ORIGINAL ARTICLE ████████

Symptom characteristics and clustering in children and adolescents undergoing or being off cancer chemotherapy

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Summary

Purpose: *To describe the prevalence of symptoms, their characteristics and distress and to define symptom clusters occurring among children and adolescents receiving chemotherapy or having completed their treatment.*

Methods: *Data were collected using the Memorial Symptom Assessment Scale in patients receiving chemotherapy and those who had completed it. Demographic data were collected using a questionnaire developed by the researchers, whilst information over the disease status and treatment regimens was obtained from medical records. Cluster analysis techniques were used to identify symptom clusters.*

Results: *The most common symptoms were lack of appetite, feeling nervous and lack of energy in children/adolescents who were receiving chemotherapy. Feeling nervous, feeling sad and lack of energy were the most common symp-*

toms in children/adolescents who had completed chemotherapy. The most distressing symptoms were nausea, hair loss and vomiting in patients aged 10-18 years, being on treatment. Five symptom clusters were identified in children and adolescents who were both undergoing or being off chemotherapy.

Conclusion: *Children/adolescents receiving chemotherapy experience multiple symptoms that persist over time. Symptom distress is relatively higher among children/adolescents undergoing chemotherapy. Knowledge from this study can provide a starting point to investigate the stability of symptom clusters in different age groups and over various periods of time.*

Key words: chemotherapy, Memorial Symptom Assessment Scale, pediatric cancers, symptom clusters, symptom prevalence

Introduction

Children with cancer experience multiple symptoms as a result of their disease and/or its treatment. Only a few studies have been published concerning multiple symptoms experienced by pediatric cancer patients [1,2]. Because experiences of pediatric cancer patients differ greatly from those of adults, a need exists to identify and characterize the many symptoms developing in the pediatric oncology population [3]. Severe symptom distress may delay scheduled treatments, the effectiveness of treatment protocols, and the rehabilitation process. Clinically, the most common severe symptoms experienced by children and/or adolescents with cancer include pain, nausea, vomiting, fatigue, drowsiness, and alopecia [1,4-7]. Professional oncology care providers are responsible for assessing and relieving multiple symptoms. Patients undergoing cancer chemotherapy

seldom present with a single symptom but usually suffer from multiple symptoms and distress concurrently. For this reason, symptom assessment needs multidimensional scales. Hedström et al. [4] discovered that the most common causes of distress in a group of 121 children with cancer were treatment-related pain, nausea, and fatigue. Collins et al. [1] described the most common physical symptoms (prevalence >35%) in a group of 160 children with cancer as lack of energy, pain, drowsiness, nausea, cough, and lack of appetite. Yeh et al. [2] found lack of concentration and pain to be concomitant with this reported lack of energy.

Recent studies related to symptom management in adults have focused on symptom clusters, but this is still in its infancy [8-10]. Research is needed to identify the occurrence of symptom clusters in children and adolescents with cancer [8]. To date, only few studies have addressed the symptom clusters [2,9]. In addition, only

empirical studies have provided evidence or foundational knowledge of the symptom clusters experienced by children with cancer; therefore, this new area should be explored so that the acquired knowledge to be used for symptom management [2,9].

The purpose of this study was to use an analytic procedure to define symptom clusters occurring in pediatric cancer patients, determine the prevalence of symptoms, their characteristics, and to compare children currently receiving anticancer chemotherapy with children who had completed treatment.

Methods

For the purpose of this analysis, only the baseline data of children and adolescents aged 10-18 years were used to describe the prevalence of symptoms. Patients were eligible for the study if they had been diagnosed with cancer, were chronologically and cognitively aged 10-18 years, spoke Turkish, their health was stable enough for them to participate in the study, being treated only with chemotherapy, or having had completed their treatment at least one month before and were willing to participate in the study. Patients were recruited from 4 medical centers in western Turkey. Among 182 patients aged 10-18 years who were approached, 7 declined participation, 5 had cognitive disabilities, 2 were receiving radiotherapy and 4 were

not in stable health status. In total, 164 patients and one parent for each patient were recruited for data analysis. The response rate was 90%.

Procedures

The present study was a secondary analysis of data collected from a reliability and validity study [10] conducted at 4 large teaching medical centers in western Turkey. Data collection from the primary study started after receiving institutional review board approval. Patients and parents were provided with information about the study, and verbal consent was obtained. After parental consent and patient assent were obtained, participants were given the relevant questionnaires (Figures 1 and 2). Most families returned the questionnaires during their stay at the hospital or clinic. If the questionnaire was not returned before the patient or parent left the hospital follow-up phone calls (as many as two) were made if the data had not arrived by the end of the following week. Of 164 patients, only 4 patients and their parents returned their questionnaires when they came back to hospital. Demographic and clinical data were collected from the participants' medical records.

Measures

Data were collected using the Memorial Symptom Assessment Scale (MSAS 10-18) adapted by Col-
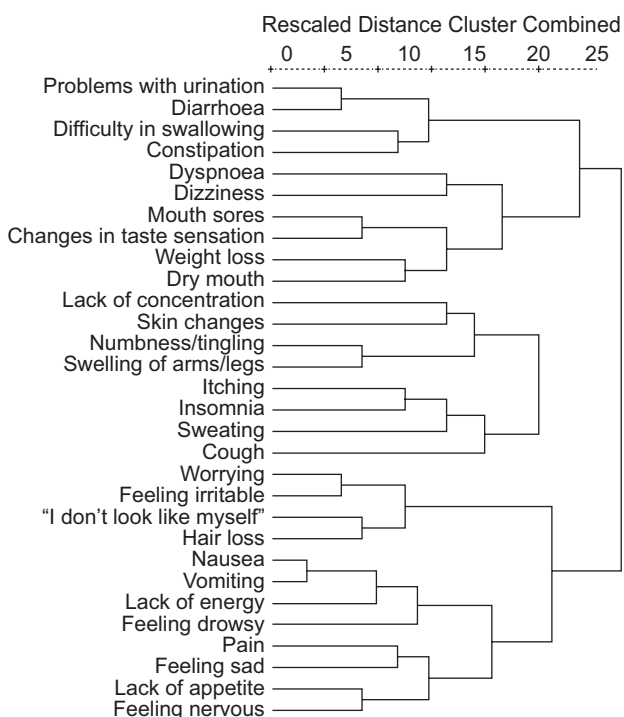

Figure 1. Cluster tree of symptoms of children/adolescents being on chemotherapy.
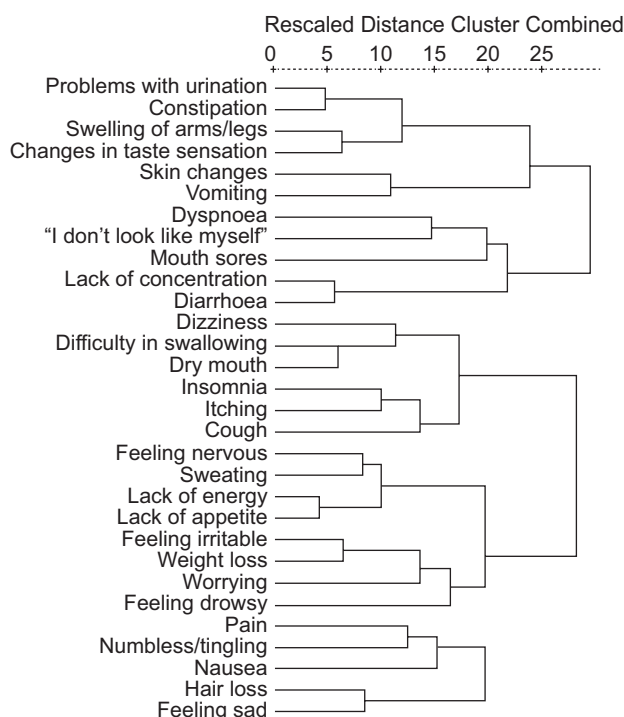

Figure 2. Cluster tree of symptoms of children/adolescents being off chemotherapy.

lins et al. for use in children [1]. The MSAS 10-18 is a patient-rated instrument used to assess patients' experiences during the previous week. The first of its 2 parts measures the occurrence of each symptom and has a yes-or-no format, whereas the second part consists of Likert-type scales of 3 dimensions-frequency, severity, and distress. Frequency and severity are rated on a separate 4-point Likert scale from 1 (almost never) to 4 (almost always). Distress is scored as 1 (not at all) to 4 (very much). Twenty-two symptoms were evaluated for each of the 3 dimensions; frequency was not relevant for 8 symptoms (e.g., weight loss), and for these only severity and distress were assessed [1].

The reliability and validity of the scale had been tested by Atay et al. [10] for use in Turkish population and demonstrated a Cronbach's alpha coefficient of 0.93 for the scale in general, 0.92 for the physical subscale, 0.93 for the psychological subscale, and 0.93 for the global distress index.

Data analysis

Methodological issues in cluster research included lack of consensus on cluster definition, instruments, study design, and statistical analyses used to identify clusters [11,12]. 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 distressing symptoms. The Ward's method [13] with Euclidean distance as the similarity measure was used to establish the number of clusters (beginning with each symptom). Cluster analysis also may be used to generate diagrams that are helpful for visualizing the clustering of symptoms [13]. All of the data were entered into SPSS 15.0 (SPSS Inc.) twice, and data were compared to ensure accuracy.

Results

Description of sample

In this study, 164 children/adolescents (79 boys and 85 girls) with cancer and one of their parents participated. Ninety-four were on chemotherapy and 70 had completed treatment. Their mean age was 13.9±2.1 years. The types of cancer included leukemia (n = 68; 41.5%), lymphoma (n = 32; 19.5%), and a variety of solid tumors (n=44; 26.8%; Table 1).

Symptom prevalence and distress

The prevalence of symptoms and distribution of prevalence scores experienced by the patients are presented in Table 2. Most commonly occurring symptoms in children being on treatment were lack of appetite and lack of energy. Nevertheless, feeling nervous was reported with the highest prevalence both in patients receiving chemotherapy and those who had completed treatment (Table 2).

The symptoms associated with high distress ("quite a bit" to "very much") in more than 20% of the children/adolescents receiving chemotherapy were nausea and dry mouth (Table 2).

Symptom clusters

Symptom clusters were identified from the cluster analysis in patients being on and off treatment are shown in Table 3.

Five symptom clusters were identified in patients receiving chemotherapy:
1. Cluster 1: problems with urination, diarrhea, difficulty in swallowing, constipation.
2. Cluster 2: dyspnoea, dizziness, mouth sores, changes in taste sensation, weight loss, dry mouth.
3. Cluster 3: lack of concentration, skin changes, numbness/tingling, swelling of arms/legs, itching, insomnia, sweating, cough.
4. Cluster 4: worrying, feeling irritable, "I don't look like myself", hair loss.
5. Cluster 5: nausea, vomiting, lack of energy, feeling

Table 1. Characteristics of children and adolescents with cancer (n=164)

Characteristics	Patients, n	%
Age (years)		
mean (±SD)	13.9±2.1	
10-12	46	28
13-15	72	44
16-18	46	28
Gender		
Female	79	48.2
Male	85	51.8
Diagnosis		
Leukemias	68	41.5
Lymphomas	32	19.5
Bone tumors	20	12.1
Solid tumors	44	26.8
Treatment		
On chemotherapy	94	57.3
On follow-up	70	24.7
Outpatients	72	43.9
Inpatients	92	56.1

Table 2. Prevalence and characteristics of symptoms determined by the MSAS

Symptoms	All patients		On treatment		Off treatment	
	Overall prevalence %	Distress QB-V* %[a]	Overall prevalence %	Distress QB-VM* %[a]	Overall prevalence %	Distress QB-VM* %[a]
Lack of appetite	**63.4**	9.8	**75.5**	13.9	47.1	4.3
Nausea	**55.5**	**40.7**	70.2	**30.9**	35.7	5.8
Hair loss	40.2	**15.8**	52.1	**20.2**	24.3	**10**
Feeling nervous	**71.3**	13	**72.3**	12.8	**70.0**	**14.3**
Lack of energy	62.2	7.9	**72.3**	10.6	**48.6**	4.1
Vomiting	34.8	14.1	45.7	**19.4**	20.0	5.7
Dry mouth	32.3	**21.3**	38.3	4.3	24.3	2.8
Pain	51.2	9.7	57.4	11.7	42.9	8.1
Feeling drowsy	53.0	7.9	59.6	8.5	44.3	5.8
Feeling sad	54.9	12.2	59.6	12.8	**48.6**	**11.4**
Sweating	51.2	9.7	42.6	11.7	7.1	–
Weight loss	31.7	2.4	37.2	3.2	24.3	1.4
Worrying	32.9	6.7	37.2	7.4	27.1	5.7
Mouth sores	23.2	6.1	26.6	5.3	18.6	7.1
Cough	32.9	13.4	35.1	4.3	30.0	–
Dizziness	23.2	4.3	24.5	5.3	21.4	2.9
Changes in taste sensation	23.8	3.7	33	3.3	12.9	4.3
Skin changes	25.6	4.2	33.0	6.4	15.7	1.4
Feeling irritable	26.2	6.1	28.7	7.5	22.9	4.3
Numbness/tingling	29.9	6.0	30.9	3.2	28.6	10
Constipation	11.0	3.0	19.1	5.3	–	–
"I don't look like myself"	31.7	13.4	45.7	20.2	12.9	4.3
Insomnia	25.0	9.1	26.6	9.6	22.9	8.6
Diarrhoea	15.9	3.0	14.9	2.1	17.1	4.3
Itching	20.1	3.0	19.1	3.2	13	1.9
Lack of concentration	23.2	4.9	25.5	3.2	20	10
Dyspnoea	12.8	1.8	14.9	1.1	10.0	2.9
Difficulty in swallowing	11.0	5.5	10.6	4.3	11.4	2.9
Problems with urination	5.5	1.2	5.3	1.1	5.7	1.4
Swelling of arms/legs	11.6	2.4	14.9	4.3	5.6	1.9

*Percentage distress defined as "quite a bit to very much". Bold numbers indicate the highest prevalence. The remaining numbers indicate a >20% prevalence. MSAS: Memorial Symptom Assessment Scale (10-18)

drowsy, pain, feeling sad, lack of appetite, feeling nervous (Table 3, Figure 1).

Also, 5 symptom clusters were observed in patients being off treatment:
1. Cluster 1: problems with urination, constipation, swelling of arms/legs, changes in taste sensation, skin changes, vomiting.
2. Cluster 2: dyspnoea, "I don't look like myself", mouth sores, lack of concentration, diarrhea.
3. Cluster 3: dizziness, difficulty in swallowing, dry mouth, insomnia, itching, cough.
4. Cluster 4: feeling nervous, sweating, lack of energy, lack of appetite, feeling irritable, weight loss, worrying, feeling drowsy.
5. Cluster 5: pain, numbness/tingling, nausea, hair loss, feeling sad (Table 3, Figure 2).

Discussion

Symptoms experienced by children or adolescents while on or off chemotherapy constitute limited evidence-based information. In the current study the most prevalent symptoms were feeling nervous, lack of appetite and nausea. Clinically, the most common severe symptoms experienced by adolescent cancer patients include pain, nausea, vomiting, fatigue, drowsiness, lack of appetite and alopecia [1,2]. Hedström et al. [14,15], using structured telephone interviews 4-8 weeks after diagnosis or disease relapse, found that the most common symptoms included alopecia, weight loss/gain, fatigue and mucositis. Enskär and von Essen [16,17] used the Life Situation Scale for Adolescents (LSS-A) with cancer to investigate the experienced

Table 3. Symptom clusters experienced by children/adolescents with cancer

On treatment	Off treatment
Problems with urination	Problems with urination
Diarrhoea	Constipation
Difficulty in swallowing	Swelling of arms/legs
Constipation	Changes in taste sensation
	Skin changes
	Vomiting
Dyspnoea	Dyspnoea
Dizziness	"I don't look like myself"
Mouth sores	Mouth sores
Changes in taste sensation	Lack of concentration
Weight loss	Diarrhoea
Dry mouth	
Lack of concentration	Dizziness
Skin changes	Difficulty swallowing
Numbness/tingling	Dry mouth
Swelling of arms/legs	Insomnia
Itching	Itching
Insomnia	Cough
Sweating	
Cough	Feeling nervous
Worrying	Sweating
Feeling irritable	Lack of energy
"I don't look like myself"	Lack of appetite
Hair loss	Feeling irritable
	Weight loss
	Worrying
	Feeling drowsy
Nausea	Pain
Vomiting	Numbness/tingling
Lack of energy	Nausea
Feeling drowsy	Hair loss
Pain	Feeling sad
Feeling sad	
Lack of appetite	
Feeling nervous	

symptoms, and found that symptoms may be predominantly physical during active chemotherapy in the early phases of treatment. These and the present study showed some differences in the symptoms experienced which could be explained by the use of different scales and cultural dissimilarities. Lack of appetite accompanied by persistent nausea and vomiting suggests that effective treatment strategies for the management of these symptoms are often lacking in pediatric oncology.

As for children being off treatment, symptoms experienced were psychological (feeling nervous, lack of energy and feeling sad). Enskär and Essen [17] described the use of a symptom scale they developed for children with cancer and found that two-thirds of the subjects experienced physical symptoms. Children undergoing chemotherapy were significantly more likely to report their concern about hair loss (47 vs. 10%), nausea (47 vs. 14%), and fatigue (65 vs. 43%) compared with children who had completed treatment. Baggot et al. [18] stated that symptom occurrence rates were highest in the week following chemotherapy administration. In children not receiving chemotherapy, symptoms prior to chemotherapy administration were feeling sad (43.8%), irritability (41.5%), and worrying (40.6%).

The results of this study confirm earlier reports and show that children receiving chemotherapy report more physical problems than a comparative group with children who had completed chemotherapy.

In clinical practice, patients being on treatment seldom complain for one symptom and usually suffer from multiple symptoms simultaneously. A number of studies have evaluated the prevalence of multiple symptoms in children with cancer, and assessment of distressing symptoms is very important for these patients. The current study showed that patients who had received chemotherapy recently had significantly more symptoms distress than those without chemotherapy. However, nausea and hair loss were amongst the symptoms causing the most distressing condition in those receiving treatment. In contrast, Yeh et al. [2] reported that physical symptoms such as difficulty in swallowing, mouth sores and nausea caused most distress in their patient sample; these findings were demonstrated in a more recent study by the same group of researchers [19] which showed that Taiwanese adolescents with cancer were more likely to report somatic than psychological problems. Enskär et al. [17] reported, however, that fatigue, pain, changes in weight, eating problems and hair loss caused both physical and psychological distress in their sample of adolescent cancer patients. Collins et al. [1] showed that difficulty in swallowing, hair loss and insomnia caused most distress. A semi-structured telephone survey of 56 newly diagnosed cancer patients between 13 and 18 years of age by Hedström et al. [14] found that hair loss, weight loss, fatigue and mucositis caused most distress 4-8 weeks after diagnosis. Enskär and Essen [16] published that more than half of the adolescents and young adults undergoing treatment reported problems such as pain, weight change, eating problems and hair loss, compared to 12-35% among those being off treatment. However, psychological distress was equally prevalent in both groups. In previous studies, adolescents have reported confinement [20-22] as well as a great number of the adolescents and young adults reported thinking about having cancer and wondering why, as well as worrying about the future. These findings support previous results demonstrating that anxiety and uncertainty about the future are frequent problems among children and adolescents [20-22].

Such findings indicate the importance for those working with cancer in adolescents of being alert to the fact that the treatment period is connected with more problems related to physical distress than the period after treatment, whereas aspects of psychological distress are equally prevalent during both time periods. Children receiving chemotherapy and those who had completed treatment may not provide true differences between these 2 phases (on/off treatment), since the same children were not studied during both phases. To draw firm comparisons about children's experiences being on and off cancer treatment a longitudinal study is necessary.

Associations between chemotherapy and symptom clusters

The present study used an analytic procedure to determine symptom clusters from the self-reported data of pediatric patients. Our study included all of the symptoms reported by the patients, and the data were analysed with the statistical method of cluster analysis. This strategy avoids the exclusion of symptoms that have lower prevalence (e.g., problems with urination) but still may have some correlations with other symptoms that are more prevalent (e.g., vomiting). This method of including all symptoms is supported by a recent comprehensive literature review which indicated that neither a definitive nor a common agreement of how to select symptoms for cluster evaluation has been reached [23]. Thus, all of the symptoms should be included when clustering the symptoms experienced by the patients. To date, definitive conclusions regarding the symptoms included in a cluster are uncertain [8]. The decision about the number of clusters was based on the researcher's judgment, with a variety of indexes to reference but with no consensus criteria at this point. Our findings support the definition of the symptom cluster proposed by Dodd et al. [24] that consists of 3 or more symptoms related to each other and occurring together.

Most of the symptom cluster studies [25-29] found nausea and vomiting in the same symptom cluster. Chen and Lin [30] performed a confirming factor analysis on the M.D. Anderson Symptom Inventory and found lack of appetite, nausea and vomiting in the same symptom cluster. In the current study, nausea and vomiting fell into the same cluster in patients receiving chemotherapy.

Hockenberry and Hooke [28] defined fatigue, sleep disturbances, and pain as symptom cluster experienced by children and adolescents during chemotherapy. Hockenberry et al. [9] characterized fatigue, sleep disturbances, nausea and vomiting as symptom cluster experienced by children and adolescents receiving cis-

platin, doxorubicin, or ifosfamide chemotherapy. Although correlations among the symptoms (fatigue, sleep disturbances, nausea and vomiting) were weak, when fatigue and sleep disturbances were clustered they created a significant impact on depressive symptoms and behavior changes in adolescents one week after chemotherapy. Yeh et al. [2] found nausea, vomiting, lack of appetite, pain, and changes in food tasting in the same cluster. The items grouped together in cluster 5 (fatigue, sleep disturbances, depression etc.) were partially consistent with the literature about adults [24,25] and pediatric cancer patients [2,27].

In the group receiving chemotherapy, excretory systems' symptoms (diarrhea or loose bowel movement, problems with urination, constipation) and eating difficulties-related symptoms (difficulty in swallowing) composed a cluster in the present study. In patients who had completed their treatment similar symptoms (problems with urination, constipation, swelling of arms/legs, changes in taste sensation, skin changes, vomiting) also composed a cluster.

Worrying, feeling irritable, "I don't look like myself" and hair loss formed a cluster in patients receiving chemotherapy. Similarly, in children being off treatment, feeling nervous, feeling irritable, and worrying fell into the same cluster, whilst Ivanova et al. [28] reported that emotional stress and sadness formed a separate cluster in their analysis. Gleason et al. [29] identified a symptom cluster called "psychological status" which included sadness, depression and anxiety in their study on patients newly diagnosed with brain tumors, although again, this study was conducted on adult patients. Chen and Lin [30] also found a psychological symptom cluster using the M.D. Anderson Symptom Inventory which included distress and sadness. There is general agreement in the literature that psychological symptoms form a distinctive cluster, although the use of different symptom assessment scales in many of the studies means that these symptoms and the clusters identified are not easily compared since the terminology used is not consistent.

Weight loss, mouth sores, changes in taste sensation and dry mouth composed another symptom cluster. Other symptoms included in this cluster might be caused by weight loss. Further studies are needed to examine the relationship among symptoms. However, dyspnoea and dizziness are not within the cluster for unknown reasons, yet in the off treatment group these symptoms were seen in different symptom clusters.

In this study, another symptom cluster consisted of skin problems (skin changes, swelling of arms/legs, itching and sweating). However, lack of concentration, numbness/tingling, insomnia and cough were not in the

cluster for unknown reasons. In the off treatment group, swelling of arms/legs, itching and sweating were clustered with different symptoms. Yeh et al. [2] also found itching and skin changes to be in the same cluster, a finding similar to the present study.

To date, definitive conclusions regarding the symptoms included in a cluster are still uncertain [31, 32]. Disease-related factors influencing the symptom experiences in children with cancer include the type and stage of cancer, time since diagnosis, length of treatment, and type of chemotherapy administered. There is no common agreement at this time regarding the basis or criteria for selecting symptoms to be evaluated for clustering. Further exploration of relationships among related symptoms will provide a foundation for developing future interventions for symptom distress experienced by children and adolescents with cancer.

Conclusion

The present study demonstrated that children and adolescents undergoing chemotherapy for their cancer or being off treatment experience a wide variety of symptoms. Whilst some of these symptoms are related to the disease process, many can also be attributed to the treatment itself. Nurses should have a better understanding of these symptoms so that they can play a more significant role in symptom assessment and management in younger patients. Symptom clusters clearly have the capacity to influence disease progression, patient adherence, and the outcomes of chemotherapy, and may also affect the functional status and quality of life in children and adolescents affected by cancer. Investigating comparable dimensions of a symptom cluster within the same timeframe using analogous instrument scaling methods must continue to be an important research focus for future investigation of symptom clusters experienced during treatment for childhood cancer. In the meantime, it is hoped that the findings of this study can help raise awareness of their complexity in cancer patients at every age and can provide a guideline for clinical symptom assessment and management.

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