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by Sri Ramdaniati

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Relationship between Anxiety and Fatigue in Leukemia Patients on Quality of Life with Nausea and Vomiting as an Intervening Factor

Sri Ramdaniati¹, Sri Kusmiati², Lia Herliana³

Department of Nursing, PUI-PK (HADE Centre) Poltekkes Kemenkes Tasikmalaya, Tasikmalaya, Indonesia

Abstract

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***Correspondence:** Lia Herliana, Department of Nursing, PUI-PK (HADE Centre) Poltekkes Kemenkes Tasikmalaya, Tasikmalaya, Indonesia. E-mail: liaherliana3@gmail.com
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AIM: This study aims to identify anxiety and fatigue in children with leukemia on the quality of life.

METHODS: Current research was implemented through a descriptive study with a cross-sectional design on children suffering from leukemia and undergoing a series of chemotherapy cycles. Through this design, the researcher measured the dependent variable, independent variable, and mediator variable at the same time with a sample of 82 people. Data collection was further done using PEDSQL 3 for cancer module. Meanwhile, the analysis used is path analysis which involves nausea and vomiting as a mediator.

RESULTS: The results showed that the factor that had a direct relationship with the child's quality of life was nausea and vomiting ($p < 0.05$) which was then analyzed using Sobel analysis resulting that nausea and vomiting were not a mediator of fatigue and anxiety. Therefore, it is necessary to pay attention to every nursing care practitioner to intervene in order to reduce anxiety and fatigue in children according to their condition.

CONCLUSION: Anxiety and fatigue together have a relationship with nausea and vomiting in pediatric patients suffering from leukemia and undergoing chemotherapy. Nausea and vomiting have a significant direct relationship with quality of life. Anxiety and fatigue have a direct relationship with quality of life without being mediated by nausea and vomiting variables

Introduction

Leukemia is one of the most common types of cancer in the world. Based on the results of the *Global Cancer Observatory*, the incidence of leukemia at all ages and genders in 2020 is 474,519 with the mortality rate is 311,594. Meanwhile, when viewed by the age group, the number of leukemia sufferers in the age range of 0–19 years old is 80,491 people. The results of the next survey explained that among this number, 58.21% of them are males [22]. There are currently several types of leukemia procedures that have been carried out by the medical team. The existing procedure includes chemotherapy, radiotherapy, bone marrow transplantation, and steroids. Each of these therapeutic procedures has a different impact on the patient's health and subsequent development. Leukemic patients will face various side effects that will impact their quality of life [1]. *National Cancer Institute* [2] also explained that there are four treatment options for leukemia, especially for acute lymphoblastic leukemia (ALL) in children, namely, chemotherapy, radiation, bone marrow transplantation, and targeted therapy. The therapy that is considered very effective for leukemia is chemotherapy. Chemotherapy is considered effective in the treating cancer, maintaining and restraining the

spread of cancer cells, slowing down the growth of cancer cells, as well as killing cancer cells that spread to the other parts of the body and reducing the symptoms caused by cancer. Patients with leukemia are divided into three stages, those are the induction, consolidation, and maintenance [3].

Chemotherapy is one of the most widely used medical procedures for treating cancer, including leukemia. However, this treatment has side effects. The use of chemotherapy can lead to an increase in free radicals in the blood. The research carried out by Hadinegoro *et al.* [3] explained that cancer cells and chemotherapy drugs produce free radicals that cause oxidative stress characterized by increased levels of *malondialdehyde* (MDA) in plasma. Cancer patients undergoing chemotherapy treatment experience oxidative stress which is characterized by an increase in free radicals and a decrease in the function of primary antioxidants (endogenous antioxidants) such as *superoxide dismutase* (SOD), *catalase* (CAT), and *glutathione peroxidase*.

Chemotherapy causes side effects that vary from mild to severe. It depends on the dose and chemotherapy regimen given. Cytostatic effects on normal mitotically active cells such as blood cells, gastrointestinal tract cells, skin, hair, and reproductive organs can cause side effects [3].

Side effects that can occur include gastrointestinal symptoms such as nausea and vomiting, stomatitis, diarrhea, and constipation; myelosuppression in the form of anemia, leukopenia, and thrombocytopenia; alopecia, liver, and kidney disorders [4]. The side effects of chemotherapy that is felt by many children have been described by Prisani and Rahayuningsih [5]. The results of their research stated that 60% of children experienced severe category of fatigue, 56.7% had severe sleep-wake disorders, 60% had severe pain, 53.3% had mild nausea, 53.3% had mild mood disorders, and 53.3% had severe changes in appearance. Furthermore, the results of the research conducted by Wijayanti *et al.* [6] also explained some of the side effects of chemotherapy, including nausea, vomiting, hair loss, mouth sores, diarrhea, decreased appetite, fatigue, anemia, constipation, and dry skin. In more detail, Herfiana and Arifah [7] also described the physiological effects of chemotherapy on children with leukemia, including 80% of baldness/alopecia, 56.7% of nausea, 53.3% of vomiting, 46% of decreased appetite, 63.3% of thrush, 10% of diarrhea, 46.7% of fatigue, 43.3% of increased risk of infection characterized by fever 43.3% of cough, 26.7% of flu, and 46.7% of bleeding. Based on the results of these studies, alopecia, canker sores, fatigue, pain, as well as nausea and vomiting are the most common side effects of chemotherapy in pediatric patients with leukemia. Nausea and vomiting are one of the scary side effects for sufferers and their families. This condition causes stress for sufferers and their families which sometimes make sufferers and their families choose to stop the therapy cycle. Parents often do not have the heart to see their children suffer. Discontinuation of the therapy cycle has the potential to increase cancer progression and reduce patient life expectancy [4]. The incidence of nausea and vomiting in each child undergoing chemotherapy always varies. Several studies have stated that older children have a higher tendency to nausea and vomiting [8]. In other studies, it can be explained that the length of therapy, the type of cytostatic drug used and the type of antiemetic have an influence on nausea and vomiting in pediatric patients with leukemia undergoing chemotherapy [9]. Conditions that occur as an effect of chemotherapy result in an influence on the quality of life of children. Quality of life is an individual's evaluation of his function and well-being in various areas of life in accordance with the culture, values, and expectations of the individual [10]. This quality of life is multidimensional in nature, involving physical, psychological, social, and environmental aspects. Sidabutar *et al.* [11] stated that the quality of life of school-age children with cancer is not quantitative but qualitative, looking at the 5 dimensions of life belonging to James Varni [12]. The results of this study explain that interpersonal conditions and personal conditions of a person greatly affects their quality of life. School-age children who develop cancer at an early stage actually have a lower quality of life than

those at an advanced stage. Another study conducted by Hilda *et al.* [13] suggested that children with cancer, especially leukemia has a lower quality of life compared to their siblings, in terms of physical, social, emotional, and school functions. This is supported by research in Pakistan which shows the same thing [14].

The aim

This research was done aiming to identify the relationship between anxiety and fatigue on quality of life with nausea and vomiting as the mediator.

Methods

Research design

Current research was implemented through a descriptive study with a *cross-sectional* design on children suffering from leukemia and undergoing a series of chemotherapy cycles. Through this design, the researcher measured the dependent variable, independent variable, and mediator variable at the same time. The research flow is (Figure 1):

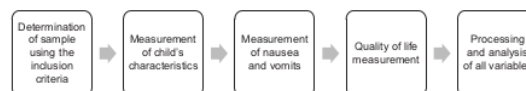


Figure 1: Research flow

Time and place

This research was carried out in two hospitals including Al Ihsan Bale Endah Hospital and Al Islam Hospital Bandung as well as Ambu Cancer House. The study began in January 2021, where the data collection was carried out for 5 months starting from September 2021 to January 2022.

Population and sample

Population

1. The target population in this study were all pediatric patients suffering from leukemia who were treated at Al Islam Hospital Bandung, Al Ihsan Hospital, and Ambu Cancer House.
2. The sample

The samples involved in this study were children suffering from leukemia and were treated at the Al Islam Hospital in Bandung, Al Ihsan Bale Endah Hospital, and the Ambu Cancer House. These samples were taken using a *consecutive sampling technique*, with the following inclusion criteria: pre-school children

to adolescents aged 3-18 years; currently, undergoing chemotherapy at any stage; and able to interact well. Meanwhile, the exclusion criteria are as follows: Children who have decreased consciousness and uncooperative parents.

Data collection instrument

1. Biodata and characteristics of the children including the treatment obtained during chemotherapy
2. Anxiety, which includes 28 question items answered by the children or assisted by the parents. The children answered yes or no, according to their current condition. The question items consisted of 22 positive and six negative question items with the score of 0–1. The higher the score obtained, the higher the anxiety suffered by the children. This questionnaire was modified from ZSRAS and TMAS that have been used and tested regarding its validity and reliability with r value of 0.947 and alpha value of 0.973 [15].
3. Fatigue. In this variable, two kinds of tools are used, namely the *parent fatigue scale* (PFS) for children aged < 7 years and the *children fatigue scale* (CFS) for children older than 7 years. PFS consists of 17 question items with alternative answers and different scores, namely (1) Does not feel fatigue at all, (2) Slightly feels fatigue, (3) Somewhat feels fatigue, (4) Quite feels fatigue, and (5) Heavily feels fatigue. CSF consists of 14 questions with the same alternative answers. This questionnaire has been used in several studies, namely the research of Hendrawati *et al.* and Novrianda *et al.* [16]. The validity scores for the two instruments are in the range of 0.509–0.884 with a Cronbach alpha value of 0.984 [17].
4. Nauseous and vomit. The instrument used in this variable is the *Rhodes Index for Nausea Vomiting and Retching* (RINVR). This questionnaire was used for adults as well as for children. It has eight question items with a rating range of 1 – 4, so the highest score for nausea and vomiting is 32.
5. Quality of life variable was measured using PEDsql from Varny [18], namely, PEDSQL 3.0 for cancer module. This questionnaire has 27 items with a value range of 0–4, so the maximum value of this instrument is 112.

Data

The analysis of the data collected was conducted using path analysis, which is a regression analysis involving mediator or intervening variables. The mediator variable is a variable that affects the

relationship between the independent variable and the dependent variable [19]. In this study, patient characteristics were the independent variable, nausea and vomiting as a mediator variable, and quality of life as the dependent variable. These conditions are described in the following form (Figure 2):

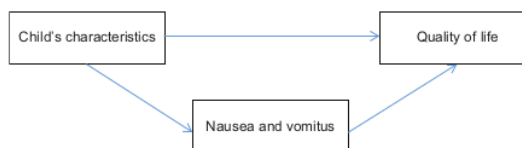


Figure 2: Patient characteristics

Research results

Table 1 explains that the average value of anxiety which is at a value of 7 is in the range of 0–20, the child with the highest anxiety score is at a score of 20, while the lowest is at a score of 0. Furthermore, fatigue has a range of 14–85 with a mean score of 37. The highest score of nausea and vomiting is 43, while the highest score of the quality of life is 66.

Table 1: Overview of anxiety, fatigue, nausea, and quality of life in children with leukemia undergoing chemotherapy

Variable	Mean	Standard deviation	Min-Max
Anxiety	7.707317	4.712704	0–20
Fatigue	37.54878	8.901592	19–60
Nausea and Vomiting	4.158537	4.997455	0–18
Quality of Life	31.76829	15.71608	0–66

Table 2 shows that the variables of anxiety and fatigue have a significant relationship with nausea and vomiting.

Table 2: The correlation between anxiety and partial fatigue with nausea and vomiting in pediatric patients with leukemia undergoing chemotherapy

Variable	Correlation Coefficient	Significance
Anxiety	0.3899	0.0003
Fatigue	0.3519	0.0012

Table 3 explains that anxiety, fatigue, as well as nausea and vomiting have a significant positive relationship with the children's quality of life ($p = 0.000$).

Table 3: The relationship between anxiety, fatigue and nausea partially with quality of life of children with leukemia undergoing chemotherapy

Variable	Correlation	Significance
Anxiety	0.5148	0.0000
Fatigue	0.6757	0.0000
Nausea Vomiting	0.4340	0.0000

The path analysis performed follows the following pattern (Figure 3):

Based on Table 4, it can be interpreted that the equation regression 1 (Table 3) shows that the beta

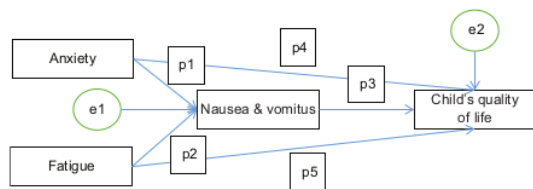


Figure 3: Path analysis 1

coefficient of the anxiety variable of 0.299 is the path value of p1 with a p value of 0.057. This indicates that children's anxiety does not have a significant effect on children's nausea and vomiting. Furthermore, the beta coefficient value of the fatigue variable of 0.085 is the path value/path p2 with a p value of 0.307. It means that fatigue does not have a significant effect on children's nausea and vomiting. In regression equation 2, it was found that the anxiety beta coefficient is 1.047 which is the path value of p4 with a p value of 0.961, meaning that anxiety has no effect on the quality of life of the children. Furthermore, the beta coefficient value of the fatigue variable of 0.202 is the path value of p4 with a p value of 0.000, which means that fatigue has a significant effect on the quality of life. Furthermore, beta coefficient value for the nausea variable is 0.702, which is the path value p3 with a p value of 0.013. This indicates that nausea and vomiting have a significant direct effect on children's quality of life.

Table 4: First equation regression test results: Effect of anxiety and fatigue variables on nausea vomiting

Variable	Coefficient	Standard error	Sig.	95% CI	R ²
Anxiety	0.299	0.155	0.057	-0.009-0.609	0.1632
Fatigue	0.085	0.822	0.307	-0.079	-0.248
cons	-1.329	2.443	0.588	-6.192-3.534	Table

The values obtained from the above test are then entered into the equation, so that the following equation is obtained.

1. Nausea and vomiting = -1.329 + 0.299 anxiety + 0.085 fatigue + 0.915

Based on the above equation, it is found that if anxiety increases by 1 point, nausea and vomiting will increase by 0.299 as well. In addition, if fatigue increases by 1 point, nausea and vomiting will increase by 0.085 points as well. In addition, anxiety and fatigue affect nausea and vomiting by 16.32% ($R^2 = 0.1632$) although they do not statistically effect.

2. Quality of life = -10.614 + 0.019 anxiety + 1.047 fatigue + 0.702 nausea and vomiting + 0.708

Based on the second equation above, it is found that if anxiety increases by 1 point, the quality of life will decrease by 0.019, if fatigue increases by 1 point, the quality of life will decrease by 1.047, and if nausea and vomiting increase by 1 point, the quality of life will decrease by 0.702. Furthermore, anxiety, fatigue, as well as nausea and vomiting affect the quality of life by 50.05% ($R^2 = 0.5005$)

Therefore, the path analysis Figure 4 and the path values are listed below:



Figure 4: Path analysis 2

The results of the path analysis above and Table 5 show that the amount of anxiety that will directly affect the quality of life is 0.019, while the amount of fatigue affects the quality of life is 1.047. In this case, the amount of the indirect effect will be calculated by multiplying the indirect coefficient, namely;

1. Total effect of anxiety on quality of life = (0.019) + (0.299 × 0.702) = 0.229
2. Total effect of fatigue on quality of life = (1.047) + (0.085 × 0.702) = 1.107
3. Total effect of nausea and vomiting on quality of life is 0.702

Table 5: Regression test results second equation: the effect of anxiety and fatigue variables on quality of life through nausea and vomiting

Variables	Coefficient	of Error	Sig.	95% CI	R ²
Anxiety	0.019	0.389	0.961	-0.755-0.793	0.5005
Fatigue	1.047	0.202	0.000	0.644-1.450	
Nausea	0.702	0.275	0.013	0.154	
Vomiting_cons	-10614	5.985	0.080	-22.529-1.302	

Furthermore, to know whether the mediator variable is significant or not, indicated by the multiplication of the coefficients above, it will be tested using the Sobel test by the assistance of online Sobel test calculator to obtain the t value as written in Table 6:

Based on the Table 6, it can be interpreted that the coefficient of indirect effect (through the mediator/intervening variable) is not significant, so that the nausea and vomiting variable cannot be considered as a mediator variable for the independent variable.

Table 6: Sobel test results on the effect of mediator variables on quality of life

Effect	t count	p value	Beta
Anxiety on quality of life through nausea and vomiting	0.9311 (t>1.96)	0.352 (p>)	0.229
Fatigue on quality of life through nausea and vomiting	0.96042 (t>1.96)	0.96042 (t>1.96)	0.96042 (t>1.96)

Discussion

In terms of the quality of life of children suffering from leukemia, the average score obtained was 31.77, which is much lower than the research carried out by Novrianda *et al.* [16] of 69.2, research conducted by Nurhidayah *et al.* [20] of 49.23, and research conducted by Sung *et al.* [21] of 63.33. This is very possible due to the use of different instruments. In this study, the instrument used was PEDSQL 3.0 for cancer module as applied by Nurhidayah *et al.* [20], while Novrianda *et al.* [16] and

Sung *et al.* [22] both used PEDSQL 4.0 *generic core scale*. The quality of life value in this study is also lower than the research conducted by Hilda *et al.* [13] which has an average score of 42.1. Hesketh further explained that nausea and vomiting in chemotherapy patients are influenced by several factors. These factors include age, gender, alcohol consumption, chemotherapy dose, and the level of emetogenesis of chemotherapy drugs/cancer drugs used [13], [16], [20], [21].

In this bivariate analysis, it was also explained that fatigue had a significant positive relationship with nausea and vomiting ($p < 0.05$) although the degree of correlation is weak ($r 0.351$). This can theoretically be explained that nausea and vomiting cause the input of food or nutrients into the patient's body to decrease which will have an impact on the entry of nutrients into cells. As a result, the body's cells will break down the fat in the body as an effort to produce energy. The breakdown of free fatty acids from fat tissue will result in the accumulation of ketones in the body. Changes in metabolic processes cause a decrease in metabolism or disruption in ATP regeneration. ATP or adenosine triphosphate is an important source of energy for muscle and bone contraction. This will cause fatigue and reduce the physical abilities of cancer patients [23].

Further analysis at the bivariate stage is to see the relationship between the independent variables and the quality of life of children. Based on testing at this stage, the variables that have a significant relationship with the quality of life of children are fatigue, anxiety, as well as nausea and vomiting, while age, gender, and other variables do not have a significant relationship. This is in line with the research conducted by Novrianda *et al.* [16] which explains that there is no relationship between children's age and quality of life ($p = 0.905$). This could be because most of the children in this study had undergone chemotherapy for an average of more than 12 months, and only a small proportion had undergone chemotherapy for < 1 year. This condition provides an opportunity for children to start adapting to the conditions they face on a daily basis and accepting all procedures that must be followed with full awareness. The role of parents, especially maternal support in this condition, is very necessary while accompanying children in following all chemotherapy protocols that must be followed [24].

Anxiety is a condition that is often found in children with cancer, including leukemia, in addition to other psychosocial problems such as sadness, disappointment, stress, and depression [13], [25], [26]. According to Saddock and Saddock [27], anxiety is a response to certain threatening situations and is a normal thing that is accompanied by development, change, new experiences in finding self-identity, and life. Anxiety is a subjective feeling of restless mental tension as a general reaction of the inability to cope with a problem or lack of security. These uncertain feelings are generally unpleasant which will later cause physiological and psychological changes [27]. Baytan *et al.*'s research in Turkey [28] explains

that anxiety in children with leukemia is higher than the anxiety of healthy siblings. Pouraboli *et al.* [29] in a study in Iran also explained that the average anxiety in children with leukemia was quite high [28], [29].

In this study, fatigue has a fairly strong positive correlation with quality of life with an r value of 0.676 and together with anxiety can affect children's quality of life by 50% ($p < 0.005$). This is in line with research by Hanifia [30] which explains that fatigue has a strong positive correlation with quality of life in pediatric patients with ALL undergoing chemotherapy with $r 0.677$ (p value 0.00). Another study that also shows the same thing is the study conducted by Ambrella *et al.* [31] who conducted a study on 42 children with leukemia. The results of their research explained that there was a significant relationship between fatigue and quality of life ($p < 0.05$). Fatigue experienced by children with leukemia can be caused by various things. In addition to nausea and vomiting, anemia is also the most common cause of fatigue in cancer patients [31]. Anemia is caused by a side effect of chemotherapy which also destroys healthy red blood cells. This will have an impact on the transport of oxygen and nutrients into the cells, so that the cells do not have enough energy [3]. The effects of chemotherapy also result in the release of cytokine substances such as TNF (tumor necrosis factor) and interleukins that cause anorexia. Anorexia occurs because cytokines such as interleukin-1 (IL-1) and tumor necrosis factor (TNF) will cause an increase in corticotropin-releasing hormone (CRH), a neurotransmitter in the central nervous system that suppresses appetite and glucose-sensitive neurons, causing a decrease in food intake. This results in weight loss, muscle mass, and anemia so that cancer patients with advanced stages tend to experience fatigue [32]. All of these things, if not addressed, will have a direct impact on the quality of life of children with leukemia.

Conclusions

Anxiety and fatigue together have a relationship with nausea and vomiting in pediatric patients suffering from leukemia and undergoing chemotherapy. Nausea and vomiting have a significant direct relationship with quality of life. Anxiety and fatigue have a direct relationship with quality of life without being mediated by nausea and vomiting variables.

Acknowledgment

This study has limitations in the number of samples, because it was only conducted on 82 children

suffering from leukemia aged between 3 - 18 years old. Therefore, some variables have an abnormal distribution. In addition, data collection cannot be carried out in hospitals as a whole because there are still some hospitals that do not allow data collection directly related to the pandemic, so some data were taken at Ambu Cancer Foundation, which is a halfway house that treats cancer patients, including children with leukemia.

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