

SYMPTOM CLUSTER AND QUALITY OF LIFE IN CHILDREN WITH LEUKEMIA RECEIVING CHEMOTHERAPY

Bantita Naruemandecha¹, Tipaporn Wonghongkul^{2,*}, Jutarat Mesukko³, and Srimana Niyomkar³

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Abstract

Leukemia was mostly found in children younger than 15 years old. Children with leukemia suffer from multiple symptoms associated with chemotherapy. The objectives of this examination were aimed to describe symptom experience and quality of life, to identify symptom clusters, and to examine the interrelation between symptom clusters and the quality of life in 320 children with leukemia receiving chemotherapy. The purposive sampling method was adopted to choose samples from among eight tertiary hospitals. The research instruments included the Demographic and Medical Record Form, the Thai Memory Symptom Assessment Scale, and the Thai Pediatric Quality of Life Inventory. Data analysis was performed using the descriptive statistics, exploratory factor analysis, and Spearman's rank correlation coefficient. The results demonstrated that 1) the five most common symptoms included hair loss, nausea, loss of appetite, vomiting, and taste disorder. Hair loss was identified the most common symptom while taste disorder was the most severe, and "I don't look like myself" was the most distress symptom, 2) based on severity, five factors were of the total variance explained by 88.54% (neuropsychological discomfort, image and nutrition symptom, vasomotor symptom, general discomfort, and GI symptom), 3) based on distress, five factors were of the total variance explained by 82.88% (neuropsychological discomfort, GI and nutrition symptom, general discomfort, self-image and oral discomfort, and vasomotor symptom), and 4) All five symptom clusters based on either severity or distress had the statistically significant negative correlation with the quality of life.

Keywords: Symptom cluster, quality of life, children, leukemia, chemotherapy

Introduction

Leukemia was the most common type of cancer in children aged less than 15 years worldwide (WHO, 2017). The incidence rate of leukemia varied from region to region, ranging from 17.94 per 100,000 in Asia and Oceania to 37.74 per 100,000 in America, Canada, and Europe (Steliarova *et al.*, 2017). In Thailand, cancer was ranked as the third leading cause of death in children after accident and

¹ Faculty of Nursing, Chiang Mai University, Chiang Mai, 50200, Thailand. E-mail: bantita@sut.ac.th

² Department of Medical Nursing, Faculty of Nursing, Chiang Mai University, 110 Intawaroros Road, Muang District, Chiang Mai, 50200, Thailand. Tel. +66-53-935-020, E-mail: tipaporn.w@cmu.ac.th

³ Department of Pediatric Nursing, Faculty of Nursing, Chiang Mai University, Chiang Mai, 50200, Thailand.

* Corresponding author

infectious disease (Ministry of Public Health, 2018). From 2008 to 2014, the trends of the incidence rates remained increasing from 24.5 to 38.1 per 100,000 children less than 15 years old (Samantarath *et al.*, 2018).

Chemotherapy was the primary treatment modality for leukemia in children (Hockenberry *et al.*, 2017). The standard treatment protocol for children with leukemia comprised five chemotherapy treatment phases, including; induction, consolidation and CNS prophylaxis, interim maintenance, delayed intensification of re-induction, and maintenance phase (Thai Pediatric Oncology Group, 2016). Unfortunately, their efficacy in treating cancer with a cytotoxic agent had the unfavorable complications of normal tissue with rapid cell turnover (Zwerdling *et al.*, 2018). Thus, the leukemic children undergoing cancer treatment hardly experienced a single symptom in clinical practice; rather, they had suffered multiple symptoms concurrently.

In present study, symptom cluster in children with leukemia receiving Chemotherapy was discussed. Symptom cluster was referred to as a concurrence of two or three symptoms that were interrelated to each other (Dodd *et al.*, 2001). Two approaches implemented to identify symptom clusters included a priori and an empirically derived symptom cluster approach. A priori or clinically relevant approach rested on the identification of symptoms by the researchers that could be related with prior studies, while an empirically derived or statistical approach such as exploratory factor analysis or cluster analysis was adopted to identify the symptom cluster (Hair *et al.*, 2010).

A priori symptom cluster approach were used to identify from among commonly reported symptoms in cancer pediatric. The cluster comprised at least two to three symptoms. Prior studies in children with mixed type of cancer indicated the interrelation between fatigue with sleep impairment, behavior change, and distress (Hockenberry *et al.*, 2017), and fatigue with sleep-wake problems (Erickson *et al.*, 2013). An empirical symptom cluster approach were used to identify the cluster. The literature review described the symptom clusters in cancer children in four different countries. First, an examination of 144 children with mixed types of cancer in Taiwan, symptom clusters were developed, including: sensory discomfort and body image; circulatory and respiratory problems; fatigue, sleep, and distress; body image and eating difficulties; and gastrointestinal irritation and pain (Yeh *et al.*, 2008). Second, an examination of 131 children with mixed types of cancer in America revealed three clusters classified as a chemotherapy sequel; comprising physical side effects, mood

disturbance and neuropsychological discomfort (Baggott *et al.*, 2012). Third, a recent longitudinal study in Turkey examined in 54 children with mixed types of cancer, described five symptom clusters with the first 3 months post-diagnosis of cancer, and described a wide range of physical and emotional symptoms (Atay *et al.*, 2012). Lastly, the study of 108 children with mixed types of cancers in China illustrated two clusters; general symptoms and gastrointestinal symptoms (Tseng *et al.*, 2008). In Thailand, symptom cluster in children with leukemia receiving chemotherapy was not found in previous study.

Quality of life in children was defined as a multidimensional construct, comprised of the children's perception of the impact of disease and treatment on their functioning in the various domains of life; including physical, emotional, social and school (Varni *et al.*, 1999). Regarding the level of quality of life in children with cancer, the results of the previous studies were dissimilar. Some studies revealed that cancer children reported the cancer-threatening quality of life (van Riel *et al.*, 2014; Barakat *et al.*, 2015), while some other researchers reported high quality of life (Lyon *et al.*, 2014). In Thailand, children with cancer undergoing chemotherapy reported the favorable level of quality of life (Punthmatharith *et al.*, 2008). The aforementioned study in quality of life in children with cancer, overall quality of life inconsistencies because some studies revealed that adolescents with cancer reported higher quality of life than others.

Symptom cluster and quality of life in children with leukemia receiving chemotherapy were determined to be the major outcome of the cancer experience among children. It was reported that single symptom had statistically significant negative correlation with quality of life (Erickson *et al.*, 2013; Gordijn *et al.*, 2013; Nolan *et al.*, 2014). However, there were no empirical studies of symptom clusters approach, nor the studies of Thai children with leukemia receiving chemotherapy reporting the relationship with the quality of life and symptom cluster.

In summary, leukemia was mostly found in children younger than 15 years old. Chemotherapy was a major, but causes side effects cancer treatment. The gaps of knowledge are as follows; 1) There were a restricted number of researches conducted with an empirical symptom clusters approach, 2) The samples of the previous studies were heterogeneous for a type of cancers and the characteristics of symptom cluster studied were just some attributes, 3) Symptom cluster with regard to severity and distress was not found in previous studies, and 4) No investigations of symptom cluster based on severity and distress in Thai children with

leukemia receiving chemotherapy and no reporting the relationship between the symptom cluster and quality of life was found. To fill these gaps, the research questions of this study were to 1) What are symptoms prevalence, frequency, severity, distress, and quality of life in children with leukemia receiving chemotherapy; 2) What are symptom cluster based on symptom severity and symptom distress in children with leukemia receiving chemotherapy; 3) What are the relationships between symptom cluster and quality of life in children with leukemia receiving chemotherapy. Therefore, this study was aimed to describe symptom experience and quality of life and to identify symptom clusters, and to examine the relationships between symptom clusters and quality of life. The study of symptom clusters and quality of life in children with leukemia receiving chemotherapy was helpful because the knowledge gained could be helpful to nurses and health care providers to recognize symptoms including prevalence, frequency, severity, and distress, as well as symptom clusters, and quality of life. This would be expected to be useful to improve symptom management and treatment outcomes.

Materials and Methods

Research Design and Setting

A cross-sectional, descriptive correlational study was used in this study to describe symptom experience and quality of life, to identify symptom clusters, and to investigate the relationships between symptom clusters and quality of life in children with leukemia receiving chemotherapy.

The study protocol was reviewed and approved by the Ethical Committees of the Institutional Review Board (IRB), the Faculty of Nursing of the Chiang Mai University (2560-full035). It was submitted to the Institutional Review Board of the eight hospitals for ethic approval. A number of selected Thai hospitals were common in chemotherapy regimens based on the cancer treatment practices of the Thai National Protocol.

Participants

The number of participants was selected from among the population. Inclusion criteria for participants included as follows; 1) aged of 10-15 years, 2) legible and discern Thai language, 3) diagnosed with leukemia, 4) receiving chemotherapy at induction phase, and 5) voluntarily willing to participate in the study with parent's permission. Exclusion criterion included those patients who were disabled to complete the

questionnaires due to severe pain, severe nausea/vomiting, or life-threatening conditions.

Calculation on sample size was based on statistical analysis and prior studies. In factor analysis, the number of cases was greater than the number of variables. The preferable ratio was a minimum of 10 subjects to each variable to generalize the results to the entire population (Dixon, 2005), and Hair *et al.* (2010) demonstrated that at least five subjects per a variable were accepted, however; the more acceptable size was 0:1 ratio. In this study, calculate sample size based on Dixon (2005) and Hair *et al.* (2010), as the symptoms included approximate 32 items; the number of the samples was 160-320 samples to address the purposes of the study adequately, and 320 cancer children were chosen in this study. A list of children with leukemia from each hospital was prepared under the inclusion criteria.

The number of sampling technique in each of the eight hospitals was calculated using the proportionate sampling technique based on the database on children with leukemia in 2015. A name list of children with leukemia in each hospital was created under the inclusion criteria. The proportionate sampling technique for calculation based on the statistical analysis was used in this study. According to the formula proposed by Neil (2010) for a number of samples in each group to calculate using the proportionate sampling technique, a total of 320 subjects were recruited from the selected hospitals.

Data were collected from September 2017 to April 2018 after obtaining approval from the Ethical Committees of the Institutional Review Board. The researcher explained the purpose, methods, and process of the study to the pediatric ward and informed them that their personal information was protected and that there would be no harm of dropping out during the study; subsequently, consent to participate was received. Then, the questionnaires were filled out at the same time in a room by patients and the time for answering the questionnaires was approximately 20 min.

Research Instruments

In this study, three questionnaires were comprised of the Demographic and Medical Record Form, the Thai Memorial Symptom Assessment Scale, and Thai Pediatric Quality of Life Inventory.

The researcher-developed Demographic and Medical Record Form was to collect the following data: 1) respondents' demographic data, age, sex, education, household income, and lead family caregiver, and 2) medical history; including weight, height, body mass index, other co-morbid diseases,

duration of being diagnosed of leukemia, and medicine usage.

The Memorial Symptom Assessment Scale was originally developed by Portenoy *et al.* (1994), and translated into Thai by Suwisith *et al.* (2008). The 32-item self-report questionnaires comprise four dimensions; prevalence, frequency, severity, and distress. On frequency, 4-point Likert-scale was assigned (from 1 = never to 4 = always). On severity 4-point Likert-scale was assigned (from 1 = mild to 4 = mostly severe). On distress, 5-point Likert-scale was assigned (from 1 = slightly to 5 = mostly persistent). In the event of absent symptom, 0 was referred (Portenoy *et al.*, 1994). The 'zero' score was referred to any scale dimensions in the event that the patients experience no symptom or none prevalence of symptoms. However, if the patients reported symptoms, score calculation on frequency, severity, and distress were included (Portenoy *et al.*, 1994). In this study, the reliability of Thai-MSAS was tested for one-day test-retest reliability, using the Pearson's Correlation in a pilot study of twenty leukemia pediatric patients receiving chemotherapy. In test-retest, the results showed significantly and highly stable coefficients on symptom prevalence, frequency, severity, and distress in twenty cases by 0.82, 0.90, 0.90, and 0.92 respectively. For the overall 320 cases, the internal consistency with Cronbach's alphas was significantly and highly correlated by 0.88, 0.85, 0.92, and 0.90, respectively.

Thai Version of Pediatric Quality of Life Inventory was originally developed by Varni (1999) and was translated into Thai language by Sritipsukho *et al.* (2013). The self-report 23-item questionnaire consists of four domains including; physical functioning, emotional functioning, social functioning, and school functioning. The five-point Likert rating scale ranges from 0 (never) to 4 (always). To interpret results, the 0-4 scale reversed-scoring items were linearly transformed to 0-100 points (never = 100, almost never = 75, sometimes = 50, usually = 25, and always = 0), the higher scores indicate better quality of life (Sritipsukho *et al.*, 2013). In this study, the Thai Peds-QOL was validated for internal consistency with the Cronbach alpha in twenty leukemia pediatric patients, were significantly and highly correlated at 0.90 for the pilot study, and 0.92 for the overall sample of 320 cases.

Data Analysis

Data analysis is in the line the research questions and the statistical analysis implement included as follows:

1. Descriptive statistics were used to describe demographic and clinical characteristics of the study. Nominal data (age, gender, educational level,

family income, main caregiver) were described by frequency and percentage. Interval data (BMI, number of co-morbidity, duration of chemotherapy, type of chemotherapy) were described by percentage. Overall and individual symptoms (prevalence frequency, severity, and distress) were explained with frequency and percentage, while the QOL was analyzed in terms of mean and standard deviation.

2. Factor analysis was used to identify groups of similar items. In this study, factor analysis was employed to identify the optimal number of symptom clusters based on severity and distress. Symptom clusters were classified by using two methods including statistical analysis approach by exploratory factor analysis and etiology or mechanism analysis.

3. Spearman's rank correlation coefficient were used to test the correlation between symptom cluster and quality of life. Kolmogorov-Smirnov test was used to examine the normality data of the quality of life variables. The results demonstrated that the Thai Peds-QOL was interval data, and non-normal distribution. Thus, Spearman's rank correlation coefficient were used.

Results

This section contains the participant characteristics, symptoms and symptom cluster, and relationships between symptom cluster and quality of life.

Participant Characteristics

Demographically, the pediatric age was in the range between 10 and 15 years old ($\bar{x}$ = 11.48, SD = 1.82). Most respondents were mainly male (60.94%) and primary education (64.06%). Most of them stayed with family (68.13%). The total household income was in the range between 6,500 and 42,000 Thai Baht per month ($\bar{x}$ = 13,500, SD = 308.27). Clinically, about half of samples were underweight (51.25%), almost half of them had comorbidity disease (43.13%), and gastrointestinal ulcer was mostly found in comorbidity disease (52.17%). The total duration of chemotherapy treatment for these pediatric patients ranged between 2-33 days ($\bar{x}$ = 20.66, SD = 2.24). The major types of chemotherapy included Prednisone (96.25%), Plant Alkaloid (82.19%), Antimetabolites (71.56%), Antibiotics (66.25%), Alkylating Agents (40%), and Miscellaneous (25.62%).

Descriptive statistics of quality of life including means and standard deviations were used to describe overall quality of life and four subscales. The mean score of overall QOL was 63.82 (SD = 21.57) in possible values 0 to 100, and four subscales of QOL were social function 70.63 (SD =

24.62), emotional function 63.22 (SD = 23.85), physical function 62.76 (SD = 23.58), and school function 59.50 (SD = 27.76).

Symptoms and Symptom Cluster in Children with Leukemia Receiving Chemotherapy

Symptoms: this part presents four sections including prevalence, frequency, severity, and distress.

Prevalence, the five most common symptoms included hair loss (94.38%), nausea (91.56%), loss of appetite (89.69%), vomiting (88.75%), and taste disorder (86.25%). *Frequency*, the five mostly often occurring symptoms included hair loss (77.15%), nausea (44.71%), lack of energy (41.91%), itching (35.98%), and "I don't look like myself" (29.03%). *Severity*, the five most severe symptoms included taste disorder (88.77%), hair loss (80.13%), lack of energy (46.32%), nausea (34.47%), and weight loss (31.50%). *Distress*, the five most very distress were "I don't look like myself" (54.44%), lack of energy (46.69%), nausea (40.61%), vomiting (31.34%), and hair loss (28.81%).

Symptom clusters: this section were analyzed using principle component analysis (PCA) with oblique rotation to explore symptom cluster based on severity and distress (Table 1).

Symptom cluster based on severity, five factors explained overall by 88.54% of variance, including neuropsychological discomfort, image and nutrition symptom, vasomotor symptom, general discomfort, and GI symptom.

Factor 1 Neuropsychological discomfort consisted of thirteen symptoms. The factor loading scores in this symptom cluster ranged from 0.708 to 0.952, indicating a strong relationship between symptoms and factors. The cluster was named "Neuropsychological discomfort" in accordance with main symptoms relating to Neuro discomfort; including dizziness, diarrhea, difficulty swallowing, skin changes, urination problems, pain, numbness in hands or feet, vomiting, and constipate. Psychological discomfort included worrying, feeling sad, feeling drowsy, and feeling irritable. The first factor represented the eigenvalue of 17.69% and 57.08% of all the variation for symptoms explained in this cluster. The homogeneity of this cluster was high as represented by Cronbach's alpha 0.997.

Factor 2, image and nutrition symptom consisted of seven symptoms. The factor loading scores in this cluster ranged from 0.574 to 0.909, indicating a strong relationship between symptoms and factors. The cluster was named "Image and nutrition symptom" in accordance with main symptoms relating to image symptom including "I don't look like myself", weight loss, and hair loss.

Nutrition symptom included lack of energy, mouth sore, dry mouth, and taste disorder. The second factor represented the eigenvalue of 4.49% and 14.49% of all the variation for symptoms explained in this cluster. The homogeneity of this cluster was high as represented by Cronbach's alpha 0.923.

Factor 3, vasomotor symptom consisted of three symptoms including sweats, feeling nervous, and cough. The factor loading scores in this cluster ranged from 0.845 and 0.923, indicating a strong relationship between symptoms and factor. The third factor represented the eigenvalue of 2.43% and 7.8% of all the variation for symptoms explained in this cluster. The homogeneity of this cluster was high as represented by Cronbach's alpha 0.962.

Factor 4, general discomfort consisted of six symptoms including difficulty sleeping, edema, shortness of breath, itching, feeling bloated, and difficulty concentrating. The factor loading scores in this cluster ranged from 0.753 to 0.979 indicating a strong relationship between symptoms and factor. The fourth factor represented the eigenvalue of 1.71 % and 5.51% of all the variation for symptoms explained in this cluster. The homogeneity of this cluster was high as represented by Cronbach's alpha 0.956.

Factor 5, GI symptom consisted of two symptoms including nausea, and loss of appetite. The factor loading scores in this cluster ranged from 0.837 to 0.890, indicating a strong relationship between symptoms and factors. The fifth factor represented the eigenvalue of 1.13% and 3.63% of all the variation for symptoms explained in this cluster. The homogeneity of this cluster was high as represented by Cronbach's alpha 0.862.

Symptom cluster based on distress, five factors explained overall by 82.88% of variance. The factors were named neuropsychological discomfort, GI and nutrition symptom, general discomfort, self-image and oral discomfort, and vasomotor symptom.

Factor 1, neuropsychological discomfort consisted of seven symptoms. The factor loading scores in this cluster ranged from 0.733 to 0.954, indicating a strong relationship between symptoms and factor. The cluster was named "Neuropsychological discomfort" consistent with symptoms that mainly related to neuro including urination problems, itching, dizziness, skin changes, and diarrhea. Psychological discomfort including feeling drowsy and feeling irritable. The first factor represented the eigenvalue of 12.29 and 39.65 % of all the variation for symptoms explained in this cluster. The homogeneity of this cluster was high as represented by Cronbach's alpha 0.961.

Factor 2, GI and nutrition symptom consisted of six symptoms. The factor loading scores in this

Table 1. Exploratory factor analysis symptom cluster loadings based on severity and distress, and comparison of similarities among symptom cluster

Symptoms	Neuropsychological discomfort		Image and nutrition symptom		Self-image and oral discomfort		Vasomotor symptom		General discomfort		GI symptom	GI and nutrition symptom
	Severity	Distress	Severity	Distress	Severity	Distress	Severity	Distress	Severity	Distress	Severity	Distress
Dizziness	0.952	0.935										
Worrying	0.936			0.890								
Diarrhea	0.929	0.906										
Difficulty swallowing	0.920			0.928								
Skin changes	0.910	0.914										
Problems urination	0.895	0.947										
Feeling sad	0.893			0.809								
Pain	0.891			0.867								
Tingling in hand or feet	0.868			0.887								
Feeling drowsy	0.836	0.954										
Feeling irritate	0.826	0.733										
Vomiting	0.735										0.944	
Constipation	0.708			0.879								
Lack of energy			0.909								0.897	
I don't look like myself			0.888	0.769								
Mouth sore			0.867	0.628								
Dry mouth			0.861	0.916								
Weight loss			0.797	0.865								
Taste change			0.734								0.864	
Hair loss			0.574								0.734	
Sweats					0.923	0.817						
Feeling nervous					0.921	0.939						
Cough					0.845			0.839				
Difficulty sleeping							0.979	0.940				
Swelling of arm or leg							0.944	0.941				
Shortness breath							0.929	0.868				
Itching		0.939					0.854					
Felling bloated							0.805	0.957				
Difficulty concentrate						0.951	0.753					
Nausea											0.890	0.881
Lack of appetite											0.837	0.917
Total symptoms	13	7	7	10	3	3	6	5	2	6		
Eigenvalue	17.69	12.29	4.49	2.13	2.43	1.39	1.71	3.02	1.13	6.87		
Variance explained	57.08	39.65	14.49	6.86	7.83	4.49	5.51	9.73	3.63	22.15		
Accumulated variance	57.08	39.65	71.57	46.51	79.40	51.00	84.91	60.73	88.54	82.88		
Cronbach's alpha	0.977	0.961	0.923	0.958	0.962	82.88	0.956	71.53	0.862	0.943		
Similar Rate Based on Severity	46.15% (6 of 13)		57.14% (4 of 7)		66.66% (2 of 3)		66.66% (4 of 6)		100% (2 of 2)			
Similar Rate Based on Distress		85.71% (6 of 7)		40% (4 of 10)		66.66% (2 of 3)		80% (4 of 5)		33.33% (2 of 6)		

cluster ranged from 0.734 to 0.944, indicating a strong relationship between symptoms and factor. The cluster was named “GI and nutrition symptom” as consistent with main symptoms relating to GI symptom including vomiting, loss of appetite, and nausea. Nutrition symptom included lack of energy and taste disorder. The second factor represented the eigenvalue of 6.87 and 22.15 % of all the variation for symptoms explained in this cluster. The homogeneity of this cluster was high as represented by Cronbach's alpha 0.943.

Factor 3, general discomfort consisted of five symptoms including feeling bloated, swelling of arms or legs, difficulty sleeping, shortness of breath, and cough. The factor loading scores in this cluster ranged from 0.839 to 0.957 indicating a strong

relationship between symptoms and factor. The third factor represented the eigenvalue of 3.02 and 9.73% of all the variation for symptoms explained in this cluster. The homogeneity of this cluster was high as represented by Cronbach's alpha 0.945.

Factor 4, self-image and oral discomfort consisted of ten symptoms. The factor loading scores in this cluster ranged from 0.628 to 0.928, indicating a strong relationship between symptoms and factor. The cluster was named “Self-image and oral discomfort” as consistent with main symptoms relating to self-image discomfort including worrying, numbness in hands or feet, constipation, pain, weight loss, feeling sad, and “I don't look like myself”. Oral discomfort included difficulty swallowing, dry mouth, constipation, and mouth

Table 2. Aspects of quality of life associated with symptom cluster

Aspects of QOL	Symptom cluster			
	Severity		Distress	
	Odds Ratio	95% CI	Odds Ratio	95% CI
School function	4.14	2.20–7.80	3.15	1.76–5.65
Physical function	2.91	1.60–5.28	2.91	1.44–5.87
Emotional function	2.31	1.32–4.06	2.34	1.57–3.58
Social function	2.28	1.09–4.77	2.32	1.33–4.07

sore. The fourth factor represented the eigenvalue of 2.13 and 6.86 % of all the variation for symptoms explained in this cluster. The homogeneity of this cluster was high as represented by Cronbach's alpha 0.958.

Factor 5, vasomotor symptom consisted of three symptoms including difficulty concentrating, feeling nervous and sweats. The factor loading scores in this cluster ranged from 0.817 to 0.951, indicating a strong relationship between symptoms and factor. The fifth factor represented the eigenvalue of 1.39% and 4.49% of all the variation for symptoms explained in this cluster. The homogeneity of this cluster was high as represented by Cronbach's alpha 0.891.

Relationships between Symptom Cluster and Quality of Life in Children with Leukemia Receiving Chemotherapy

In this study, two approaches used to test the correlation between symptom cluster and quality of life including a Spearman's rank correlation coefficient and odds ratios approach.

First, the quality of life values were found to be interval data, and non-normal distribution. Thus, Spearman's rank correlation coefficient were used. Based on severity, five clusters including neuropsychological discomfort, image and nutrition symptom, vasomotor symptom, general discomfort, and GI symptom had statistically significant negative correlation with quality of life (-0.465, -0.360, -0.352, -0.620, and -0.598 respectively, all $p < 0.01$). Based on distress, five clusters including neuropsychological discomfort, GI and nutrition symptom, general discomfort, self-image and oral discomfort, and vasomotor symptom had statistically significant negative correlation with quality of life (-0.422, -0.505, -0.664, -0.389, and -0.377 respectively, all $p < 0.01$).

Second, the quality of life values were found to be ordinal and nominal variable. Thus, odds ratio were used. The estimated odds ratios with 95% confidence intervals for the associations between the aspects of quality of life including social, emotional, physical, and school and symptom cluster based on severity and distress. Based on severity, all aspects of QOL including school function (OR 4.14, 95% CI 2.20–7.80), physical

function (OR 2.91, 95% CI 1.60–5.28), emotional function (OR 2.31, 95% CI 1.32–4.06), and social function (OR 2.28, 95% CI 1.09–4.77), were statistically associated with symptom cluster based on severity. Based on distress, all aspects of QOL including school function (OR 3.15, 95% CI 1.76–5.65), physical function (OR 2.91, 95% CI 1.44–5.87), emotional function (OR 2.34, 95% CI 1.57–3.58), and social function (OR 2.32, 95% CI 1.33–4.07), were statistically associated with symptom cluster based on distress (Table 2).

Discussion

In this section, the interpretation of the main findings and discussion according to the research questions was focused, including characteristics of symptoms, characteristics of quality of life, symptom cluster based on severity and distress, and relationship between symptom cluster and quality of life.

Characteristics of Symptoms

The discussion is presented for hair loss, nausea, lack of energy, taste change and "I don't look like myself". Hair loss and nausea were the most prevalent, frequent, severe, distress and lack of energy was reported with high frequency, severity, distress symptom, while taste change was the most severe symptom, and "I don't look like myself" was the most distress symptom.

Hair loss showed a high prevalence, frequency, severity, and distress in this study. Hair loss could begin from a few days to 2-3 weeks after commencing chemotherapy treatment (Sullivan *et al.*, 2018). Prevalence rates of hair loss during chemotherapy in the previous study ranged from 90 to 100% (Hockenberry *et al.*, 2017). The children receiving chemotherapy including methotrexate, doxorubicin, and cyclophosphamide was induced the most frequent and severe effects. The chemotherapy worked by interfering with the more rapidly dividing cells of the body, including not only cancer cells but also hair follicles (Howard, 2017). The children perceived their hair to fall out severely immediately following the intervention, but in fact it happened several weeks in the later stage, and the

problems with hair loss were interrelated with the development of emotional distress aspects (Hockenberry *et al.*, 2017), were likely to be interrelated the change in attractiveness, femininity, and caused the children to lose their mental self-image and self-confidence with their body image (Howard, 2017).

Nausea showed a high prevalence, frequency, severity, and distress in this study. Prevalence rates of nausea during chemotherapy in the previous study ranged from 50 to 100% (Hockenberry *et al.*, 2017; Baggott *et al.*, 2012). The children receiving myelosuppressive chemotherapy had a direct effect on the anticipatory nausea, and increased significantly for the week in which chemotherapy was rendered (Walker *et al.*, 2010). The chemotherapy agents induced releasing of serotonin and substance P from the cells of the gastric mucosa, which then sent signals to induce nausea and/or vomiting (Girish and Manikandan., 2007). The children were likely to perceive nausea and vomiting as hindrance to eating, causing eating difficulties even with familiar foods and drinks (Hockenberry *et al.*, 2017).

Lack of energy showed a high frequency, severity, and distress in this study. The previous study demonstrated a predictable pattern of lack of energy within a cycle of chemotherapy, where lack of energy peaks during the week after chemotherapy administration before declining until the next administration (Erickson, 2013). The children receiving myelosuppressive chemotherapy could be induced inflammatory cytokine. The cytokine acted on brain regions and affects changes of monoamines, prostaglandins and substance P that involve hormones, inflammatory, and neurotransmitter (Owens and Mindell, 2011). The corticosteroids in cycle of chemotherapy interrelated with physical activity such as pain, fatigue, and sleep impairment (Khamboon *et al.*, 2015). The children were likely to perceive lack of energy as unpredictable and had severe difficulty falling asleep, night-time awakening, and daytime sleepiness (Hinds *et al.*, 2013).

Taste disorder was the most severe symptom in this study. Taste disorders were described as loss of taste perception, decreased or increased sensitivity of taste, and perceived distorted taste (Boltong and Keast, 2012). Chemotherapy included destruction or interference and cellular turnover of the epithelial cells of the taste receptors, altered number or structure of taste cell receptors, as well as secondary effects such as chemotherapy induced severity of physical change including mucositis, neurotoxicity, detected drug secretion in saliva, and change in sense of sweet, salty, sour, or bitter tastes (Hockenberry *et al.*, 2017). A change in sense of

food tastes caused a dislike for food, leading to loss of appetite or weight loss (Walker *et al.*, 2010).

"I don't look like myself" was the most distress symptom. This finding could be clarified in term of the modifications in self-perception that the male pattern baldness, weight reduction, absence of vitality, poor skin appearance (Erickson, 2013), which are brought about by chemotherapy and influenced all immature physically and genuinely trouble (Hockenberry *et al.*, 2017). The children may have the discernment that "I don't look like myself" and the issues with male pattern baldness were related with formative parts of enthusiastic trouble (Hockenberry *et al.*, 2017), which may be connected to modification of engaging quality, womanliness, and might make the kids lose their confidence and fearlessness with their self-perception.

Characteristics of Quality of Life

From this study's findings revealed a lowest score on total QOL (Mean 63.82), lowest score on school functioning (Mean 59.50), and the highest score on social functioning (Mean 70.63). Although, different in setting, and participants' ages from the current study. A previous studies, Ruksrithong (2015) studied in Thai children and adolescents with cancer age between 5-15 years. The result found that lowest score on school functioning (Mean 68.3) and the highest score on social functioning (Mean 85.0). Similarity, in the U.S. adolescents with cancer age between 15-18 years reported the lowest score on school functioning (Mean 58.9) and the highest score on social functioning (Mean 75.4) (Smith *et al.*, 2013). In addition, Taiwanese children with cancer age between 7-18 years reported the lowest score on school functioning (Mean 72.2) and the highest score on social functioning (Mean 88.6) (Pan *et al.*, 2016).

Symptom Cluster Based on Severity and Distress

The discussion included a comparison of symptom cluster based on severity and distress, explanation of similarities of the symptoms within the cluster, and previous study (Table 1).

Neuropsychological discomfort based on severity and distress. The neuropsychological discomfort cluster based on severity was 46.15%, while similarities rate based on distress was 85.71%. Common symptoms were found in clusters, including dizziness, diarrhea, skin changes, urination problem, feeling drowsy, and feeling irritable. Recent research identified four symptoms: dizziness, skin changes, feeling drowsy and feeling irritable was consistent with previous research in children (Baggott *et al.*, 2012), and adults with cancer (Suwisith *et al.*, 2008; Huang *et al.*, 2018).

Chemotherapy including fluorouracil, methotrexate, and cyclophosphamide could affect or harm the CNS system in cranial nerves causing conditions; peripheral nerve fibers sending signals to skeletal muscle and internal organs and glands (Grisold *et al.*, 2014); cognitive or thought-process changes including feeling drowsy and feeling irritable (Wampaalu *et al.*, 2016); movement disorder and balance including dizziness; and sensory problems including skin changes (Grisold *et al.*, 2014). Moreover, chemotherapy had a direct effect on the autonomic nervous system including sympathetic and parasympathetic nerves were reduced releasing of postganglionic fibers from these ganglia travel in the hypogastric and pelvic nerves which could cause bladder and bowel dysfunction including diarrhea and urination problems (Purves *et al.*, 2017).

Image and nutrition symptom cluster based on severity and self-image and oral discomfort cluster based on distress. The image and nutrition cluster based on severity was 57.14%, while similarities rate based on distress was 40%. Four Common symptoms found in both clusters including "I don't look like myself", mouth sore, dry mouth, and weight loss, were consistent with previous research in children (Tseng *et al.*, 2008; Baggott *et al.*, 2012), and adults with cancer (Chongkham-ang *et al.*, 2018). The literature review regarding four symptoms including "I don't look like myself", mouth sore, dry mouth, and weight loss found in previous studies; the symptom cluster was related to the side effects of chemotherapy treatment. Chemotherapy including methotrexate, doxorubicin, and cyclophosphamide had a direct effect on the epithelial cell of the taste receptors (Huang *et al.*, 2018), and more rapidly dividing cells of the body, not only cancer cells but also hair follicles (Howard, 2017), can also cause change in body images, the deficient intake of foods and water promote dry mouth, mouth sore, as well as weight loss in the patients (Shosha *et al.*, 2013). Weight loss yielded a concern of body image concerns, particularly in younger women. Body image was referred to the mental and self-image and feelings of an individual about their body (Shosha *et al.*, 2013). The study of children with cancer in the perception that their hair immediately fell out after starting treatment, in fact this happened several weeks later. Hair loss, skin changes, and weight loss could be affected by chemotherapy which all these influenced the patients' appearance, and personality. The perceived impaired body image did not only affect the female, but male patients as well (Khamboon *et al.*, 2015).

Vasomotor symptom cluster based on severity and distress. The vasomotor cluster based on severity and distress was 66.66%. Two Common symptoms found in both clusters were sweats and

feeling nervous, consistently with the previous research examined in children (Tseng *et al.*, 2008; Baggott *et al.*, 2012), and adults with cancer (Chongkham-ang *et al.*, 2018). The literature review for the symptoms found a "vasomotor symptom cluster", was related to vasoactive chemicals such as vasodilator acetylcholine that was known for causing an increase in blood flow in cell-tumor by vasomotor changes; the perspiration and vasodilatation interrelated with night sweats and hot flashes appears to be regulated by the thermoregulatory nucleus, located in the preoptic area of the hypothalamus (Davis *et al.*, 2011). Norepinephrine and serotonin were involved with the complex neuroendocrine pathway controlling the thermoregulatory zone, which could cause hyperthermia. The thermoregulatory nucleus regulated core body temperature and worked to keep it within a homeostatic range called the thermoregulatory zone (Davis *et al.*, 2011). Chemotherapy, including methotrexate causes estrogen withdrawal that increases serotonin and norepinephrine receptors in the hypothalamus (Cameron *et al.*, 2016). In pediatric, a difficulty concentrating neuroendocrine pathway that could be related with an excess sweating during the night and feeling of hot throughout the body (Atay *et al.*, 2012; Baggott *et al.*, 2012).

General discomfort cluster based on severity and distress. The general discomfort cluster based on severity was 66.66%, while similarities rate based on distress was 80%. Four Common symptoms were found in both clusters including difficulty sleeping, swelling of arms or legs, shortness of breath, and bloating. Four symptoms were consistent with the previous research examined in children (Tseng *et al.*, 2008) and adults with cancer (Chongkham-ang *et al.*, 2018; Phligbua *et al.*, 2013). The literature review on symptom cluster found a short duration of nighttime sleep in pediatric patients were interrelated with shortness of breath, respiratory systems interrelated to a hypothalamic-pituitary axis can result in unsteady melatonin secretion, contributing to sleep-wake disturbances (Owens and Mindell, 2011). The indirect side effects of chemotherapy caused suffering, emotional discomfort and a stressful life.

GI symptom cluster based on severity and GI and nutrition symptom cluster based on distress. The GI cluster based on severity was 100%, while similarities rate based on distress was 33.33%. Common symptoms were found in both cluster including nausea, and loss of appetite. The study found that the symptoms were consistent with the previous findings in children (Tseng *et al.*, 2008; Yeh *et al.*, 2008; Atay *et al.*, 2012) and adults (Skerman *et al.*, 2009). The literature review on

symptoms cluster found chemotherapy a cause of acute damage to the gastric and intestinal mucosa, leading to loss of epithelium and induced mitotic arrest of crypt cells leading to an increase in the ratio of immature secretory crypt cells to mature villous enterocytes (Yarbro *et al.*, 2017). The increased volume of fluid that leaves the small bowel exceeds the absorptive capacity of the colon, leading to mucosal changes interrelated with apoptosis, such as epithelial vacuolization and goblet cell hyperplasia, suggestive of mucin hypersecretion (Yarbro *et al.*, 2017). Nausea was an unpleasant sensation of an urge to disgorge and was accompanied by multiple symptoms due to the decreased parasympathetic and increased sympathetic nervous system inducing physical severity: salivation increased in blood pressure, heart rate, and decreased GI motion (Purves *et al.*, 2017). These symptoms induced or promoted other symptoms such as loss of appetite, decreased drinking or consuming which induced dehydration, loss of appetite, and lack of energy feeling (Khamboon *et al.*, 2015).

Overall, five pairs of symptom clusters were compared based on severity and distress was shown in Table 1. Based on severity, the symptom concurrence rates among neuropsychological discomfort, image and nutrition symptom, vasomotor symptom, general discomfort, and GI symptom clusters were 46.15, 57.14, 66.66, 66.66, and 100.0%, respectively. Based on distress, the symptom concurrence rates among neuropsychological discomfort, self-image and oral discomfort, vasomotor symptom, general discomfort, and GI and nutrition symptom cluster were 85.74, 40, 66.66, 80, and 33.33%, respectively. The finding of this study suggests further examination to investigate the difference between these two symptom characteristics (severity and distress). The symptoms could be classified into a same cluster according to the relationship and/or common causes of diseases.

Relationship between Symptom Cluster and Quality of Life

This study provided important information about the relationship between QOL and symptom cluster based on severity and distress in children with leukemia receiving chemotherapy in Thailand. The entire five symptom clusters based on either severity or distress had statistically significant negative correlations with the quality of life in children with leukemia receiving chemotherapy. The relationships between symptom cluster based on severity and distress and quality of life in this study was discussed with the contribution grounded from previous researches.

Neuropsychological discomfort cluster based on severity and distress had statistically significant negative correlation with QOL ($r = -0.465$, and -0.422 , $p < 0.01$; respectively). The relationship in the explanation contributed to nervous system and chemotherapy dependent psychological symptoms (Grisold *et al.*, 2014). This affected physical and psychological on the patients' life and could affect overall QOL, might be because it could occur a delay in cognitive development during the episodes of prolonged illness or as a result of complications from treatments (Purves *et al.*, 2017). The pediatric patients with cancer were likely to be restricted cognitively; for instance, difficulty with abstract and conceptual thinking (Donnan *et al.*, 2015). As 60% children undergoing cancer treatment including chemotherapy experienced cancer-related cognitive problems including ability to understand abstract that they developed a negative viewpoint and could aggravate a negative impact on the QOL of the pediatric Leukemia patients. However, since this is a pilot examination of the relationship between QOL and neuropsychological discomfort cluster, further study of children with cancer is required in support to the finding.

Image and nutrition symptom cluster based on severity and self-image and oral discomfort cluster based on distress had statistically significant negative correlation with QOL ($r = -0.360$, and -0.389 , $p < 0.01$; respectively). Chemotherapy might induce symptoms and physical changes (e.g., hair loss, weight loss, skin change) and psychological change (e.g., feeling worry, depression). These changes could influence the mental function, appearance, and personality on cancer patients (Howard, 2017). Consistent with previous studies suggesting that adolescents with cancer suffering from their unpleasant appearance as resulted from changes in body, especially hair loss and weight gain (Howard, 2017), they reported the feeling of extreme upset with their physical changes (Shosha, 2016).

Vasomotor symptom cluster based on severity and distress had statistically significant negative correlation with QOL ($r = -0.352$, and -0.377 , $p < 0.01$; respectively). The relationship in the explanation might relate to vasodilator of the chemotherapy dependent autonomic nervous system (Cameron *et al.*, 2016). The perspiration and vasodilatation interrelating with night sweats and hot flashes could interrelate with sleep disorder and emotional disturbances (Thurston *et al.*, 2008), as well as decreased cognitive functions, and could lead to social impairment and withdrawal of physical activity and it had a significantly effect on their overall QOL (Mandolesi *et al.*, 2018).

General discomfort cluster based on severity and distress had statistically significant negative

correlation with QOL ($r = -0.620$, and -0.664 , $p < 0.01$; respectively). The relationship in the explanation might contribute to chemotherapy because the chemotherapy induces some severe symptoms during first week post-chemotherapy treatment (Sullivan *et al.*, 2018). General discomfort cluster included difficulty sleeping, fatigue and pain that partly had an effect on the QOL. A difficulty to sleeping in a night-time, the children might perceive a lack of energy in daytime, worse physical activity and psychosocial discomfort (Medic *et al.*, 2017). The cancer children were unenergetic to partake in school activities, loss of active feeling, emotionally and socially impaired performance, as well as the impact on overall QOL (Hockenberry *et al.*, 2017).

GI symptom cluster based on severity and GI and nutrition symptom cluster based on distress had statistically significant negative correlation with QOL ($r = -0.598$, and -0.505 , $p < 0.01$; respectively). GI symptom cluster including nausea, vomiting, and loss of appetite might affect the patient both physical, and psychological. Severe nausea had impact in the physical QOL dimension and interfered with daily living in children with cancer (Samantarath *et al.*, 2018).

However, if considering epidemiology, odds ratio were used to test the correlation between symptom cluster and aspects of quality of life. All aspects of QOL including social function, emotional, function, physical function, and school function were statistically associated with symptom cluster based on severity and distress. The highest odds ratio on school functioning items indicates that children are often unable to attend school for some period of time following a diagnosis of leukemia. School is a major part of a child's life, and changes to the regular daily schedule can cause children to feel upset and sad. The odds ratio of social functioning was the lowest among the four aspects of quality of life. The lowest odds ratio of social functioning items indicate that children perceived themselves to be getting along with other teens and that their peers want to be friends with them. Since few empirical studies were conducted regarding the relationship between symptom clusters and quality of life in the specific group of samples, and more studies under the same topic would be needed to remedy the lack of empirical studies.

Conclusion and Implications

Conclusion and implications regarding nursing and clinical practice with children with leukemia receiving chemotherapy were presented as follows: This study provides evidence that children with leukemia receiving chemotherapy had multiple

symptoms and each symptom comprised four dimensions (prevalence, frequency, severity, and distress). Thus, the outcomes can help nurses and health care providers to apprehend symptom experience in the domains of the prevalence, frequency, severity, and distress, as well as symptom clusters more obviously.

All symptom clusters in this study had statistically significant negative correlation with QOL. Therefore, health care providers should recognize these clusters and provide a health care service to eliminate or decrease the symptoms within the clusters. It was found that the general discomfort cluster based on severity and distress showed a strong relationship with QOL. Therefore, non-pharmacological psychosocial management should focus on this group of patients. Symptom clusters management might improve the QOL of this group of patients. Such a nursing intervention program should be multidisciplinary and not only manage the physical symptoms and therapy associated side effects, but also target the patients' emotional status and changes to their daily lives.

As it's known that symptoms cluster could trigger the investigation of other symptoms within the cluster and bring about the improvement on clinical assessment techniques and symptoms remission within the cluster. An intermediate strategy could target only one of the symptoms for intervention and follow its effect on the other interrelated symptoms in the cluster

Recommendations for Future Research

In this study, the symptom cluster based on severity and distress had negative relationships with quality of life. As not many studies explored this relationship of symptom cluster and quality of life in this group, more studies are needed to explore the relationships in this group with other phased of chemotherapy and needed to explore long-term changes of symptom cluster associated with leukemic children. In addition, causal relationships among the cluster and quality of life are needed to provide strong evidence.

Conflicts of interest

The authors declare no conflict of interest.

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