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Malnutrition as Risk Factor for Febrile Neutropenia in Children with Acute Lymphoblastic Leukemia

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Abstract

BACKGROUND: Acute lymphoblastic leukemia (ALL) is the most common malignancy in children. Febrile neutropenia is one of medical emergencies in ALL patients. One of the risk factors that associated with febrile neutropenia is malnutrition. Malnutrition reduces the body's immunity that increases the incidence of infection.

AIM: The aim of the study is to prove malnutrition as risk factor in children with ALL who had febrile neutropenia

METHODS: This case-control study with samples a hundred children aged 1 month to 18 years old with ALL at Sanglah Hospital Denpasar between 2015 and 2021. Subjects were grouped into two, those with febrile neutropenia and without febrile neutropenia. The relationship between malnutrition and febrile neutropenia were analyzed using chi-square bivariate analysis test.

RESULTS: A hundred subjects were divided into two groups with 50 subjects in each group. Bivariate analysis showed significant association between malnutrition and febrile neutropenia (OR 4.53; 95%CI 1.95–10.51; $p < 0.001$).

CONCLUSION: Malnutrition acts as risk factor for febrile neutropenia in children with ALL.

Introduction

Nutrition has an important role in the immune system. The majority of patients with malignancy are malnourished, as many as 85% of patients. Malnutrition can interfere immune system [1], causing susceptibility to infection. One of the complications that often occur in children with malignancy is febrile neutropenia [2].

Acute lymphoblastic leukemia (ALL) is the most common malignancy in children under 15 years old with incidence 2–5 cases/100,000 children. The highest incidence occurs at age 2–5 years [3]. The mortality rate in children with ALL based on data from Cipto Mangunkusumo Hospital (RSCM) and Darmais Cancer Hospital in 2006–2010 was 20–30% [4]. Febrile neutropenia is one of the complications of chemotherapy with mortality rate 0.7–3.9% [5]. Febrile neutropenia is an emergency condition in hematology due to decrease of neutrophils, as one of the body's main defenses system against microbes, thus patients become susceptible to severe infections and death [6]. The incidence of febrile neutropenia can be influenced by the number of granulocytes and regimen of chemotherapy [7]. Another risk factors that influence the occurrence of febrile neutropenia are divided into patient-related risk factors such as age, gender, comorbid disease, and nutritional status. Other risk factors were type of malignancy and treatment modality [7], [8]. Malnutrition increase the risk of febrile neutropenia in children with malignancy [9]. Research from India showed strong association between malnutrition and mortality in children with hematological malignancies who were treated for febrile neutropenia [10].

Malnutrition is one of the factors that can reduce child's immune system to fight infection, [11] due to hormonal changes and decreased cytokine response [12]. The incidence of febrile neutropenia in severely malnourished group was higher than non-malnourished group ($p < 0.001$) [13]. Malnutrition itself can affect the number of neutrophils in the blood. Neutropenia that occurs in malnourished patients is caused by decrease proliferation of blood cell in bone marrow [14]. Malnutrition induces mesenchymal stem cells in the spinal cord to differentiate into adipogenic tissue that causes hematopoiesis failure and neutropenia in malnourished conditions [15].

A cross-sectional study conducted by Hidayat *et al*. found that 58% of children with ALL was good nutritional status [16]. This is because the research subjects are patients who have just been diagnosed

with ALL, meanwhile the incidence of malnutrition is found frequently in late-period [17]. Administration of chemotherapy in induction phase is a risk factor for febrile neutropenia [8]. Febrile neutropenia occurred mostly in the 1st week and 2nd week of induction phase, namely 47% and 43%, respectively [18]. This was caused by the condition of neutropenia that had occurred before chemotherapy was given, due to infiltration of cancer cells in the bone marrow which was aggravated by the administration of chemotherapy, resulting in febrile neutropenia [16].

Loeffen *et al*. found that malnutrition in children with malignancy was not associated with febrile neutropenia in the 1st year after diagnosis [18]. Meanwhile, study in Sardjito Hospital [19], found the relationship between malnutrition and the incidence of febrile neutropenia in children with ALL. Data regarding the relationship between malnutrition and febrile neutropenia are still controversial. This study was conducted to prove whether malnutrition is risk factor for febrile neutropenia in children with ALL, therefore early intervention can be carried out.

Materials and Methods

This case-control study was carried out with sample children who suffer ALL and divided into case group and control group. Those groups were matched based on the chemotherapy phase, namely the induction phase. Furthermore, both groups were assessed for their nutritional status. The research design can be seen in Figure 1. The population of this study was children aged 1 month–18 years old whom were diagnosed with ALL and hospitalized or controlled in pediatric outpatient clinic, Sanglah Hospital.

Data was taken from medical records. Samples were determined by consecutive sampling.

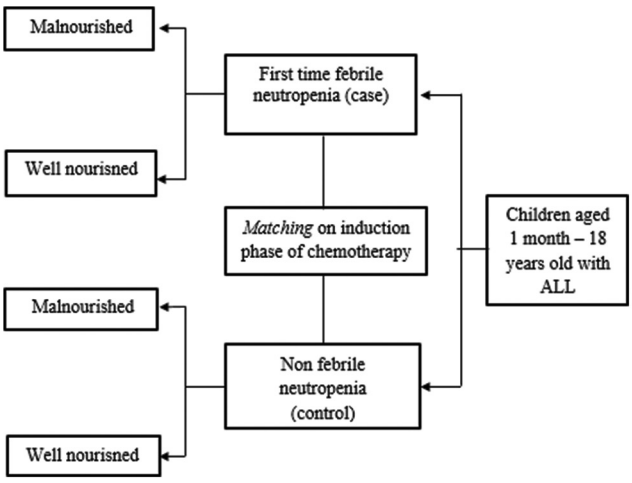

Figure 1: Scheme of research

Inclusion criteria for case group:

1. Children aged 1 month - 18 years old who were diagnosed with ALL and had febrile neutropenia for the 1st time during induction phase of chemotherapy
2. Hospitalization at Sanglah Hospital.

Inclusion criteria for control group:

1. Children aged 1 month–18 years who were diagnosed with ALL and without febrile neutropenia for the 1st time during the induction phase of chemotherapy
2. Inpatient or outpatient treatment in pediatrics department of Sanglah hospital.

Exclusion criteria for case and control group:

1. Fever within 6 h due to transfusion of blood or its products
2. Fever due to phlebitis caused by infusion, central venous catheters, and urinary catheters
3. Patients with thyroid disease, namely hyperthyroidism, hypothyroidism, goiter, thyroid tumors
4. Incomplete medical record data.

Sample size in this study was 100 subjects, 50 children in control group and 50 children in case group. Then, matching was applied, based on chemotherapy phase. Malnutrition is divided into undernutrition and overnutrition. Undernutrition has clinical manifestations such as wasting, acute malnutrition, chronic malnutrition, stunting, underweight, vitamin, and mineral deficiency. Overnutrition is overweight and obesity.

Those nutritional status was determined based on measurement of anthropometric status using the 2006 World Health Organization (WHO) growth curve and the 2000 Centers for Disease Control curve. If there is organ enlargement, nutritional status was assessed using upper arm circumference. Nutritional status is divided into (1) Poor nutrition (<70%), (2) Less nutrition (70–90%), (3) Good nutrition (90–110%), and (4) Over nutrition/obesity (>110%). Furthermore, it is divided into malnourished and well-nourished.

Febrile neutropenia is a syndrome consisting of 2 symptoms, namely fever which is defined as oral temperature 38.3°C (101°F) at least in 2 measurements with minimum 12 h, and neutropenia is defined as an Absolute Neutrophil Count <500 cells/mm^3 or <1000 cells/mm^3 with a tendency to decrease within 48 h The absolute neutrophil value in blood was measured by laboratory examination with the ADVIA 2120 device in laboratory. This study took samples with febrile neutropenia for the first time after being diagnosed with ALL. The diagnosis of febrile neutropenia was made by doctor in charge of the patient in hemato-oncology division and this data was taken from medical records.

Descriptive analysis was conducted to describe the general characteristics of the subjects. Variables with categorical scale would be displayed in terms of relative

frequency (amount and percentage). Variables with normal distribution of numerical scale would be displayed in the form of mean and standard deviation (SD), whereas if the data were not distributed normally, it would be displayed in median and interquatile ranges. Bivariate analysis was performed to assess the risk of malnutrition for febrile neutropenia in children with ALL by using Chi-square. Data analysis was performed by using SPSS version 26.

This research has obtained ethical clearance from the Research and Development Unit (R and D) of Medical Faculty, Udayana University/Sanglah Hospital No: 57/UN14.2.2.VII.14/LT/2021 as well as a research permit at Sanglah Hospital Denpasar with Number: LB.02.01/XIV 2.2.1/14123/2021.

Results

This research was carried out at Sanglah Hospital by taking data from medical records of pediatric patients aged 1 month–18 years who were newly diagnosed with ALL who received treatment from January 2015 to June 2021. During the study period there were 121 patients whom met inclusion criteria and 21 patients were excluded because of incomplete medical record. A total of 100 patients participated in this study.

The median age of subjects was 5 years with an age range of 1–15 years old, where most of the subjects (77%) were <10 years old. Characteristics of subjects with febrile neutropenia age <10 years were 80%; male gender was 58%; ALL morphology was L2 86%; high-risk stratification was 64%; and length of hospitalization <10 days was 54%. Subjects with febrile neutropenia who experienced malnutrition were 70% and 34% had hipoalbumin. Details of samples' characteristics data are shown in Table 1.

Table 1: Characteristic of samples

Characteristics	Febrile neutropenia (n = 50)	Non-febrile neutropenia (n = 50)
Age, n (%)		
<10 years old	40 (80)	37 (74)
≥10 years old	10 (20)	13 (26)
Gender, n (%)		
Male	29 (58)	23 (46)
Female	21 (42)	27 (54)
Morphology of ALL, n (%)		
L1	7 (14)	6 (12)
L2	43 (86)	44 (88)
L3	0 (0)	0 (0)
Risk stratification, n (%)		
Standard risk	17 (34)	19 (38)
High risk	33 (66)	31 (62)
Hipoalbumin, n (%)		
Yes	17 (34)	19 (38)
No	33 (66)	31 (62)
Leght of hospitalization, n (%)		
<10 days	27 (54)	46 (92)
≥10 days	23 (46)	4 (8)
Blood culture, n (%)		
Positive		
Gram positive bacteria	8 (16)	0 (0)
Gram negative bacteria	6 (12)	0 (0)
Negative	36 (72)	0 (0)
Urine culture, n (%)		
Positive		
Gram positive bacteria	3 (6)	0 (0)
Gram negative bacteria	4 (8)	0 (0)
Negative	36 (72)	0 (0)

ALL: Acute lymphoblastic leukemia.

Table 2: Bivariate analysis of risk factors for febrile neutropenia

Variables	Febrile neutropenia		OR (CI 95%)	p-value
	Yes (n = 50)	No (n = 50)		
Malnutrition, n (%)				
Yes	35 (67)	17 (33)	4.53 (1.95–10.51)	<0.001
No	15 (31)	32 (69)		

Urine and blood cultures were performed in 50 subjects with febrile neutropenia. Growth was found in urine culture of seven subjects and blood culture of 14 subjects. Three of growth urine cultures showed gram-positive bacteria (*Enterococcus faecalis and Enterococcus gallinarum*) and 4 of them were gram-negative *(Escherichia coli, Pseudomonas aeruginosa, and Acinetobacter baumannii)*. Positive blood culture result was found in 14 subjects, eight of which showed gram-positive bacteria *(Staphylococcus aureus, Staphylococcus hemolyticus, and Streptococcus agalactiae)*, and six of them were gram-negative *(Pseudomonas aeruginosa, Salmonella sp., Cupriavidus pauculus*).

Bivariate analysis using Chi-square test and presented in odds ratio (OR) with 95% confidence interval (CI) showed that malnutrition is positively related to the incidence of febrile neutropenia in children with ALL 4.53 times (95% CI: 1.95–10.51; p < 0.001) (Table 2).

Discussion

In this study, the median age of subjects was 5 years with youngest age 1 year and oldest age 15 years, in which 77% of them were <10 years old. Research from in 113 children with ALL in India had subjects with median age 8 years with range 6 months–16 years [20]. Ozdemir *et al*. in Turkey found 96 children with ALL who had febrile neutropenia, 64.5% of the subjects aged 1–6 years and the rest more than 6 years [21]. This is similar to what was found in this study, which 52% of children with ALL aged <10 years had febrile neutropenia.

This study was dominated by male subjects 52% similar with study in RSCM which 58% of the subjects also male gender. Research by Lyman *et al*. found that female gender has risk 1.32 times for the occurrence of neutropenic fever [7]. The morphology of ALL in this study was dominated by L2, which was 87% of subjects, followed by L1 13%. The results of this study are different from Roganovic [22], which found 85% of children with ALL had L1 morphology, followed by 14% had L2 and 1% had L3. The study also found 64% were in the high-risk group. Research by Hapsari *et al*. found that 75% of the subjects were in standard risk group and had no association with the incidence of febrile neutropenia in children with ALL [23].

Blood and urine cultures were performed in 50 subjects with febrile neutropenia, 7 subjects showed

growth from urine culture and 14 subjects showed growth from blood culture. Positive urine cultures in 4 out of 7 cultures showed growth of gram-negative bacteria, while positive blood cultures in 8 out of 14 cultures showed growth of gram-positive bacteria. Research by Gulhan *et al*. in 134 pediatric subjects with cancer and febrile neutropenia in Turkey, 29 of 38 blood cultures showed growth of gram-positive bacteria, 18 of which were *Staphylococcus* sp [24]. Another study found that from 80 cultures were examined, 69 cultures showed bacterial growth, 35 of which were gram-positive. *Staphylococcus* sp. became the most frequent growth bacteria, as many as 23 subjects [22]. Currently, gram-positive bacteria are the main cause of febrile neutropenia.

This is thought to be caused by various factors, including increase of oral mucositis due to chemotherapeutic drugs, long-term usage of intravenous catheters, and increase usage of prophylactic antibiotic regimens for gram-negative bacteria [22], [25].

The data in this study showed a significant relationship between nutritional status and the incidence of febrile neutropenia, in which malnutrition was 4.53 times greater risk of experiencing febrile neutropenia compared to subjects who were not malnourished ($p < 0.001$). This result is in line with Agnes *et al*. whom stated malnutrition was significantly higher in febrile neutropenia compared to the control group ($p = 0.03$) [19]. A multivariate study of Ramamoorthy *et al*. showed malnutrition had significant effect on the incidence of recurrent febrile neutropenia ($p = 0.031$) [20]. Draper *et al*. found that children with nephroblastoma in South Africa also showed significant relationship between malnutrition as measured by various parameters (Weight for age, height for age, weight for height, mid-upper arm circumference, triceps skinfold thickness and body mass index) and neutropenia [26].

In patients with malignancy, the body responds by producing tumor necrosis Factor (TNF), interleukin (IL)-1, and IL-6. TNF suppresses the action of lipoprotein kinase, causing reduced fat storage, while IL-1 and IL-6 break down protein and reduce albumin synthesis. Both of these conditions lead to malnutrition in children with ALL. Malnutrition in cancer patients will cause impaired immune function, resulting in increased incidence of infection, toxicity due to chemotherapy, decreased quality of life, and death [27].

The relationship between malnutrition and infection is a bidirectional relationship. Malnutrition causes atrophy of the thymus and abnormal development of peripheral lymphoid organs, resulting in long-term immune disorder characterized by leukopenia, decreased ratio of CD4 and CD8, and increased number of circulating immature T cells. This reduces functional T cells, increase undifferentiated lymphocytes and suppress the activity of serum complement. Moreover, in conditions of malnutrition, the immune defense of the epithelial barrier is also abnormal, namely changes in the mucosal architecture of intestines, such as flattening of microvilli, decrease of lymphocytes in Peyer's patches, and decrease of immunoglobulin A secretion. In the digestive tract of malnourished patients, there is also decrease in the ability of phagocytes to eliminate pathogens. On the other hand, infection itself also contributes to malnutrition, such as gastrointestinal infections which will cause diarrhea; human immunodeficiency infection/ acquired immunodeficiency syndrome, tuberculosis and other chronic infections thus cause cachexia and anemia. In addition, intestinal parasitic infections also can cause anemia and impaired absorption [2].

Israels *et al*. showed that malnourished children were significantly associated with decreased chemotherapy clearance and increased level of chemotherapy in the blood, both of which are evidence of increased chemotherapy-induced toxicity in malnourished patients [28].

Early nutritional intervention increases immunity and tolerability of cancer patients to therapy. The presence of nutritional interventions can also reduce the frequency and duration of neutropenia. Routine measurements also needed to ensure adequate nutrition. In addition to nutritional interventions, chemotherapy dose adjustments need to be considered to reduce the incidence and severity of chemotherapy-induced toxicity [13]. Another markers of nutritional status is serum albumin levels. In this study, albumin level had no significant effect on the occurrence of febrile neutropenia during the induction phase in children with ALL ($p = 0.677$). These results are in line with Hapsari *et al*. in children with ALL in Indonesia, where hypoalbuminemia had no significant effect on the incidence of febrile neutropenia ($p = 0.271$) [23]. Draper *et al*. also showed that there was no significant difference in albumin levels between the febrile neutropenic group and the non-febrile neutropenic group [26]. A study in lung cancer patients in Japan showed that there was no significant difference in albumin levels in patients with febrile neutropenia and without febrile neutropenia during the induction phase ($p = 0.1$) in chemotherapy [25]. A significant association between decreased albumin levels 4 weeks after the induction phase in patients with and without febrile neutropenia was found. Sala *et al*. stated that low albumin level indicates acute inflammatory reaction, as well as increase of catecholamines and TNF in response to malignancies that cause various inflammatory reactions, resulting protein breakdown and decreased albumin levels [25].

However, limitations in this study were: this study did not analyze other risk factors other than malnutrition and did not divide groups based on the week of chemotherapy phase to distinguish the cause of febrile neutropenia was the underlying disease or infection. Moreover, both in the case and control groups, most of them were classified as high risk,

which certainly affected the high incidence of febrile neutropenia and acts as real confounding factor.

Conclusion

Malnutrition is a risk factor for febrile neutropenia in children with ALL.

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