



RELATIONSHIP BETWEEN PLATELET COUNT AND BLEEDING INCIDENCE IN ACUTE LEUKIMIA

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ABSTRACT

Background: Acute leukemia is a disease caused by abnormal maturation of hematopoietic cells in the bone marrow. Acute leukemia is classified based on the hematopoietic cells involved, which consist of Acute Myeloblastic Leukemia (AML) and Acute Lymphocytic Leukemia (ALL). Acute leukemia condition can cause thrombocytopenia which occurs due to somatic mutations in the bone marrow so the formation process of platelet is disrupted. A certain decrease in the number of platelets can increase the risk of bleeding in patients. **Objective:** To analyze the relationship between platelet count and bleeding in acute leukemia patients. **Method:** This study was an analytic observational study with a cross-sectional approach and analyzed the relationship between platelet count and bleeding in acute leukemia patients. Samples were taken from medical records of acute leukemia patients (AML and ALL) who fulfil inclusion and exclusion criteria from RSUD Ulin Banjarmasin. **Results:** Based on the analysis, there was no relationship between platelet count and bleeding in acute leukemia patients, both types of AML and ALL ($p > 0.05$). It is also known that the highest number of platelets in acute leukemia patients types AML and ALL is found in the range of platelet counts that fall into the category of severe thrombocytopenia ($> 20.000 - \leq 50.000/\mu\text{L}$). The bleeding incident that occurred in acute leukemia patients in this study were very diverse including petechiae, gingival bleeding, epistaxis, menometrorrhagia and gastrointestinal bleeding. **Conclusion:** There is no relationship between platelet count and bleeding incidence in acute leukemia patients of LMA and LLA types.

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INTRODUCTION

Leukemia is a malignant disease caused by the formation of abnormal immature blood cells. Leukemia is classified based on the abnormal hematopoietic cells involved, such as lymphoid, myeloid, a mixture of both, or cells that have not differentiated into lymphoid or myeloid cells. Acute leukemia consists of acute myeloblastic leukemia (AML) and acute lymphocytic leukemia (ALL).¹⁻⁵

Acute leukemia arises from abnormal maturation of hematopoietic cells in the bone marrow. These immature cells continue to proliferate until their numbers exceed normal physiological limits. In acute myeloid leukemia (AML), the primary abnormality involves non-lymphocytic white blood cells, whereas in acute lymphoblastic leukemia (ALL), the defect

occurs in the production and maturation of lymphoid-lineage white blood cells.^{1,2} According to data from the American Cancer Society, an estimated 20,050 new cases of AML were diagnosed in the United States in 2022, with the majority occurring in adults. AML has also been reported to be more prevalent in men than in women. In contrast, approximately 6,660 new cases of ALL were reported in the United States in 2022, with this leukemia type being most common among children under the age of five.⁶

The etiology and risk factors of acute leukemia include:

1. Genetic conditions

Genetic disorders such as Down syndrome, Li-Fraumeni syndrome, hereditary bone marrow failure syndrome (Fanconi anemia and



Shwachman-Diamond syndrome) may be one of the causes of acute leukemia.^{7,8}

2. History of chemotherapy

A history of chemotherapy over a period of time may cause cytotoxic effects on cells, resulting in chromosomal abnormalities and genetic mutations.⁹

3. Benzene exposure

Benzene is a human carcinogen.¹⁰ Toxic substances from benzene also cause bone marrow disorders, myelodysplasia, preleukemic stasis, and hematologic abnormalities that can trigger leukemia.¹¹

4. Radiation

High doses of radiation increase the risk of leukemia through DNA damage.¹² Radiation itself can come in the form of radiation from bombs, X-rays radiation and CT scans.^{13,14}

Thrombocytopenia is a common complication in patients with leukemia and can lead to serious bleeding events.¹⁵ It is defined as a platelet count of fewer than 150,000/mm³ in the systemic circulation.¹⁶ Platelets play a crucial role in supporting the vascular endothelium and maintaining the structural integrity of blood vessels; therefore, when their numbers fall below normal levels, the risk of bleeding increases.¹⁷

Thrombocytopenia can be classified into four levels based on the amount of platelets in the blood, namely:^{18,19}

- Mild thrombocytopenia: > 100,000 - 150,000/ μ L
- Moderate thrombocytopenia: > 50,000 - 100,000/ μ L
- Severe thrombocytopenia: > 20.000 - $\leq$ 50,000/ μ L
- Severe thrombocytopenia: $\leq$ 20,000/ μ L

Thrombocytopenia can lead to spontaneous bleeding, which typically occurs at platelet counts $\leq$ 20,000/mm³.²⁰ Bleeding severity is categorized into four levels based on the amount of blood loss, comprising mild bleeding (levels 1 and 2), moderate bleeding (levels 2, 3, and 4), and severe bleeding (levels 3 and 4).²¹ Mild bleeding manifestations such as petechiae, gingival bleeding, and epistaxis commonly occur in patients with acute leukemia who have platelet counts below 20×10^9 /L. Moderate bleeding, including hematuria, hematemesis, and melena, may also occur at platelet counts around 20×10^9 /L, although these events are less frequent.²²

METHODS

This research was cross sectional study with total 38 patient in Ulin Banjarmasin Hospital during the period of November 2019 to February 2020 as a respondent. Patient divided into two group that consisted of 19 patient with AML and 19 patient with ALL. SPSS application was used to analysed the correlation between variable in this study with Pearson Test.

RESULTS AND DISCUSSION

Characteristics of subjects in this study can be seen in Table 1. Patient with AML patients consist of 10 male patient (52.6%) and 9 female patient (47.4%). Patient with ALL consist of 7 male patient (36.8%) and 12 female patient (63.2%). The age distribution of patient with AML was 17 people in <60 years category, and 2 patient in $\geq$ 60 years category with mean or average age of AML patients was 38.8 years. The age distribution of ALL patients was <60 years old as many as 19 people and there were no subjects (0.0%) with age >60 years. The mean or median age of patients with ALL was 32.7 years.

In this study, of the total subjects of acute leukemia patients, female patients were found more than male patients, with 17 male patients (44.7%) and 21 female patients (55.3%). This result is generally inconsistent with many previous studies, such as the statement of the American Cancer Society (ACS), where from the data they collected, male patients were found more than female patients.^{1,2}

To date, there is no research that can definitively explain why this happens, but there are studies that say that men with leukemia have a genetic mutation located on the X chromosome. This mutation causes damage to tumor suppressor genes, whose function normally inhibits cancer cell division.²⁴

Based on the data of ALL patients in this study, the number of female patients was found to be higher than male patients, with 12 female patients (63.2%) and 7 male patients (36.8%). Just like in AML patient, many existing studies show that ALL patients are more dominated by males than females. However, one of the previous studies that had similar results to this study was a study by Gupta et al. (2019) in America. Out of a total of 90 subjects, 39 people (43.3%) were male and 51 people (56.7%) were female.²⁵



The difference in research results between one and another may occur due to differences in research subject criteria, research locations, research variables, and other factors. The age distribution in this study of patients with AML acute leukemia was dominated by patients aged 31-40 years, as many as 6 individuals (31.6%), with a mean subject age of 38.8 years. In fact, AML acute leukemia is more

common in adults.² In 19 LLA patients, the most common age group was 31-40 years, with 6 patients (31.6%), followed by patients aged <20 years, with 5 patients (26.3%). The median age of LLA patients was 32.7 years. According to the American Cancer Society (ACS), LLA acute leukemia tends to affect younger patients than LMA patients.¹

Table 1. Characteristics of Research Subjects

Characteristics	AML	ALL	Whole Population
Number of Patients	19 (50.0%)	19 (50.0%)	38 (100%)
Age			
<60 years	17 (89.5%)	19 (100%)	36 (94.7%)
≥60 years	2 (10.5%)	0 (0.0%)	2 (5.3%)
Gender			
Male	10 (52.6%)	7 (36.8%)	17 (44.7%)
Female	9 (47.4 %)	10 (63.2%)	19 (55.3%)
Organ Enlargement			
Hepatomegaly	2 (10.5%)	0 (0.0%)	2 (5.3%)
Splenomegaly	2 (10.5%)	0 (0.0%)	2 (5.3%)
Lymphadenopathy	3 (15.8%)	6 (31.6%)	9 (23.7%)
Platelet Count (/n LLA)			
Normal (1/1)	191.000	256.000	223.500 (± 54.080)
Mild Trombocytopenia (2/4)	123.500 (± 24.750)	109.000 (± 9.380)	113.800 (± 15.210)
Moderate Trombocytopenia (4/5)	77.250 (± 25.800)	72.800 (± 14.790)	74.800 (± 19.100)
Severe Trombocytopenia (7/6)	34.600 (± 9.490)	30.300 (± 8.210)	32.600 (± 8.830)
Very severe Trombocytopenia (5/3)	12.000 (± 4.640)	12.000 (± 5.570)	12.000 (± 4.600)
Types of Bleeding			
Ptekie	1	1	2
Gingiva bleeding	3	1	4
Epistaxis	1	1	2
Menometrorrhagia	1	-	1
Gastrointestinal bleeding	4	2	6

Table 2. Results of the Correlation Test of Platelet Count with Bleeding Incidence in the Entire Population of Acute Leukemia Patients

	Bleeding Incident			
	Patient with AML		Patient with ALL	
	p	r	p	r
Platelet Count	1.556	0.474	0.630	0.730

Based on the data from this study, out of 19 AML patients, 2 patients (10.5%) had hepatomegaly, 2 patients (10.5%) had splenomegaly, and 3 patients (15.8%) had lymphadenopathy. The occurrence of organ and lymphatic enlargement in acute leukemia patients may be due to leukemic cells infiltrating these organs, causing clinical manifestations of organ enlargement.²⁴ From the results of this study, hepatomegaly and splenomegaly were found more in AML patients, but lymphadenopathy was found more in ALL patients. This result was accordance with

Hamid (2013) that mentioned in his study that lymphadenopathy is more common in ALL patients than in AML.²⁶

In this study, most of the patients with acute leukemia experienced severe thrombocytopenia, 13 patients out of a total of 38 patients. Thrombocytopenia is a condition that commonly seen in patients with acute leukemia, a disorder in which the number of platelets in the bloodstream is less than 150,000/mm³.¹⁶ Thrombocytopenia in leukemia often occurs due to abnormalities in the bone marrow



caused by mutations.¹⁵ There is an abnormal somatic mutation of hematopoietic progenitor cells that results in the overproduction of a group of abnormal clones.⁹ This overproduction suppresses the hematopoietic process, resulting in a decrease in platelet production.¹⁶ Thrombocytopenia can lead to vascular leakage even though there is no injury to the blood vessels.

Thrombocytopenia can lead to vascular leakage even in the absence of vascular injury. This is because platelets can assist the vascular endothelium in maintaining the structural integrity of blood vessels, so a lower than normal platelet count can cause bleeding. Clinical manifestations of bleeding due to thrombocytopenia include petechiae or purpura, gingival bleeding, gastrointestinal bleeding, menorrhagia to cerebral hemorrhage.²⁷

Correlation test showed that there was no correlation between platelets count with incidence of bleeding in patient with AML and ALL with $p > 0.05$. Only 14 cases of bleeding were found in a total of 38 patients with acute leukemia, 9 cases in AML patient and 5 cases in ALL patient.

The types of bleeding in this study for both AML and ALL subjects were very diverse, including petechiae, gingival bleeding, epistaxis, hematemesis, menometrorrhagia, melena, and gastrointestinal bleeding, with these types of bleeding randomly distributed across the range of platelet levels without any discernible pattern.

The discrepancy between the results of the study and the original hypothesis may be caused by several other factors that were not examined in this study, namely the patient's condition on presentation to the hospital, fluid replacement, nutritional status, platelet size, platelet shape, duration of thrombocytopenia, the function of plasma protein factors that support platelet function, such as vWF and ADP, and other platelet aggregation factors, where these protein factors affect platelet performance in performing their functions. There are also tissue repair factors, immune response, and vasoconstriction ability, which are different in each patient.^{28,29} This study has a design that evaluates platelet count alone as one of the triggering factors for bleeding in acute leukemia patients, while from the discussion it is concluded that bleeding can be influenced by many factors, not just platelet count alone, in evaluating these factors, further examinations are needed, such as examining

coagulation and fibrinolysis, coagulation factor levels, platelet function, and also other biomolecular parameters.

CONCLUSION

There is no association between platelet count and bleeding incidence in AML and ALL acute leukemia patients. The platelet counts found in this study were highly variable in both AML and ALL. There are many types of bleeding in acute leukemia patients.

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