81		6.09	1.28		11.08	2.27		6.44	1.37		7.25	1.73	
Off (n = 36)	8.56	1.92		5.75	1.13		11.33	2.66		5.75	1.00		6.11	1.43	
Pain status			−4.63***			−2.95**			−4.36***			−3.09**			−10.37***
No pain (n = 85)	8.41	1.43		5.74	0.99		10.47	2.22		5.98	1.11		6.02	1.30	
Pain (n = 59)	9.85	2.06		6.39	1.47		12.12	2.24		6.68	1.48		8.32	1.32	
Functional status[b]			−0.54			−1.12			−0.40			1.61			2.08
Good (n = 95)	8.94	1.75		5.92	1.12		11.08	2.12		6.37	1.35		7.19	1.71	
Poor (n = 48)	9.13	2.07		6.19	1.48		11.27	2.83		6.00	1.19		6.56	1.70	

N = 144

* p < 0.05; ** p < 0.01; *** p < 0.001

[a] F test values for clusters 1, 2, 3, 4, and 5 were 1.32, 0.85, 3.22*, 1.39, and 1.59, respectively.

[b] One participant did not respond.

tional status. Combining subjective (self-reported) and objective (biomarker) data can help researchers examine the connection between subjective and objective factors and increase the understanding of symptom clusters.

Clinical implications of this study are limited by the cross-sectional nature of the data. However, clinicians have to be aware that patients experience multiple symptoms simultaneously. When a patient experiences highly prevalent symptoms within a cluster, clinicians need to assess for other symptoms within a cluster.

Conclusion

Five symptom clusters were identified in older Taiwanese children with cancer. The study findings are consistent with existing literature that fatigue, sleep, and depression are clustered together. However, pain was not clustered with fatigue, sleep, and depression, but with symptoms related to gastrointestinal irritation. The findings from the present study need to be replicated before symptoms within clusters can be recognized as definitive. The findings can provide a guideline for clinical symptom assessment and management.

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