

Received : 2024-08-21    Revised : 2024-10-21    Accepted : 2024-11-11    Published : 2024-12-30

# ANALYSIS OF RISK FACTORS FOR ANEMIA AND NEUTROPENIA POST-CHEMOTHERAPY IN PATIENTS WITH ACUTE LYMPHOBLASTIC LEUKEMIA AT SAMARINDA HOSPITAL

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**Abstract:** Chemotherapy is the main therapy in the treatment of acute lymphoblastic leukemia and can change the body's hematological parameters during therapy. Haematological side effects that commonly occur after chemotherapy include anemia and neutropenia. The aim of this study was to determine the risk factors for anemia and neutropenia in patients with acute lymphoblastic leukemia after chemotherapy. This research is retrospective analytic with cross sectional data collection methods. The type of data used is secondary data from medical records of patients diagnosed with acute lymphoblastic leukemia. Data were analyzed using SPSS version 25.0. The research results obtained from this study were that there was a significant relationship between chemotherapy regimen and the incidence of anemia in acute lymphoblastic leukemia patients ( $p=0.001$ ), and a significant relationship was found between age and chemotherapy regimen and the incidence of neutropenia in acute lymphoblastic leukemia patients ( $p= 0.005$  and  $p=0.011$ ). The conclusion obtained is that risk factors for chemotherapy regimens have a significant relationship between the incidence of anemia. In addition, the risk factors of age and chemotherapy regimen have a significant relationship between the incidence of neutropenia. Risk factors aged 12-25 years have the opportunity to increase the risk of neutropenia by 0.231 times greater than risk factors for chemotherapy regimens

**Keywords:** anemia, chemotherapy, leukemia, neutropenia, risk factors

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## 1. Introduction

Leukemia is a malignant blood cell disease characterized by irregular and uncontrolled proliferation of white blood cells and manifested by the presence of abnormal cells in the peripheral blood. Acute lymphoblastic leukemia often occurs in the age range 0-14 years. The next highest incidence rate occurs in older adults, namely over the age of 40 years (Rahmat *et al.*, 2022). Leukemia is the 15th most frequently diagnosed cancer (2.4% of total cases) and the main cause of cancer death (3.2% of total cancer deaths) (Bray *et al.*, 2018). WHO (2019), shows that in the last five years the incidence of leukemia was 35,870 cases and deaths reached 11,314 people.

The main therapy in the treatment of acute lymphoblastic leukemia is chemotherapy. Chemotherapy can increase the potential for side effects due to damage to normal cells that are rapidly mitotic and immunosuppressed as an effort to prevent drug rejection reactions. This can cause myelosuppression or a decrease in the production of platelets, white blood cells and red blood cells in the bone marrow which can change the body's hematological parameters during therapy. The incidence of myelosuppression is neutropenia (4.67%) and

anemia (2.2%) (Azkia *et al.*, 2021). Anemia is a hematological disorder that can be found in cancer patients and can worsen the patient's clinical condition.

Anemia can occur because there is a functional disturbance in the production of red blood cells which are damaged during chemotherapy treatment. As many as 50% of cancer patients who receive anticancer therapy experience anemia (Radziwon *et al.*, 2020). Anemia can delay the implementation of chemotherapy, have an impact on fatigue and reduce the patient's quality of life as well as a reduced response to chemotherapy. The results of research at the Abdul Wahab Sjahranie Hospital in Samarinda for the 2014-2015 period showed that the incidence of anemia was 9% of 21 cases of acute lymphoblastic leukemia patients (Lufritayanti *et al.*, 2018).

Neutropenia is one of the hematological side effects that can occur due to chemotherapy. The incidence and severity of neutropenia is influenced by non-genetic factors, such as age, disease, type and stage of cancer and genetic factors. Neutropenia is a condition that occurs in patients with Absolute Neutrophil Count (ANC) values that decrease to  $\leq 500$  cells/mm<sup>3</sup> (Lucas *et al.*, 2018).

The results of research at Hasan Sadikin Hospital in Bandung showed that of 181 cases of leukemia patients, 87 patients suffered from neutropenia, amounting to 48%. Based on reports from RSCM Jakarta, it shows that the incidence of neutropenic fever at the Dharmais Cancer Hospital in Jakarta is 26.8%, Dr. Hospital. Soetomo is Surabaya 33% and Kandou Hospital Manado 22% (Mulyani *et al.*, 2017). Budiana and Febiani (2017), showed that neutropenia can occur during chemotherapy and can cause life-threatening complications as well as reduce the intensity of chemotherapy and increase patient mortality. Neutropenia is also designated as a medical and oncological emergency that has a high mortality rate.

Hematology is a parameter for doctors to determine treatment response. The response to treatment can be seen from the patient's hematological profile so that it can be concluded that the treatment given has been good. Acute lymphoblastic leukemia has several factors that are thought to influence chemotherapy failure, including age, gender, nutritional status, white blood cell count, anemia, and slow initiation of antibiotics in patients with neutropenia (Pasala *et al.*, 2021).

Based on these data, this study aims to determine the risk factors for anemia and neutropenia in patients with acute lymphoblastic leukemia after chemotherapy so that it is hoped that it can provide information, consideration and prevention of anemia and neutropenia.

## **2. Materials and Methods**

The population of this study were all acute lymphoblastic leukemia patients at the Abdul Wahab Sjahranie Hospital in Samarinda who were included in the inclusion criteria and exclusion criteria. There are 37 medical records of acute lymphoblastic leukemia patients during the period January 2020 to December 2022. The inclusion criteria for this study are 1) acute lymphoblastic leukemia patients who have undergone chemotherapy, 2) patients experiencing anemia with hemoglobin levels (men  $<13$  g/dL and women  $<12$  g/dL), 3) the patient has neutropenia with an Absolute Neutrophil Count (ANC) value  $\leq 1500$  cells/mm<sup>3</sup> 4) the patient has clear medical record data, namely age, weight, gender, height, number of ANC and hemoglobin levels. The exclusion criteria for this study were 1) patients who

experienced anemia before undergoing chemotherapy, 2) patients who experienced neutropenia with fever.

Patients are declared anemic if they have a hemoglobin level, namely men <13 g/dL and women <12 g/dL, while patients are declared neutropenic if they have an Absolute Neutrophil Count (ANC) value  $\leq 1500$  cells/mm<sup>3</sup>. The distribution of variables studied was age, gender, nutritional status, and chemotherapy regimen. Based on age grouping, patients were divided into four groups, namely 0-11 years, 12-25 years, 26-45 years and 45-65 years. Nutritional status is seen from the Body Mass Index (BMI) value which is based on body weight in kilograms divided by body height in meters squared according to the classification of the World Health Organization (WHO) Western Pacific Region, (2000), namely underweight (<18.5), normal (18.5-22.9), overweight (with a risk of obesity) (23-24.9), obese ( $\geq 25$ ). Data were collected on the variables of nutritional status and chemotherapy regimen after the patient underwent chemotherapy treatment.

Data analysis was used to determine the correlation of research variables using SPSS (Statistical Package for Social Science). The data analysis used in this research is univariate, bivariate and multivariate analysis using the Chi-Square test, Mann Whitney and logistic regression. Chi-Square and Mann Whitney tests were used to determine the relationship between one variable and another variable and the level of significance in this study was stated if  $p < 0.05$ . Researchers used Odds Ratio (OR) analysis to find out how significant these variables are. An Odds Ratio (OR) value < 1 means that the related factor reduces the possibility of anemia and neutropenia, whereas if the Odds Ratio (OR) value > 1 means that the related factor increases the possibility of anemia and neutropenia. Multivariate testing is used to analyze the relationship between two or more risk factors using logistic regression.

### 3. Results and Discussion

There were 37 acute lymphoblastic leukemia patients used in this study. Table 1 shows that most acute lymphoblastic leukemia patients are in the age range 0-11 years and are male. The majority of acute lymphoblastic leukemia patients experience anemia and neutropenia. The chemotherapy regimen for acute lymphoblastic leukemia patients is dominated by Vincristine – Methotrexate IT.

**Table 1. Distribution of Pasien Demographic Characteristics**

Variable	Frequency	Percentage
Age		
Children (0-11 year)	21	56.8%
Teenagers (12-25 year)	10	27.0%
Mature (26-45 year)	3	8.1%
Elderly (45-65 year)	3	8.1%
Gender		
Man	19	51.4%
Woman	18	48.6%
Nutritional status		
Underweight (IMT $\leq 18,5$ )	21	56.8%
Normal (IMT 18,5-22,9)	12	32.4%

Overweight (IMT 23-24,9)	1	2.7%
Obesitas (IMT $\geq$ 25)	3	8.1%
Anemia		
Yes (Hemoglobin $\leq$ 13 g/dL)	29	78.4%
No (Hemoglobin $\geq$ 13 g/dL)	8	21.6%
Neutropenia		
Yes (ANC $\leq$ 1500 sel/mm <sup>3</sup> )	20	54.1%
No (ANC $\geq$ 1500 sel/mm <sup>3</sup> )	17	45.9%
Chemotherapy Regimen		
Vincristine	13	35.1%
Vincristine - Methotrexate IT	19	51.4%
Vincristine - Methotrexate IT - Cytarabine	4	10.8%
Vincristine - Methotrexate IT - Dounorubicin - L-Asparaginase	1	2.7%

### 3.1 Risk Factors for Anemia in Acute Lymphoblastic Leukemia

Anemia is a hematological disorder in patients with low hemoglobin levels, namely men  $<13$  g/dL and women  $<12$  g/dL (Radziwon *et al.*, 2020). Data on the risk factors for anemia based on age were mostly in the 0-11 year age range, with 17 patients with a percentage of 81.0%. The results of bivariate analysis show a p value = 0.563, so age is not proven to increase the risk of anemia. This is in line with research conducted by Hidayati *et al.*, 2020 which showed that there was no significant relationship between the incidence of anemia and the patient's age. Cancer patients undergoing chemotherapy have hemoglobin levels that decrease rapidly, especially in the age range over 65 years (Wahyuni *et al.*, 2022).

The results of the analysis of risk factors for anemia by gender occurred most often in men, namely 16 patients with a percentage of 55.2%. The results of bivariate analysis showed a p value = 0.314 and an OR value of 2.051 with a 95 CI% 0.411-10.238, so gender was not proven to increase the risk of anemia. These results are in line with research by Huzaizah *et al.*, 2023 which concluded that there was no significant relationship between the incidence of anemia in chemotherapy patients and gender (Huzaizah *et al.*, 2023). This is related to the problem of iron deficiency with increasing needs (blood supply and physical growth) so that if men lack nutritional intake it will cause anemia (Huzaizah *et al.*, 2023).

Patients with anemia have an impact on impaired response to treatment and decreased survival, where male patients have better survival in the body mass index range  $>25$  kg/m<sup>2</sup> (Grenlee *et al.*, 2017). Data on risk factors for anemia on nutritional status showed that 15 patients (71.4%) were underweight. This can be caused by the quality of the food from iron sources consumed by the patient, the formation of red blood cells can be disrupted if they do not consume enough food containing iron sources, resulting in a lack of hemoglobin and causing anemia. The results of bivariate analysis show a p value = 0.563, so nutritional status is not proven to increase the risk of anemia.

**Table 2. Risk Factors for Anemia in Acute Lymphoblastic Leukemia**

Risk Factor	Yes n (%)	No n (%)	P value	OR	95% CI
Age			0.563	-	-
Children (0-11 year)	17 (81.0)	4 (19.0)			
Teenagers (12-25 year)	8 (80.0)	2 (20.0)			
Mature (26-45 year)	2 (66.7)	1 (33.3)			
Elderly (45-65 year)	2 (2.4)	1 (33.3)			
Gender			0.314	2.051	0.411- 10.238
Man	16 (55.2)	3 (15.8)			
Woman	13 (72.2)	5 (27.8)			
Nutritional status			0.307	-	-
Underweight (IMT ≤18,5)	15 (71.4)	6 (28.6)			
Normal (IMT 18,5-22,9)	11 (91.7)	1 (8.3)			
Overweight (IMT 23-24,9)	0 (0.0)	1 (100.0)			
Obesitas (IMT ≥25)	3 (100.0)	0 (0.0)			
Chemotherapy Regimen			0.001*	-	-
Vincristine	6 (46.2)	7 (53.8)			
Vincristine - Methotrexate IT	18 (94.7)	1 (5.3)			
Vincristine - Methotrexate IT – Cytarabine	4 (100.0)	0 (0.0)			
Vincristine - Methotrexate IT - Dounorubicin-L-Asparaginase	1 (100.0)	0 (0.0)			

The chemotherapy drug regimen influences the side effects experienced by the patient. The side effect caused by drugs is anemia. These chemotherapy drugs can suppress the process of blood cell formation, resulting in a lack of red blood cell production (Fatikasari *et al.*, 2018). Chemotherapy drugs can cause worsening of the incidence of anemia, this is because the myelosuppressive effect increases throughout the chemotherapy cycle, thus influencing the increase in the incidence of anemia (Fatikasari *et al.*, 2018). At the start of chemotherapy, anemia often occurs, this is due to the influence of the drug regimen and the patient's metabolism. In this study, 18 patients (94.7%) experienced anemia in the combination of vincristine – methotrexate IT. The results of bivariate analysis showed a p value = 0.001, meaning the chemotherapy regimen was proven to increase the risk of anemia.

Methotrexate IT has a mechanism as an analogue of folic acid which then competes with folate receptors and enters the folic acid pathway to be converted into MTX polyglutamate (MTX-PG). Polyglutamate MTX (MTX-PG) will inhibit enzymes and cause hematological side effects such as anemia (Grennlee *et al.*, 2017).

### 3.2 Risk Factors for Neutropenia in Acute Lymphoblastic Leukemia

According to the Common Terminology Criteria for Adverse Events (CTCAE), Neutropenia is a condition that occurs in patients with neutrophil count values that decrease to  $\leq 1500$  cells/mm<sup>3</sup>. Neutropenia in cancer occurs when excessive cytokine production suppresses the body's immune response. Immune response disorders can occur in various non-specific immune layers (T lymphocytes and B lymphocytes). Data on the risk factors for neutropenia regarding age were mostly in the age range 12-25 years, as many as 8 patients

with a percentage of 80.0%. The results of bivariate analysis show a p value = 0.005, so age is proven to increase the risk of neutropenia. Polan *et al.*, 2019 showed that acute lymphoblastic leukemia patients were more likely to be less than 10 years old with a percentage of 66.6%. The cause of children often experiencing neutropenia is congenital (an abnormality present at birth) or genetics (Karolina *et al.*, 2017).

The results of the analysis of risk factors for neutropenia according to gender, which mostly occurred in men, showed that there were 13 patients with a percentage of 68.4%. The results of bivariate analysis showed a p value = 0.070 and an OR value of 3.405 with a 95 CI% 0.879-13.188, so gender was not proven to increase the risk of neutropenia. Polan *et al.*, 2019 shows that there are more males than females. Hormones in gender tend to influence this incident (Pratiwi *et al.*, 2021). This can occur due to changes that occur in bone marrow formation or excessive loss of white blood cells from the circulation. Neutropenia caused by disease can last only a few days to a few weeks or can even last for several months or a lifetime (Pratiwi *et al.*, 2021).

Under or over nutritional status can result in deficiencies of substances in building the immune system and can increase the risk of therapeutic toxicity and the incidence of neutropenia. Patients with malignant diseases often experience malnutrition. Malnutrition can hinder the healing process and reduce drug metabolism (Azkia *et al.*, 2021). Data on risk factors for neutropenia on nutritional status showed that 9 patients (42.9%) were underweight. The results of bivariate analysis showed a p value = 0.121, so nutritional status was not proven to increase the risk of neutropenia.

Giving anticancer drugs is the main action to eliminate cancer cells in the body. Patients who have chemotherapy therapy will experience side effects depending on the type of drug used (Pojuh *et al.*, 2019). Chemotherapy drugs not only destroy cancer cells but also attack healthy cells, especially cells that divide rapidly, this causes side effects due to chemotherapy (Liana *et al.*, 2019). In this study, 11 patients (57.9%) experienced neutropenia with the combination of vincristine – methotrexate IT. The results of bivariate analysis showed a p value = 0.011, meaning the chemotherapy regimen was proven to increase the risk of neutropenia.

**Table 3. Risk Factors for Neutropenia in Acute Lymphoblastic Leukemia**

Risk Factor	Neutropenia		P Value	OR	95% CI
	Yes n (%)	No n (%)			
<b>Age</b>					
Children (0-11 year)	7 (33.3)	14 (66.7)	0.005*	-	-
Teenagers (12-25 year)	8 (80.0)	2 (20.0)			
Mature (26-45 year)	2 (66.7)	1 (33.3)			
Elderly (45-65 year)	3 (100.0)	0 (0.0)			
<b>Gender</b>					
Man	13 (68.4)	6 (31.6)	0.070	3.405	0.879-13.188
Woman	7 (38.9)	11 (61.1)			
<b>Nutritional status</b>					
Underweight (IMT ≤18,5)	9 (42.9)	12 (57.1)	0.121	-	-
Normal (IMT 18,5-22,9)	8 (66.7)	4 (33.3)			
Overweight (IMT 23-24,9)	1 (100.0)	0 (0.0)			

Obesitas (IMT $\geq$ 25)	2 (66.7)	1 (33.3)			
Chemotherapy Regimen					
Vincristine	4 (30.8)	9 (69.2)	0.011*	-	-
Vincristine - Methotrexate IT	11 (57.9)	8 (42.1)			
Vincristine - Methotrexate IT – Cytarabine	4 (100.0)	0 (0.0)			
Vincristine - Methotrexate IT - Dounorubicin-L-Asparaginase	1 (100.0)	0 (0.0)			

### 3.3 Multivariate Analysis of Neutropenia Risk Factors for Acute Lymphoblastic Leukemia

Results of multivariate analysis of risk factors for neutropenia in acute lymphoblastic leukemia. Risk factors aged 12-25 years have the opportunity to increase the risk of neutropenia by 0.231 times greater than risk factors for chemotherapy regimens.

**Table 4. Multivariate Analysis of Neutropenia Risk Factors in Acute Lymphoblastic Leukemia**

Risk Factor	Neutropenia		P value	OR	95% CI
	Yes n (%)	No n (%)			
Age					
Children (0-11 year)	7 (33.3)	14 (66.7)	0.013	0.231	0.073- 0.733
Teenagers (12-25 year)	8 (80.0)	2 (20.0)			
Mature (26-45 year)	2 (66.7)	1 (33.3)			
Elderly (45-65 year)	3 (100.0)	0 (0.0)			
Chemotherapy Regimen					
Vincristine	4 (30.8)	9 (69.2)	0.018	0,120	0.021- 0.698
Vincristine - Methotrexate IT	11 (57.9)	8 (42.1)			
Vincristine - Methotrexate IT- Cytarabine	4 (100.0)	0 (0.0)			
Vincristine - Methotrexate IT- Dounorubicin-L-Asparaginase	1 (100.0)	0 (0.0)			

## 4. Conclusion

This research shows that among all factors, chemotherapy regimen risk factors are proven to increase the risk of anemia. In addition, the risk factors of age and chemotherapy regimen have been shown to increase the risk of neutropenia. Risk factors aged 12-25 years have the opportunity to increase the risk of neutropenia by 0.231 times greater than risk factors for chemotherapy regimens.

## Acknowledgements

The author would like to thank the Muhammadiyah University of East Kalimantan for their support.

## Conflict of Interest

All Authors declare no conflict of interest and agree with the content of the manuscript.

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