Symptom Clusters That Included Gastrointestinal Symptoms Among Children Receiving Cancer Treatments: A Scoping Review

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PROBLEM IDENTIFICATION: Composition and measurement of the gastrointestinal (GI) symptom cluster (SC) has been inconsistent; therefore, a gap exists in understanding of the GI SC. The purpose of this study was to synthesize findings from prior studies to better understand the GI SC and accompanying non-GI symptoms in children receiving cancer treatment.

LITERATURE SEARCH: PubMed®, Embase®, CINAHL®, Scopus®, and PsycINFO® databases were searched through February 2022. Of 661 articles identified, 8 met inclusion criteria.

DATA EVALUATION: A standardized investigator-developed form was used to extract data from eligible studies, including study and sample characteristics, analytic procedure, SCs that included GI symptoms, and influencing factors.

SYNTHESIS: The 12 most frequently reported GI and accompanying non-GI symptoms were identified across 20 SCs. Phi correlation coefficients were calculated as indicators of strength of association between each pair of co-occurring symptoms within an SC.

IMPLICATIONS FOR RESEARCH: Future studies should develop and test tools to comprehensively assess GI and accompanying non-GI symptoms and interventions that target shared underlying mechanisms.

KEYWORDS child; pediatric; cancer; chemotherapy; symptom; gastrointestinal tract

***ONF, 50*(3), 381–395.**

DOI 10.1188/23.ONF.381-395

Children diagnosed with cancer experience symptoms that result from their cancer and its treatment (Leahy et al., 2018). In addition, children commonly experience multiple linked symptoms simultaneously—that is, symptom clusters (referred to hereafter as "clusters") (Collins et al., 2000; Dodd et al., 2001). Findings of prior studies indicate that children reported between 1.7 and 12.7 symptoms during the active treatment phase of their illness (Baggott et al., 2011; Huijer et al., 2013; Kamkhoad et al., 2019). Synergies between co-occurring symptoms can increase children's symptom burden by generating additional symptoms (e.g., pain and disturbed sleep causing fatigue) (Hockenberry & Hooke, 2007).

Various approaches have been used to identify clusters among children with cancer including a priori (focused assessment of specific symptoms known to be prevalent in a particular clinical population) or de novo (assessment of a broader range of symptoms to identify clusters) approaches (Miaskowski, 2016). Most studies used the de novo approach to assess symptoms and applied statistical techniques (Atay et al., 2012; Baggott et al., 2012; Yeh et al., 2008) to identify clusters. The number of resulting clusters in prior studies has ranged from 1 to 10, with inconsistent labeling across studies of clusters comprised of similar symptoms (Baggott et al., 2012; Williams et al., 2012; Yeh et al., 2008). For example, the mood disturbance cluster consists of difficulty concentrating, feeling nervous, feeling sad, worrying, and feeling irritable (Baggott et al., 2012), and the fatigue, sleep disturbance, and depression cluster includes difficulty concentrating, difficulty sleeping, fatigue,

feeling drowsy, feeling sad, worrying, feeling irritable, and sweating (Yeh et al., 2008). Despite the noted inconsistencies, information about clusters provides insight into underlying mechanisms and, therefore, potential intervention targets (Kwekkeboom, 2016).

Gastrointestinal Symptoms Among Children With Cancer

Gastrointestinal (GI) symptoms are the most common symptoms reported by children with cancer or their proxies (Johnston et al., 2018; Linder et al., 2018). In this scoping review, the term "GI symptoms" refers to symptoms directly related to GI tract structures and functions, including dry mouth, mouth sores, difficulty swallowing, sore throat, jaw pain, nausea, vomiting, lack of appetite, changes in how foods taste and feel in the mouth, weight loss, diarrhea, and constipation (Collins et al., 2000; Williams et al., 2012). Together, these symptoms contribute to difficulty with eating, leading to undernourishment, which could contribute to poorer clinical outcomes (Green et al., 2010). Loeffen et al. (2015) found that children with undernourishment at three months after diagnosis had significantly higher rates of febrile neutropenia during the first year following their cancer diagnosis and poorer survival rates.

Prior studies identifying clusters among children being treated for cancer found GI symptoms in most clusters. However, the findings from these studies have been inconsistent. For example, Li et al. (2020) found a cluster with only GI symptoms and named it "the GI cluster," and some studies found that non-GI symptoms, such as sweating (Baggott et al., 2012), clustered with GI symptoms. Mixed results regarding GI cluster components could hinder the development and testing of interventions to control GI symptoms and overall symptom burden. Synthesis of findings from prior studies of clusters is needed to better understand the GI cluster and accompanying non-GI symptoms in children receiving cancer treatment.

To address this need, the current authors performed a systematic scoping review to map (providing access to user-friendly summaries of the included studies [Miake-Lye et al., 2016]) research of GI clusters in children aged 18 years or younger and receiving treatment for pediatric cancer to identify (a) GI symptoms that consistently cluster and (b) non-GI symptoms that regularly accompany GI symptoms. This review will inform development of comprehensive tools to assess GI symptoms and common accompanying non-GI symptoms, and their responsiveness to existing and novel approaches to managing GI clusters in children during cancer treatment in the future.

The research questions are as follows:

- What methods were used to assess children's symptoms and identify clusters?
- What clusters with GI symptoms were found, and what were the clusters named?
- What demographic, clinical, and environmental factors contributed to children's risk of clusters that included GI symptoms?

Methods

The scoping review was guided by the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) extension for scoping reviews (Tricco et al., 2018).

Search and Data Sources

The search strategy was developed in consultation with a health sciences librarian. Databases searched were PubMed®, Embase®, CINAHL®, Scopus®, and PsycINFO® through February 2022. Relevant studies were identified based on Medical Subject Headings (MeSH) terms, and other search terms included synonyms and related terms for the following four key concepts: child, cancer, symptoms, and clusters. Reference lists for studies identified through computerized database searches were hand searched to find additional studies that may be eligible for inclusion in the scoping review.

Eligibility Criteria

Studies were eligible for recruitment in this scoping review if they were (a) peer-reviewed, data-based studies (research studies that involve data collected from study participants) identifying clusters that included GI symptoms for children (aged 18 years or younger) diagnosed with cancer undergoing cancer treatment and (b) published in English. Reviews, study protocols, and conference abstracts were excluded from this review.

Data Extraction Process

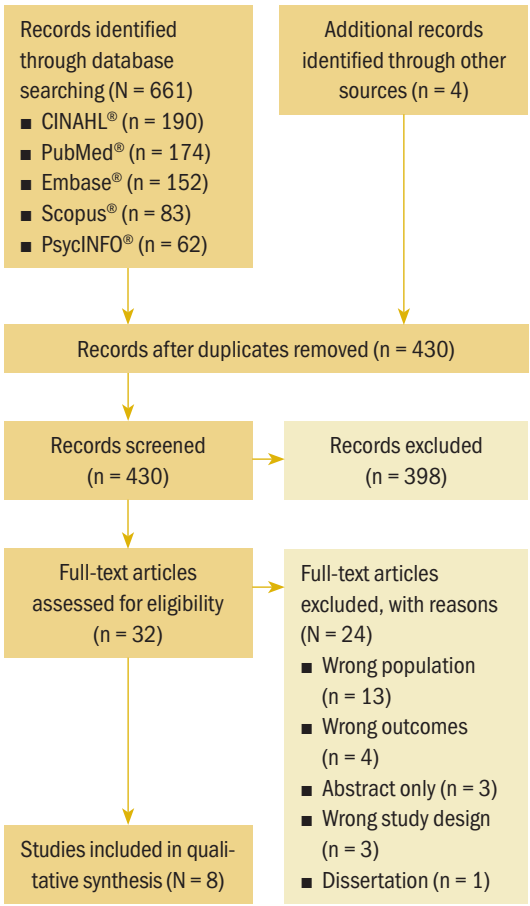
All articles identified from the electronic databases search were screened for eligibility. Two authors (D.K. and R.P.) independently screened the titles and abstracts of all identified articles, reviewed their results, and came to an agreement on studies eligible for full-text review and possible inclusion in the review. Then, these two authors reviewed the full texts and determined study eligibility. After conversation, the reviewers achieved 100% agreement about

which identified studies were eligible for inclusion. They drafted and piloted an investigator-developed extraction tool with two studies, which was revised and used with all subsequent studies to be included in the review. The tool included study characteristics (purpose, design, and sample), methods (symptom assessment tool and analytic approach), and outcomes (clusters with GI symptoms and other findings related to clusters with GI symptoms). The two authors separately extracted data from the articles selected for full-text review and met regularly to discuss and resolve any discordances in data extraction.

In the course of enacting the data extraction plan, two studies (Atay et al., 2012; Wu et al., 2019) were found to have used distinctive methods or symptom measurement tools to identify clusters. Atay et al. (2012) used a longitudinal design to explore clusters at three time points during active treatment. Because the eight other included studies were cross-sectional with one data collection time point, for overall consistency, this review focused on the results from the first data collection time point in Atay et al. (2012).

In terms of symptom measurement tools, Wu et al. (2019) used the 13-item Symptom Distress Scale (SDS) to capture the level of distress caused by children's symptoms. The SDS includes 13 items to index 12 symptoms (including constipation and diarrhea) typically experienced by populations with cancer (McCorkle & Young, 1978). The bowel pattern item measures the level of distress caused by bowel discomfort. Therefore, the SDS bowel pattern item was viewed as an indicator of distress from either constipation or diarrhea for this scoping review.

FIGURE 1. PRISMA Flow Diagram



PRISMA—Preferred Reporting Items for Systematic Reviews and Meta-Analyses

Data Synthesis

Extracted data were placed into a matrix. Descriptive statistics (frequency) and narrative methods were used to depict the data within each matrix column. All so-called GI clusters ("the GI cluster" [Li et al., 2020]), other named clusters ("neuropsychological discomforts cluster" [Baggott et al., 2012]), and unnamed clusters were summarized and included in the synthesis of common GI and accompanying non-GI symptoms across studies. Because studies used different symptom assessment tools, symptoms assessed varied across tools, and the tools used different names for similar symptoms (lack of energy in the Memorial Symptom Assessment Scale [MSAS] 10–18 [Collins et al., 2000] and fatigue in the SDS [McCorkle & Young, 1978]), the current analysis encompassed symptoms measured in at least 50% of the included studies.

Proportions calculation started with finding studies that measure a specific GI symptom. Among these studies, the authors used the number of identified clusters with this specific GI symptom as the numerator, and they used the total number of identified clusters that included at least one GI symptom as the denominator. For example, nausea was measured in five studies. These studies identified a total of 30 clusters that included GI symptoms; 20 of the 30 identified clusters included nausea. The proportion of identified clusters that included nausea was calculated by dividing 20 by 30, then multiplying by 100, or 66.67%. To achieve the goal of this systematic scoping review—development of a more comprehensive screening tool to assess GI and accompanying non-GI symptoms and inform optimal symptom management, thus minimizing symptom burden—the

TABLE 1. Study Characteristics (N = 8)

Study (Country)	Design	Purpose	Sample	Symptom Assessment Tool	Analysis Approach
Atay, 2011 (Turkey)	Cross-sectional quantitative study	To define symptom clusters occurring in children with cancer, and to determine the prevalence of symptoms and their characteristics	■ N = 164 ■ Age = 10–18 years ($\bar{X}$ = 13.9, SD = 2.1) ■ Male: 51.8% ■ Hematologic cancer: 61% ■ Receiving chemo: 57.3%, completed treatment: 42.7%	■ MSAS 10–18 ■ Self-report ■ Recall time: during the previous week	■ Symptom prevalence ratings ■ Hierarchical cluster analysis
Atay et al., 2012 (Turkey)	Longitudinal quantitative study	To determine the prevalence of multiple symptoms and characteristics in children at 1, 2, and 3 months after cancer diagnosis	■ N = 54 ■ Age = 13–15 years ($\bar{X}$ = 14, SD = 2.23) ■ Male: 44.4% ■ Hematologic cancer: 57.4% ■ Receiving chemo at first 3 months	■ MSAS 10–18 ■ Self-report ■ Recall time: during the previous week	■ Symptom prevalence ratings ■ Hierarchical cluster analysis
Baggott et al., 2012 (United States)	Cross-sectional quantitative study	To compare the number and types of symptom clusters identified using patients' ratings of symptom occurrence and symptom severity	■ N = 131 ■ Age = 10–18 years ($\bar{X}$ = 14.8, SD = 2.5) ■ Male: 57.3% ■ Hematologic cancer: 51.2% ■ Receiving myelosuppressive chemo	■ MSAS 10–18 ■ Self-report ■ Recall time: during the previous week	■ Symptom prevalence and severity ratings ■ Exploratory factor analysis
Li et al., 2020 (China)	Cross-sectional quantitative study	To investigate symptoms, types of symptom clusters, and their influencing factors in children with acute leukemias	■ N = 159 ■ Age = 2–16 years ($\bar{X}$ = 8.92, SD = 3.33) ■ Male: 61% ■ Hematologic cancer: 100% (acute leukemia) ■ Receiving chemo	■ MSAS 10–18 ■ Parent proxy report for children aged 2–7 years ■ Self-report for children aged 8–18 years ■ Recall time: during the previous week	■ Symptom prevalence ratings ■ Exploratory factor analysis
Semerci et al., 2021 (Turkey)	Cross-sectional quantitative study	To assess symptoms and symptom clusters among inpatient and outpatient adolescents receiving cancer treatment	■ N = 26 ■ Age = 10–18 years ($\bar{X}$ = 15.04, SD = 2.8) ■ Male: 53.8% ■ Hematologic cancer: 34% ■ Receiving multiple treatment modalities	■ MSAS 10–18 ■ Self-report ■ Recall time: during the previous week	■ Symptom prevalence ratings ■ Hierarchical cluster analysis

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TABLE 1. Study Characteristics (N = 8) *(Continued)*

Study (Country)	Design	Purpose	Sample	Symptom Assessment Tool	Analysis Approach
Williams et al., 2012 (United States)	Cross-sectional quantitative study	To calibrate a child-friendly, clinically usable checklist, TRSC-C	■ N = 385 ■ Age = 5–17 years (5–11 years: 56.7%) ■ Male: 54% ■ ALL: 45%, solid tumors: 14%, nervous system tumors: 18%, and other: 23% ■ Receiving chemo: 97%, receiving chemo and radiation: 3%	■ TRSC-C ■ Nurse proxy report for children aged 5–11 years ■ Self-report for children aged 12–18 years ■ Recall time: immediately after and since the last treatment	■ Symptom prevalence ratings ■ Factor analysis
Wu et al., 2019 (Taiwan)	Cross-sectional quantitative study	To determine the best-fit models and identify phenotypes of severe symptom distress profiles for adolescents with cancer who are undergoing treatment	■ N = 200 ■ Age = 13–20 years ($\bar{X}$ = 15.68, SD = 1.97) ■ Male: 57.5% ■ Hematologic cancer: 62.5% ■ Receiving multiple treatment modalities	■ 13-item Symptom Distress Scale ■ Self-report ■ Recall time: during the previous week	■ Symptom prevalence ratings ■ Latent profile analysis
Yeh et al., 2008 (Taiwan)	Cross-sectional quantitative study	To derive symptom clusters and examine whether each cluster differed based on gender, type of cancer and disease, pain, and functional status	■ N = 144 ■ Age = 10–18.9 years ($\bar{X}$ = 14.2, SD = 2.2) ■ Male: 58% ■ Hematologic cancer: 70% ■ On multiple treatment modalities: 75%, off treatment: 25%	■ MSAS 10–18 ■ Self-report and parent proxy report (no specification of which report was used in data analysis or if both reports were used for an individual participant and how) ■ Recall time: during the previous week	■ Symptom prevalence ratings ■ Agglomerative hierarchical clustering

ALL—acute lymphoblastic leukemia; chemo—chemotherapy; MSAS—Memorial Symptom Assessment Scale; TRSC-C—Therapy-Related Symptom Checklist–Children

non-GI symptoms that most frequently accompanied GI symptoms and could also be mechanistically and reasonably linked to GI symptoms, based on what is known about underlying biologic pathways, were included in synthesis.

To examine co-occurrences of symptom pairs within clusters, phi correlation coefficients were calculated using IBM SPSS Statistics, version 27.0. The phi correlation coefficients can range from –1 to 1. A negative correlation indicates that two symptoms tend to occur in different clusters (i.e., unlikely to co-occur), whereas a positive correlation indicates that two symptoms are likely to co-occur in the same clusters, with higher positive values indicating greater

TABLE 2. Symptoms Assessed in the Symptom Assessment Tools Used in the 8 Included Studies

Symptom	MSAS 10–18	SDS	TRSC-C
A feeling of being drowsy	•		
Bleeding			•
Bruising			•
Changes in skin	•		•
Constipation	•	•	•
Cough	•	•	•
Diarrhea	•	•	
Difficulty concentrating	•	•	•
Difficulty sleeping	•	•	•
Difficulty swallowing	•		•
Dizziness	•		
Dry mouth	•		
Headache	•		•
Fatigue	•	•	•
Feeling of being nervous	•		•
Feelings of being irritable	•		•
Feelings of sadness	•		•
Fever			•
"I don't look like myself."	•	•	
Itching	•		•
Jaw pain			•
Lack of appetite	•	•	•
Less hair than usual	•		•
Mouth sores	•		•
Nausea	•	•	•
Numbness	•		•
Pain	•	•	•
Problems with urination	•		•
Shortness of breath	•	•	•
Sore throat			•

Continued in the next column

TABLE 2. Symptoms Assessed in the Symptom Assessment Tools Used in the 8 Included Studies *(Continued)*

Symptom	MSAS 10–18	SDS	TRSC-C
Sweats	•		•
Swelling of arms or legs	•		
Taste change	•		
Tripping or falling			•
Vomiting	•		•
Weight loss	•		•
Worrying	•	•	

MSAS—Memorial Symptom Assessment Scale; SDS—13-item Symptom Distress Scale; TRSC-C—Therapy-Related Symptom Checklist–Children

chances of co-occurrences. Of note, for the purpose of co-occurrence analysis, the current review focuses on the positive phi correlations. Sizes of phi correlation coefficients are interpreted at three levels as follows: small ($\varphi < 0.3$), medium ($\varphi \geq 0.3$ to < 0.5), and large ($\varphi \geq 0.5$) (Cohen, 2013).

To answer the third research question, results about factors that influenced risk of GI clusters were classified as demographic, clinical, or environmental factors.

Results

A total of 661 studies were identified through electronic database searches in February 2022, with four additional studies found through hand searching, and, ultimately, eight studies were deemed eligible for inclusion in this scoping review. Figure 1 shows the flow process for study inclusion.

Study and Sample Characteristics

Study characteristics are shown in Table 1. Included studies were published between 2008 and 2021. Three studies were conducted in Turkey, two in the United States, two in Taiwan, and one in China. All eight studies used quantitative methods. Seven studies used a cross-sectional design, and one used a longitudinal observational design (Atay et al., 2012). Six studies used the MSAS 10–18 (Collins et al., 2000) to assess symptoms, one (Williams et al., 2012) used the Therapy-Related Symptom Checklist–Children (TRSC-C) (Williams et al., 2012), and one (Wu et

TABLE 3. SCs That Included GI Symptoms (N = 8 Studies, N = 20 SCs)

Study (Country)	Number of SCs Identified	Number of SCs With at Least 1 GI Symptom	SC Name	GI Symptoms	Non-GI Symptoms
Atay, 2011 (Turkey)	5	3	Not reported	Constipation, diarrhea, and difficulty swallowing	Problems with urination
			Not reported	Dry mouth, mouth sores, taste changes, and weight loss	Dizziness and dyspnea
			Not reported	Lack of appetite, nausea, and vomiting	Fatigue, feeling drowsy, feeling nervous, feeling sad, and pain
Atay et al., 2012 (Turkey)	4	3	Not reported	Taste changes	Dizziness and worrying
			Not reported	Nausea and vomiting	Fatigue
			Not reported	Diarrhea	Sweating and difficulty sleeping
Baggott et al., 2012 (United States)	3	2	Chemotherapy sequelae cluster	Constipation, diarrhea, dry mouth, lack of appetite, nausea, vomiting, and weight loss	Sweating
			Neuropsychological discomforts cluster	Taste changes	Changes in self-appearance, dizziness, feeling drowsy, feeling irritable, pain, and skin changes
Li et al., 2020 (China)	6	3	The GI cluster	Constipation, lack of appetite, nausea, taste changes, vomiting, and weight loss	Fatigue
			The self-image disorder cluster	Mouth sores	Changes in self-appearance, hair loss, and skin changes
			The somatic cluster	Dry mouth	Cough and sweating
Semerci et al., 2021 (Turkey)	3	2	Not reported	Taste changes and weight loss	Hair loss
			Not reported	Lack of appetite, nausea, and vomiting	–
Williams et al., 2012 (United States)	7	3	Nutrition related	Lack of appetite, nausea, vomiting, and weight loss	Fatigue and hair loss
			Oropharyngeal	Difficulty swallowing, mouth sores, and sore throat	–
			Neurotoxicities	Constipation and jaw pain	Problems with urination

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TABLE 3. SCs That Included GI Symptoms (N = 8 Studies, N = 20 SCs) *(Continued)*

Study (Country)	Number of SCs Identified	Number of SCs With at Least 1 GI Symptom	SC Name	GI Symptoms	Non-GI Symptoms
Wu et al., 2019 (Taiwan)	1	1	Not reported	Lack of appetite and nausea	Changes in self-appearance, difficulty concentrating, and fatigue
Yeh et al., 2008 (Taiwan)	5	3	Body image (external concern) and eating difficulties	Constipation, difficulty swallowing, mouth sores, and weight loss	Hair loss
			Symptoms related to GI irritations and pain	Lack of appetite, nausea, taste changes, and vomiting	Pain
			Symptoms related to internal concerns of sensory discomfort and body image	Diarrhea and dry mouth	Changes in self-appearance, feeling nervous, itching, numbness, and skin changes

GI—gastrointestinal; SC—symptom cluster

al., 2019) used the SDS (McCorkle & Young, 1978). In total, these three measures assessed 37 unique symptoms (see Table 2). Most (n = 5) studies used child self-report, and three studies (Li et al., 2020; Williams et al., 2012; Yeh et al., 2008) used child self-report and proxy report by the child's parent or nurse.

In terms of approach to cluster analysis, all eight studies used symptom prevalence ratings as the variable in the analysis, and one study (Baggott et al., 2012) also used symptom severity ratings. All eight studies used statistical approaches to cluster analysis, including hierarchical cluster analysis (Atay, 2011; Atay et al., 2012; Semerci et al., 2021; Yeh et al., 2008), factor analysis (Baggott et al., 2012; Li et al., 2020; Williams et al., 2012), and latent profile analysis (Wu et al., 2019).

Study sample sizes ranged from 26 (Semerci et al., 2021) to 385 (Williams et al., 2012). Only one study (Williams et al., 2012) explicated the sample size needed for a sufficiently powered (80%) study. Male children preponderated (44.4%–61%) in samples for most included studies. Mean ages ranged from 8.92 years (SD = 3.33) to 15.68 years (SD = 1.97). Study participants were diagnosed with various pediatric cancers, predominantly (at least 34%) a hematologic cancer; one study enrolled only children diagnosed with acute leukemia (Li et al., 2020). Most studies (Atay et al., 2012; Baggott et al., 2012; Li et al., 2020; Semerci et al., 2021; Williams et al., 2012; Wu et al., 2019) focused on children in the active treatment phase and who were receiving chemotherapy, and two studies (Atay, 2011; Yeh et al., 2008) included children in active treatment or another phase of the cancer trajectory.

Clusters With GI Symptoms and Proportions of Clusters With Specific GI Symptoms

A total of 20 identified clusters included GI symptoms (see Table 3). Of the seven cross-sectional studies, the number of clusters per study that included GI symptoms ranged from one (Wu et al., 2019) to three (Atay, 2011; Li et al., 2020; Williams et al., 2012; Yeh et al., 2008). The longitudinal study (Atay et al., 2012) identified three clusters with GI symptoms at the first data collection time point.

In terms of cluster names, four studies (Atay, 2011; Atay et al., 2012; Semerci et al., 2021; Wu et al., 2019) did not explicitly name the identified clusters, and four studies did. Three of these four studies referenced GI symptoms or eating in the cluster name, whereas one study (Baggott et al., 2012) used "chemotherapy sequela cluster" to label a cluster comprised of a mix of GI and non-GI symptoms.

Thirty of the 37 symptoms assessed in the eight included studies were measured in at least four studies (50% of the included studies). Across 20 identified clusters, 12 symptoms appeared in at least 20% of the clusters. These symptoms included the

following nine GI symptoms: nausea (eight clusters), vomiting (seven clusters), lack of appetite (seven clusters), taste changes (six clusters), weight loss (six clusters), constipation (five clusters), dry mouth (four clusters), diarrhea (four clusters), and mouth sores (four clusters). The following three non-GI symptoms also appeared in at least 20% of the following clusters: fatigue (five clusters), changes in self-appearance (four clusters), and hair loss (four clusters). An additional 17 symptoms were identified as accompanying symptoms in less than 20% of the clusters.

Co-Occurrence Correlations for Symptom Pairs

Across the 31 symptoms (including jaw pain and sore throat, symptoms measured in less than 50% of total included studies) identified in 20 clusters, 26 symptoms pair with at least one symptom of the 12 most frequently reported symptoms that have statistically significant ($p < 0.05$) phi correlation coefficients (see Table 4). Only positive significant phi correlation coefficients were identified. The symptoms correlated with highest numbers of symptoms were dry mouth and changes in self-appearance (each significantly correlated with five symptoms), followed by diarrhea (significantly correlated with four symptoms), and nausea, vomiting, mouth sores, fatigue, and lack of appetite (each significantly correlated with three symptoms). The phi correlation coefficients ranged in size from $\varphi = 0.459$ to $\varphi = 0.899$; the majority (17 correlations) were medium in size. The strongest correlations were nausea with vomiting ($\varphi = 0.899$, $p < 0.01$) and nausea with lack of appetite ($\varphi = 0.899$, $p < 0.01$), followed by changes in self-appearance with skin changes ($\varphi = 0.84$, $p < 0.01$), and vomiting with lack of appetite ($\varphi = 0.78$, $p < 0.01$).

Factors Related to Risk for Clusters With GI symptoms

Of the eight included studies, three (Li et al., 2020; Williams et al., 2012; Yeh et al., 2008) explored demographic and clinical factors related to clusters that included GI symptoms. No included study examined relationships between environmental factors (e.g., sight and odor of food) and GI symptoms.

Li et al. (2020) found that biologic sex and age explained 11.4% of the variation in "the self-image disorder cluster" (mouth sores, changes in self-appearance, hair loss, and skin changes). The cluster severity was higher in female children than in male children, and in older children. Yeh et al. (2008) demonstrated that male children had significantly

TABLE 4. Phi Correlation Coefficients Among the 12 Most Frequently Reported Symptoms Included in Identified Clusters

Number	Symptom	Phi Correlation Coefficients
1	Nausea (3)	■ Vomiting ($\varphi = 0.899$, $p < 0.01$) ■ Lack of appetite ($\varphi = 0.899$, $p < 0.01$) ■ Fatigue ($\varphi = 0.707$, $p < 0.01$)
2	Taste changes (1)	■ Dizziness ($\varphi = 0.642$, $p < 0.01$)
3	Vomiting (3)	■ Nausea ($\varphi = 0.899$, $p < 0.01$) ■ Lack of appetite ($\varphi = 0.78$, $p < 0.01$) ■ Fatigue ($\varphi = 0.545$, $p < 0.05$)
4	Lack of appetite (3)	■ Nausea ($\varphi = 0.899$, $p < 0.01$) ■ Vomiting ($\varphi = 0.78$, $p < 0.01$) ■ Fatigue ($\varphi = 0.545$, $p < 0.05$)
5	Weight loss (1)	■ Hair loss ($\varphi = 0.491$, $p < 0.05$)
6	Fatigue (3)	■ Nausea ($\varphi = 0.707$, $p < 0.01$) ■ Lack of appetite ($\varphi = 0.545$, $p < 0.05$) ■ Vomiting ($\varphi = 0.545$, $p < 0.05$)
7	Constipation (1)	■ Problems with urination ($\varphi = 0.577$, $p < 0.01$)
8	Dry mouth (5)	■ Sweating ($\varphi = 0.49$, $p < 0.05$) ■ Cough ($\varphi = 0.459$, $p < 0.05$) ■ Dyspnea ($\varphi = 0.459$, $p < 0.05$) ■ Itching ($\varphi = 0 .459$, $p < 0.05$) ■ Numbness ($\varphi = 0.459$, $p < 0.05$)
9	Diarrhea (4)	■ Difficulty sleeping ($\varphi = 0.459$, $p < 0.05$) ■ Itching ($\varphi = 0.459$, $p < 0.05$) ■ Numbness ($\varphi = 0.459$, $p < 0.05$) ■ Sweating ($\varphi = 0 .49$, $p < 0.05$)
10	Changes of self-appearance (5)	■ Skin changes ($\varphi = 0.84$, $p < 0.01$) ■ Difficulty concentrating ($\varphi = 0.459$, $p < 0.05$) ■ Feeling irritable ($\varphi = 0.459$, $p < 0.05$) ■ Itching ($\varphi = 0.459$, $p < 0.05$) ■ Numbness ($\varphi = 0.459$, $p < 0.05$)
11	Mouth sores (3)	■ Difficulty swallowing ($\varphi = 0.49$, $p < 0.05$) ■ Dyspnea ($\varphi = 0.459$, $p < 0.05$) ■ Sore throat ($\varphi = 0.459$, $p < 0.05$)
12	Hair loss (1)	■ Weight loss ($\varphi = 0.491$, $p < 0.05$)

higher symptom distress related to the "symptoms related to GI irritations and pain" cluster (lack of appetite, nausea, taste changes, vomiting, and pain) than female children. Although Williams et al. (2012) did not find differences by biologic sex in the severity of any identified cluster, age influenced severity of the "nutrition related" cluster (lack of appetite, nausea, vomiting, weight loss, fatigue, and hair loss); older children (aged 12–17 years) reported higher levels of symptom severity ($p < 0.001$).

In terms of clinical factors, chemotherapy phase (induction, intensification, consolidation, or maintenance) explained 15% of the variation in "the GI cluster" (constipation, lack of appetite, nausea, taste changes, vomiting, weight loss, and fatigue) for children being treated for acute leukemias (acute lymphoblastic leukemia: 73%, acute myeloid leukemia: 27%) (Li et al., 2020). Children undergoing later phases of chemotherapy reported lower symptom severity. Similarly, chemotherapy phase explained 9.1% of variation in "the somatic cluster" (dry mouth, cough, and sweating). Children in later chemotherapy phases reported lower symptom severity (Li et al., 2020). Another included study explored symptoms as risk factors for GI symptoms. Yeh et al. (2008) found that children who reported pain also reported significantly higher distress in all three identified clusters—(a) "body image and eating difficulties" cluster, (b) "symptoms related to GI irritations and pain" cluster, and (c) "symptoms related to internal concerns of sensory discomfort and body image" cluster.

Discussion

This scoping review mapped the state of knowledge regarding clusters with GI symptoms experienced by children during treatment for cancer. The review found that statistical analysis, particularly cluster analysis, was the method most commonly used to identify clusters in the pediatric population with cancer. This finding differs from that of a review by Ward Sullivan et al. (2018), which found that most studies identifying clusters in adult populations with cancer used factor analysis statistical procedures. The current review found that symptom prevalence ratings were the most commonly used symptom dimension in pediatric oncology studies, and symptom severity ratings were the most commonly used dimension in adult oncology studies (Ward Sullivan et al., 2018).

A controversial issue in the study of clusters among oncology populations is whether samples heterogeneous in terms of cancer type, disease stage, treatment modality or agents, and so on identify different clusters than studies with homogeneous samples (Ward Sullivan et al., 2018). The current review, which included studies with either homogeneous or heterogeneous samples, found that the results regarding clusters were similar whether the sample was heterogeneous or homogeneous. For example, Baggott et al. (2012) found that children with a variety of childhood cancers (hematologic cancers: 51.2%) reported the "chemotherapy sequelae cluster" (constipation, diarrhea, dry mouth, lack of appetite, nausea, vomiting, weight loss, and sweating). Similarly, in a sample limited to children diagnosed with acute leukemia, Li et al. (2020) discovered "the GI cluster" (constipation, lack of appetite, nausea, taste changes, vomiting, weight loss, and fatigue). The similarity of results from these two studies may be affected by the high percentage of participants in the Baggott et al. (2012) study who had been diagnosed with a hematologic cancer, the most common of which is acute leukemia. Hematologic cancers are more prevalent in children than other types of pediatric cancer, and the composition of the Baggott et al. (2012) study sample seems representative of the general pediatric oncology population. Only one included study (Atay et al., 2012) used a longitudinal observational design to examine change in cluster composition over time. More longitudinal studies are needed to understand the evolution of symptoms and symptoms over time. Children in the sample should be enrolled at similar time points in their treatment regimen or illness trajectory, and frequency and timing of repeated assessments should be carefully considered.

Three different symptom assessment tools were used in the eight included studies. The MSAS, which assesses 31 symptoms commonly experienced by children diagnosed with cancer (Collins et al., 2000), was used by most studies. The other two tools assess fewer symptoms; the TRSC-C assesses 23 different symptoms (Williams et al., 2012), and the SDS uses 13 items to assess 12 symptoms (McCorkle & Young, 1978). Even though most symptoms measured by the TRSC-C or SDS were also captured by the MSAS, the MSAS does not assess sore throat, jaw pain, fever, bruising, bleeding, and tripping or falling as the TRSC-C does. Several GI symptoms (e.g., mouth sores, stomachache) are linked to pain and contribute to pain severity overall.

Pain is well known to be a complex experience (McGrath, 1994); therefore, several assessments have been developed to solely evaluate pain and capture its multidimensions (Batalha et al., 2015). For example, the Adolescent Pediatric Pain Tool captures the

intensity, location, and quality (including affective, evaluative, sensory, and temporal) dimensions of pain in children and adolescents (Jacob et al., 2014). Pain was measured in all eight included studies but with different items. In addition to the more general pain item, MSAS 10–18 measures headache and mouth sores, both of which entail pain. The TRSC-C also asks about sore throat, jaw pain, and headache, and the SDS measures pain frequency and distress level. Including these pain-related items in the tools is congruent with Duffy et al.'s (2019) findings that the types of pain associated with common cancer treatments include headache and mucositis anywhere along the GI tract, from the mouth to the anus. However, an overall pain item in conjunction with other pain-related items referencing specific locations or sources of pain could be confusing, particularly for younger children. In addition, Yeh et al. (2008) demonstrated that use of multiple scale items to index a symptom—in this case, pain—could inflate cluster severity. The results of the current review support assessment of pain separately from other symptoms and the use of multidimensional pain assessment tools.

Clusters That Included GI Symptoms

This scoping review generates a comprehensive list of GI and accompanying non-GI symptoms (a comprehensive GI cluster) for children treated with chemotherapy for cancer. The comprehensive cluster includes the 12 most frequently reported symptoms within the identified clusters across all included studies. The following nine are GI symptoms: nausea, taste changes, vomiting, lack of appetite, weight loss, constipation, dry mouth, diarrhea, and mouth sores. The other three frequently reported symptoms represent accompanying non-GI symptoms as follows: fatigue, changes in self-appearance, and hair loss. This group of symptoms resembles the "nutrition related" cluster (lack of appetite, nausea, vomiting, weight loss, fatigue, and hair loss) identified in a sample comprised of children diagnosed with various cancers (Williams et al., 2012). Both clusters include numerous GI symptoms plus the non-GI symptoms, fatigue and hair loss. The comprehensive GI cluster identified through this systematic review represents the symptoms commonly reported by children undergoing multimodal pediatric cancer treatment regimens that include chemotherapy.

Co-Occurrence Correlations for Pairs of Symptoms

In terms of concurrency of GI and other kinds of symptoms, the current review found that, among GI symptoms, nausea and vomiting were most strongly correlated ($\varphi = 0.899$, $p < 0.01$). This finding is consistent with that of a previous study showing that nausea and vomiting were a common cluster in children with cancer (Rodgers et al., 2012). Similarly, nausea was most strongly correlated with lack of appetite ($\varphi = 0.899$, $p < 0.01$), as was lack of appetite with vomiting ($\varphi = 0.78$, $p < 0.01$). Nausea and vomiting were common causes of changes in eating behaviors among children receiving cancer treatment (Klanjsek & Pajnkihar, 2016). Taste changes, which appeared in 6 of 16 included clusters, significantly correlated only with dizziness ($\varphi = 0.642$, $p < 0.01$). Baggott et al. (2012) found that the "neuropsychological discomforts cluster" included taste changes and dizziness. Some chemotherapy agents (vinca alkaloid, etoposide, and cisplatin) have been associated with sensorineural hearing loss (Altissimi et al., 2020). These agents can cause damage to the hair cells and nerves of the inner ear, which leads to sensorineural hearing loss. Dizziness is a symptom of sensorineural hearing loss (Children's Oncology Group, 2018). This finding helps explain the co-occurrence of taste changes and dizziness subsequent to treatment with agents like cisplatin, which has also been associated with taste changes.

Regarding frequently reported non-GI symptoms, fatigue was strongly correlated with nausea ($\varphi = 0.707$, $p < 0.01$), vomiting ($\varphi = 0.545$, $p < 0.05$), and lack of appetite ($\varphi = 0.545$, $p < 0.05$). Children with nausea and vomiting typically reduce their oral energy intake, which has been shown to contribute to fatigue in a sample of adolescents receiving chemotherapy (Erickson et al., 2010). Other non-GI symptoms—changes in self-appearance and hair loss—appeared in most included clusters, but only hair loss was

KNOWLEDGE TRANSLATION

- Inconsistency in symptom clusters that included gastrointestinal (GI) symptoms among children with cancer in existing studies leads to the need for mapping to understand these clusters and integrating findings to advance symptom management.
- The 12 most frequently reported symptoms across all clusters were nausea, taste changes, vomiting, lack of appetite, weight loss, constipation, dry mouth, diarrhea, mouth sores, fatigue, changes in self-appearance, and hair loss.
- Children's symptom burden and quality of life could be improved by comprehensive assessment of GI symptoms and determining effective ways of managing co-occurring symptoms.

significantly correlated with a GI symptom (weight loss). GI symptoms like nausea and vomiting begin soon after a dose of chemotherapy is given, and sometimes in anticipation of the event, whereas treatment-related hair loss and weight loss begin later and worsen over time. Further exploration of associations between GI and non-GI symptoms in children being treated for cancer is needed to better capture the children's symptom experience and symptom burden. Consequently, this in-depth understanding will inform the development of interventions to optimize management of this GI cluster in pediatric oncology populations.

Factors for Clusters That Included GI Tract Symptoms

Four factors—biologic sex, age, chemotherapy phase, and symptoms—were shown to influence risk of clusters with GI symptoms. In terms of biologic sex, females tended to report more severe symptoms in "the self-image disorder cluster" (Li et al., 2020), and males had significantly higher distress in symptoms related to the "symptoms related to GI irritations and pain" cluster (Yeh et al., 2008). These findings are congruent with studies exploring the effects of biologic sex on pain intensity among adolescents diagnosed with cancer (Firoozi & Rostami, 2012; Hechler et al., 2009). Females reported higher pain intensity than males (Hechler et al., 2009), and females' cortisol levels showed higher pain sensitivity than males' levels (Firoozi & Rostami, 2012). However, Williams et al. (2012) did not find differences by biologic sex in the severity of any identified symptom cluster.

Regarding children's age, Williams et al. (2012) found that older children reported significantly higher severity of the "nutrition related" cluster. This result is consistent with a previous study in which older children experienced more nausea and appetite disturbances (Hockenberry et al., 2021). Similarly, older children had higher risk of nausea (Dupuis et al., 2016). Risk of change in preventive antiemetics and rescue antiemetics for breakthrough nausea and vomiting was also found to be higher among older children compared to younger children (Freedman et al., 2014).

Children with acute leukemia who were receiving the later phases of chemotherapy reported lower severity of SCs that included GI symptoms (Li et al., 2020), which is consistent with the findings of studies that were not eligible for inclusion in the review. For example, nausea significantly decreased by the start of the next chemotherapy cycle among adolescents with various cancers (Ameringer et al., 2013). Fatigue decreased over the course of treatment among children newly diagnosed with acute lymphoblastic leukemia (Hockenberry et al., 2014).

The GI symptoms of nausea, lack of appetite (Li et al., 2020), and pain (Yeh et al., 2008) were found to contribute to risk of other GI and non-GI symptoms. Similarly, nausea and pain were reported as causes of fatigue among adolescents undergoing chemotherapy (Erickson et al., 2010).

In conclusion, these factors included only individual-level demographic data and clinical data of children. Therefore, future research requires more investigation in other factors from different levels, including the interpersonal level, such as parents' lack of information related to the child's changes in eating behaviors (Arpaci et al., 2018), or the environmental level, such as the hospital environment influencing children's GI symptom experience or eating behaviors.

Limitations

This review has limitations. First, some symptoms, such as distress related to appetite or lack of appetite, were labeled differently across studies based on their symptom assessment tools. Differences in labeling may have influenced the authors' synthesis process. Second, symptom measurement time point relative to treatment initiation or when the most recent treatment cycle started and/or ended was not implicitly stated in most included studies. This limited the authors' understanding of the trajectory of children's symptom experience during the course of active treatment. Also, the recall time for the past week for symptom assessment limited the authors' understanding of the evolution of symptoms and symptom co-occurrences during the recall period. Next, whereas most included studies used self-report as a gold standard for assessing children's symptom experience, some used proxy report for younger children with limited ability to understand and complete the symptom assessment tool. One included study did not explicitly say whether the symptom data were collected by child self-report and/or parent proxy report. Therefore, this review's findings include a mix of perceptions about children's symptoms during cancer therapy. Finally, because the searches identified a sole longitudinal study, this review could not demonstrate changes in symptom cluster compositions during cancer treatment.

Implications for Nursing

Implications of the findings of this review for future nursing research include that the resultant comprehensive GI cluster, which includes GI and accompanying non-GI symptoms, can inform the

development and psychometric evaluation of tools for assessing children's symptom experience relative to the GI cluster. Secondly, future studies of the GI cluster in pediatric oncology populations should use longitudinal designs and mixed methods to illuminate evolution of the GI symptoms during the active treatment phase, during a treatment cycle, or across the illness trajectory. Also, daily child-reported electronic symptom assessment via personal mobile device (Leahy et al., 2021) is recommended to explore the evolution of symptoms over time. Ideally, these reports can be shared with the child's care team to inform real-time symptom management in clinical and community settings. Lastly, future studies should investigate the modifiable factors that influence the children's GI cluster, including their parents' and clinicians' knowledge, attitudes, and beliefs about the child's symptom experience, and features of the home and clinical environments that influence children's GI symptoms and eating behaviors. Understanding multilevel factors that influence GI symptoms can inform the development of multilevel interventions to improve children's GI symptoms, and tools to comprehensively assess symptoms and the multilevel factors that contribute to those symptoms.

Oncology nurses can lead the management of children's symptom burden through comprehensive assessments and ongoing monitoring of frequently reported GI and accompanying non-GI symptoms in children during active treatment with chemotherapy, and then after treatment has ended. Secondly, clinical nurses should be sensitive to characteristics of the child and the child's treatment regimen that have been shown to influence symptom burden and severity. Lastly, clinical nurses can combine GI cluster assessment and assessment of contributing factors to develop patient-centered care plans to minimize children's symptom burden and severity, nutritional deficits, and risks of life-threatening complications to maximize the child's clinical outcomes and quality of life.

Conclusion

The current study presented a comprehensive overview of the GI cluster experienced by children undergoing cancer treatments, which includes GI and non-GI symptoms. In addition, the study identified the factors that influence these symptoms. The findings of this study can inform the development of assessment tools and effective management strategies for symptoms with shared underlying mechanisms.

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The authors gratefully acknowledge Jamie Conklin, MLIS, a nursing librarian, for search and data sources.

This study was funded, in part, by the Ramathibodi School of Nursing, Faculty of Medicine Ramathibodi Hospital, Mahidol University and the Linda Waring Matthews Research Award.

Kamkhoad, Santacroce, and Phonyiam contributed to the conceptualization and design. Kamkhoad and Phonyiam completed the data collection. Kamkhoad, Phonyiam, and Wang provided statistical support. All authors contributed to the manuscript preparation and provided analysis.

REFERENCES

Altissimi, G., Colizza, A., Cianfrone, G., de Vincentiis, M., Greco, A., Taurone, S., . . . Ralli, M. (2020). Drugs inducing hearing loss, tinnitus, dizziness and vertigo: An updated guide. *European Review for Medical and Pharmacological Sciences, 24*(15), 7946–7952. https://doi.org/10.26355/eurrev_202008_22477

Ameringer, S., Elswick, R.K., Jr., Shockey, D.P., & Dillon, R. (2013). A pilot exploration of symptom trajectories in adolescents with cancer during chemotherapy. *Cancer Nursing, 36*(1), 60–71. https://doi.org/10.1097/NCC.0b013e318250da1a

Arpaci, T., Toruner, E.K., & Altay, N. (2018). Assessment of nutritional problems in pediatric patients with cancer and the information needs of their parents: A parental perspective. *Asia-Pacific Journal of Oncology Nursing, 5*(2), 231–236. https://doi.org/10.4103/apjon.apjon_78_17

Atay, S. (2011). Symptom characteristics and clustering in children and adolescents undergoing or being off cancer chemotherapy. *Journal of the Balkan Union of Oncology, 16*(4), 751–758.

Atay, S., Conk, Z., & Bahar, Z. (2012). Identifying symptom clusters in paediatric cancer patients using the memorial symptom assessment scale. *European Journal of Cancer Care, 21*(4), 460–468. https://doi.org/10.1111/j.1365-2354.2012.01324.x

Baggott, C., Cooper, B.A., Marina, N., Matthay, K.K., & Miaskowski, C. (2012). Symptom cluster analyses based on symptom occurrence and severity ratings among pediatric oncology patients during myelosuppressive chemotherapy. *Cancer Nursing, 35*(1), 19–28. https://doi.org/10.1097/NCC.0b013e31822909fd

Baggott, C.R., Dodd, M., Kennedy, C., Marina, N., Matthay, K.K., Cooper, B., & Miaskowski, C. (2011). An evaluation of the factors that affect the health-related quality of life of children following myelosuppressive chemotherapy. *Supportive Care in Cancer, 19*(3), 353–361. https://doi.org/10.1007/s00520-010-0824-y

Batalha, L.M.C., Fernandes, A.M., de Campos, C., & Costa Gonçalves, A.M.P.M.P. (2015). Pain assessment in children with cancer: A systematic review. *Revista de Enfermagem Referência, 4*(5), 119–127. https://doi.org/10.12707/RIV14013

Children's Oncology Group. (2018). *Health link, healthy living after treatment of childhood, adolescent, and young adult cancer: Hearing loss after cancer treatment*. http://www.survivorshipguidelines.org/pdf/2018/English%20Health%20Links/21_hearing_loss%20(secured).pdf

Cohen, J. (2013). *Statistical power analysis for the behavioral sciences*. Academic Press.

Collins, J.J., Byrnes, M.E., Dunkel, I.J., Lapin, J., Nadel, T., Thaler, H.T., . . . Portenoy, R.K. (2000). The measurement of symptoms in children with cancer. *Journal of Pain and Symptom Management, 19*(5), 363–377. https://doi.org/10.1016/s0885-3924(00)00127-5

Dodd, M., Janson, S., Facione, N., Faucett, J., Froelicher, E.S., Humphreys, J., . . . Taylor, D. (2001). Advancing the science of symptom management. *Journal of Advanced Nursing, 33*(5), 668–676. https://doi.org/10.1046/j.1365-2648.2001.01697.x

Duffy, E.A., Dias, N., Hendricks-Ferguson, V., Hellsten, M., Skeens-Borland, M., Thornton, C., & Linder, L.A. (2019). Perspectives on cancer pain assessment and management in children. *Seminars in Oncology Nursing, 35*(3), 261–273. https://doi.org/10.1016/j.soncn.2019.04.007

Dupuis, L.L., Lu, X., Mitchell, H.-R., Sung, L., Devidas, M., Mattano, L.A., Jr., . . . Kadan-Lottick, N.S. (2016). Anxiety, pain, and nausea during the treatment of standard-risk childhood acute lymphoblastic leukemia: A prospective, longitudinal study from the children's oncology group. *Cancer, 122*(7), 1116–1125. https://doi.org/10.1002/cncr.29876

Erickson, J.M., Beck, S.L., Christian, B., Dudley, W.N., Hollen, P.J., Albritton, K., . . . Godder, K. (2010). Patterns of fatigue in adolescents receiving chemotherapy. *Oncology Nursing Forum, 37*(4), 444–455. https://doi.org/10.1188/10.ONF.444-455

Firoozi, M., & Rostami, R. (2012). Sensitivity to pain in children with acute lymphoblastic leukemia (ALL). *Iranian Journal of Cancer Prevention, 5*(2), 74–80.

Freedman, J.L., Faerber, J., Kang, T.I., Dai, D., Fisher, B.T., Huang, Y.-S., Li, Y., . . . Feudtner, C. (2014). Predictors of antiemetic alteration in pediatric acute myeloid leukemia. *Pediatric Blood and Cancer, 61*(10), 1798–1805. https://doi.org/10.1002/pbc.25108

Green, R., Horn, H., & Erickson, J.M. (2010). Eating experiences of children and adolescents with chemotherapy-related nausea and mucositis. *Journal of Pediatric Oncology Nursing, 27*(4), 209–216. https://doi.org/10.1177/1043454209360779

Hechler, T., Chalkiadis, G.A., Hasan, C., Kosfelder, J., Meyerhoff, U., Vocks, S., & Zernikow, B. (2009). Sex differences in pain intensity in adolescents suffering from cancer: Differences in pain memories? *Journal of Pain, 10*(6), 586–593. https://doi.org/10.1016/j.jpain.2008.11.011

Hockenberry, M., Haugen, M., Slaven, A., Skeens, M., Patton, L., Montgomery, K., . . . Arthur, M. (2021). Pediatric education discharge support strategies for newly diagnosed children with cancer. *Cancer Nursing, 44*(6), E520–E530. https://doi.org/10.1097/ncc.0000000000000947

Hockenberry, M., & Hooke, M.C. (2007). Symptom clusters in children with cancer. *Seminars in Oncology Nursing, 23*(2), 152–157. https://doi.org/10.1016/j.soncn.2007.01.001

Hockenberry, M.J., Taylor, O.A., Pasvogel, A., Rodgers, C., McCarthy, K., Gundy, P., . . . Moore, I.M.K. (2014). The influence of oxidative stress on symptom occurrence, severity, and distress during childhood leukemia treatment. *Oncology Nursing Forum, 41*(4), E238–E247. https://doi.org/10.1188/14.ONF.E238-E247

Huijer, A.-S.H., Sagherian, K., & Tamim, H. (2013). Quality of life and symptom prevalence as reported by children with cancer in Lebanon. *European Journal of Oncology Nursing, 17*(6), 704–710. https://doi.org/10.1016/j.ejon.2013.09.004

Jacob, E., Mack, A.K., Savedra, M., Van Cleve, L., & Wilkie, D.J. (2014). Adolescent pediatric pain tool for multidimensional measurement of pain in children and adolescents. *Pain Management Nursing, 15*(3), 694–706. https://doi.org/10.1016/j.pmn.2013.03.002

Johnston, D.L., Hyslop, S., Tomlinson, D., Baggott, C., Gibson, P., Orsey, A., . . . Sung, L. (2018). Describing symptoms using the symptom screening in pediatrics tool in hospitalized children with cancer and hematopoietic stem cell transplant recipients. *Cancer Medicine, 7*(5), 1750–1755. https://doi.org/10.1002/cam4.1433

Kamkhoad, D., Patoomwan, A., & Pakakasam, S. (2019). Symptom experiences and quality of life in adolescents with cancer receiving cancer treatments. *Bangkok Medical Journal, 15*(2), 173–179. https://doi.org/10.31524/bkkmedj.2019.09.009

Klanjsek, P., & Pajnkihar, M. (2016). Causes of inadequate intake of nutrients during the treatment of children with chemotherapy. *European Journal of Oncology Nursing, 23,* 24–33. https://doi.org/10.1016/j.ejon.2016.03.003

Kwekkeboom, K.L. (2016). Cancer symptom cluster management. *Seminars in Oncology Nursing, 32*(4), 373–382. https://doi.org/10.1016/j.soncn.2016.08.004

Leahy, A.B., Feudtner, C., & Basch, E. (2018). Symptom

monitoring in pediatric oncology using patient-reported outcomes: Why, how, and where next. *Patient, 11*(2), 147–153. https://doi.org/10.1007/s40271-017-0279-z

Leahy, A.B., Schwartz, L.A., Li, Y., Reeve, B.B., Bekelman, J.E., Aplenc, R., & Basch, E.M. (2021). Electronic symptom monitoring in pediatric patients hospitalized for chemotherapy. *Cancer, 127*(16), 2980–2989. https://doi.org/10.1002/cncr.33617

Li, R., Ma, J., Chan, Y., Yang, Q., & Zhang, C. (2020). Symptom clusters and influencing factors in children with acute leukemia during chemotherapy. *Cancer Nursing, 43*(5), 411–418. https://doi.org/10.1097/ncc.0000000000000716

Linder, L.A., Al-Qaaydeh, S., & Donaldson, G. (2018). Symptom characteristics among hospitalized children and adolescents with cancer. *Cancer Nursing, 41*(1), 23–32. https://doi.org/10.1097/NCC.0000000000000469

Loeffen, E.A.H., Brinksma, A., Miedema, K.G.E., de Bock, G.H., & Tissing, W.J.E. (2015). Clinical implications of malnutrition in childhood cancer patients—Infections and mortality. *Supportive Care in Cancer, 23*(1), 143–150.

McCorkle, R., & Young, K. (1978). Development of a symptom distress scale. *Cancer Nursing, 1*(5), 373–378.

McGrath, P.A. (1994). Psychological aspects of pain perception. *Archives of Oral Biology, 39*(Suppl.), 55S–62S. https://doi.org/10.1016/0003-9969(94)90189-9

Miake-Lye, I.M., Hempel, S., Shanman, R., & Shekelle, P.G. (2016). What is an evidence map? A systematic review of published evidence maps and their definitions, methods, and products. *Systematic Reviews, 5*, 28. https://doi.org/10.1186/s13643-016-0204-x

Miaskowski, C. (2016). Future directions in symptom cluster research. *Seminars in Oncology Nursing, 32*(4), 405–415. https://doi.org/10.1016/j.soncn.2016.08.006

Rodgers, C., Kollar, D., Taylor, O., Bryant, R., Crockett, K., Gregurich, M.A., & Hockenberry, M. (2012). Nausea and vomiting perspectives among children receiving moderate to highly emetogenic chemotherapy treatment. *Cancer Nursing, 35*(3), 203–210. https://doi.org/10.1097/NCC.0b013e3182281493

Semerci, R., Akgunmela Kostak, M., Eren, T., Savran, F., & Avci, G. (2021). Symptoms and symptom clusters in adolescents with cancer. *International Journal of Emerging Trends in Health Sciences, 5*(2), 14–24. https://doi.org/10.18844/ijeths.v5i2.5559

Tricco, A.C., Lillie, E., Zarin, W., O'Brien, K.K., Colquhoun, H., Levac, D., . . . Straus, S.E. (2018). PRISMA extension for scoping reviews (PRISMA-ScR): Checklist and explanation. *Annals of Internal Medicine, 169*(7), 467–473.

Ward Sullivan, C., Leutwyler, H., Dunn, L.B., & Miaskowski, C. (2018). A review of the literature on symptom clusters in studies that included oncology patients receiving primary or adjuvant chemotherapy. *Journal of Clinical Nursing, 27*(3–4), 516–545. https://doi.org/10.1111/jocn.14057

Williams, P.D., Williams, A.R., Kelly, K.P., Dobos, C., Gieseking, A., Connor, R., . . . Del Favero, D. (2012). A symptom checklist for children with cancer: The Therapy-Related Symptom Checklist–Children. *Cancer Nursing, 35*(2), 89–98. https://doi.org/10.1097/NCC.0b013e31821a51f6

Wu, W.-W., Lin, K.-C., Liang, S.-Y., & Jou, S.-T. (2019). Using a patient-centered approach to identify symptom clusters among adolescents with cancer. *Cancer Nursing, 42*(3), 198–207. https://doi.org/10.1097/ncc.0000000000000587

Yeh, C.-H., Chiang, Y.-C., Chien, L.-C., Lin, L., Yang, C.-P., & Chuang, H.-L. (2008). Symptom clustering in older Taiwanese children with cancer. *Oncology Nursing Forum, 35*(2), 273–281. https://doi.org/10.1188/08.ONF.273-281