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ORIGINAL ARTICLES

Analysis of immature platelet fraction (IPF) based on the etiology of thrombocytopenia in adult patients at Wahidin Sudirohusodo Hospital

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ABSTRACT

Background and aim: Thrombocytopenia is a common hematological disorder characterized by a platelet count below normal values. Identification of the etiology of thrombocytopenia in patients is a very important step to take because it can determine the management plan that will be given. IPF value measurement is one of non-invasive method that has been proven to have significant diagnostic value and rapid test results to determine the thrombocytopenia etiology early. This study aims to analyze the IPF value differences based on the etiology of thrombocytopenia in adult patients at Dr. Wahidin Sudirohusodo Hospital.

Methods and Material: This study used a cross-sectional design. The study sample was adult patients aged ≥18 years with thrombocytopenia <150,000 cells/μL selected using consecutive sampling technique. The research data were analyzed by the chi-square and Kruskall-Wallis test to discover the relationship between IPF value and thrombocytopenia etiology.

Results: Through the result of the Kruskal-Wallis analysis, it is known that this study shows a significant differences of the IPF value average in the subjects based on their thrombocytopenia etiologies with $p<0.001$. Furthermore, the results of the chi-square analysis indicates a significant relationship between IPF values and the etiology of thrombocytopenia with $p<0.000$.

Conclusions: IPF parameters can be used to determine the cause of thrombocytopenia because they have been shown to significantly differentiate thrombocytopenia patients based on their etiology.

Keywords: thrombocytopenia, IPF, adult, etiology, non-invasive method, platelet

INTRODUCTION

Definition and etiology

Thrombocytopenia is a common hematological disorder characterized by a platelet count below normal (<150,000 cells/μL). Platelets are non-nucleated blood cells produced in the bone marrow and are produced from the release of megakaryocyte cytoplasm, function as blood coagulants, adhere to blood vessels when vascular injury occurs and affect primary hemostasis (1). In severe thrombocytopenia (platelet levels <50,000 cells/μL), the risk of morbidity and mortality increases. In severe cases, thrombocytopenia can cause life-threatening bleeding, such as intracranial hemorrhage (2,3).

In the management of thrombocytopenia, identification of the cause of thrombocytopenia is an important step. The main mechanisms causing thrombocytopenia that are often encountered are dropped platelets production in the bone marrow and raised of platelets destruction also coagulative consumptive in the periphery. In addition, there are also other mechanisms that take part in decreasing of platelets number, namely sequestration of platelets, that occurs in congestive splenomegaly because of portal hypertension, which is marked by the occurrence of platelets redistribution from the circulation to the splenic pool (3,4).

Immature Platelet Fraction (IPF)

Identification of the thrombocytopenia etiology can be conducted by invasive and non-invasive examinations. Immature Platelet Fraction (IPF) value measurement is one of the non-invasive examination methods that shows young platelets number in the peripheral blood. The results of the IPF percentage measurement determine whether the thrombocytopenia suffered is due to impaired megakaryocyte creation in the bone marrow or raised destruction in the periphery (5). The IPF value was significantly higher in the hyperdestructive group which showed increased thrombopoiesis. This is in line by the results of a study conducted by Ali et al. (2019) which found that the IPF value was greater significantly in increased destruction/coagulative consumptive groups. In addition, research by Wyngaert et al. (2020) also showed that an increase in the IPF value of 13% indicated that the peripheral mechanism process was the cause of the thrombocytopenia cases studied (6,7).

IPF value is a new parameter that can be used as a diagnostic and prognostic to assess the level of thrombopoiesis in patients with thrombocytopenia effectively and efficiently (3,8,9). Monitoring the process of increasing platelet production, turnover, and improving thrombopoiesis through IPF values can help clinicians determine whether bone marrow examination and platelet transfusion are necessary. IPF examination has shown rapid and significant diagnostic value that is useful for determining the cause of thrombocytopenia (3,7).

MATERIAL AND METHODS

Participants

Population in this study were all inpatients with thrombocytopenia at Dr. Wahidin Sudirohusodo General Hospital Makassar. Meanwhile, the sample of this study was a population that met the inclusion. The inclusion criteria included inpatients with thrombocytopenia aged >=18 years and agreed to participate by signing an informed consent. In this study, factors that influence IPF values were not included, such as patients who had received previous platelet transfusions, use of immunosuppressants, corticosteroids, growth factors. The number of subjects was 100 people selected using consecutive sampling technique.

Procedures and measurements

The study began with a screening process conducted on all adult patients with thrombocytopenia in the inpatient ward of Dr. Wahidin Sudirohusodo General Hospital. Standard data collection (research instruments), epidemiological records, demographic data, clinical manifestations, and descriptions of Immature Platelet Fraction (IPF) values were obtained through complete blood count using the Sysmex XE-2100 Hematology Analyzer with the flow cytometry method.

Statistical analysis

The processing of research data begins with checking the completeness, continuity, and uniformity of the data (editing); and coding to facilitate data merging and analysis. Each categoric patient characteristic (gender, age, etiology, and IPF category) was presented presented in frequency distribution table while age was also presented in mean and SD because it had numeric data. Kruskal-Wallis and chi-square analysis, using SPSS version 25 application, was employed to analyze differences of the IPF value average in the subjects based on their thrombocytopenia etiologies.

The Ethics Commission of the Faculty of Medicine, Hasanuddin University Makassar, South Sulawesi, Indonesia. Based on recommendation letter Number: 920/UN4.6.4.5.31/PP36/2024, with protocol number: UH24100816, approved the study protocol and informed consent. Before data collection, all subjects were provided signed informed consent.

RESULT

Table 1. Subjects Characteristics

	Parameter	n (%)	Mean	SD
Gender	Female	57 (57)		
	Male	43 (43)		
Age	< 60 years	78 (78)	46.2	16.0
	≥ 60 years	22 (22)		
Etiology	Decreased production	59 (59)		
	Increased coagulative consumptive	17 (17)		
	Increased destruction	24 (24)		
IPF category	Low	12 (12)		
	Normal	49 (49)		
	High	39 (39)		

Source: Author's primary data, 2024

There were 100 subjects who participated in this study. The subjects' characteristics are shown in Table 1. Demographic data including gender and age while clinical data are IPF category and thrombocytopenia etiology. There were 43 male (43%) and 57 female (57%) subjects. The mean age was 46.2±16.0 years old and more than half of the subjects (78%) are at the age of <60 years. Based on the IPF value, 39 subjects (39%) were reported to have high IPF. Most subjects (59%) experienced dropped platelet production as the main cause thrombocytopenia etiology.

Table 2. Distribution of diagnosis in thrombocytopenia etiology

Etiology	Diagnosis	n (%)
Decreased production	Aplastic anemia	25 (42.4)
	MDS	17 (28.8)
	ALL	7 (11.9)
	AML	5 (8.5)
	CML	3 (5.1)
	CLL	2 (3.4)
Increased coagulative consumptive	Sepsis	13 (76.5)
	DIC	4 (23.5)
Increased destruction	ITP	24 (100)

Source: Author's primary data, 2024

Through Table 2, it is known that of the 59 subjects who experienced dropped platelet production were regrouped based on their diagnosis. Almost half of them (42.4%) were diagnosed

with aplastic anemia. In addition, most (76.5%) of the 17 subjects who experienced raised coagulative consumptive in the periphery were diagnosed with sepsis while all of subjects (24 people) who experienced raised destruction are diagnosed with Immune Thrombocytopenia (ITP).

Table 3. Kruskal-Wallis test analysis results

Parameter	Etiology	n	Mean (%)	SD (%)	p-value
IPF value	Decreased production	59	4.12	6.26	<0.001*
	Increased coagulative consumptive	17	20.27	13.11	
	Increased destruction	24	15.14	8.84	

**P<0,05 is considered significant*
Source: Author's primary data, 2024

Table 3 presents the Kruskal-Wallis analysis results in differences of the average IPF values based on each etiology. Subjects with an etiology of raised coagulative consumptive have the highest mean (20.27%) compared to other etiology. P<0.001 indicates a significant relationship between IPF values and thrombocytopenia etiology.

Table 4. Chi-square test analysis results

Etiology	IPF Category			p-value
	Low	Normal	High	
Decreased production	12 (20.3%)	42 (71.2%)	5 (8.5%)	<0.000*
Increased coagulative consumptive	0 (0%)	3 (17.6%)	14 (8.4%)	
Increased destruction	0 (0%)	4 (16.7%)	20 (83.3%)	

**P<0,05 is considered significant*
Source: Author's primary data, 2024

In Table 4, the proportion of subjects with high IPF value was reported to be significantly higher in the etiology of raised destruction (83.3%) and raised coagulative consumptive (82.4%) compared to the etiology of dropped production (8.5%), with p<0.001. This also shows a significant relationship between IPF values and etiology.

DISCUSSION

Table 1 reports that there were more female thrombocytopenia sufferers than male. These findings are in accordance with the studies of Cannavo et al. (2010) and Sinaga (2019) which

showed that more than half of the subjects studied were female (10,11). Furthermore, the results of the study showing that thrombocytopenia occurs more frequently in patients aged <60 years contradict the epidemiological study results by Moulis et al. (2018) which found that the prevalence of thrombocytopenia increases with age (12). The author found that there is still a lack of literature explaining the relationship between age, gender, and etiology of thrombocytopenia and the incidence of thrombocytopenia. The results difference of the study regarding age and gender in the subjects of this study with the study by Moulis et al. is possibly caused by the difference in the participant number, where this study only involved 100 patients from the inpatient ward of Dr. Wahidin Sudirohusodo Hospital, while the study by Moulis et al. involved 18,642 patients from all hospitals in Denmark.

The results of the bivariate analysis in Tables 4 and 5 show that subjects with peripheral thrombocytopenia etiology (raised destruction and coagulative consumptive) have a higher proportion and average IPF value than subjects with central thrombocytopenia etiology (dropped platelet production in the bone marrow). This finding is supported Ali et al. study (2019) which stated that in ITP patients due to raised destruction, the highest maximum IPF value was obtained and the IPF value could be used to separate it from thrombocytopenia etiology due to infection and coagulative consumptive. The study by Wyngaert et al. (2019) also showed a higher and statistically significant median in the peripheral thrombocytopenia group compared to the central thrombocytopenia, with a median value of 15.8% (2.9–41.3) vs. 6.2% (1.1–12.7) (6,7).

This study is also in line with Kariyawasan et al (2019), the IPF average in 62 patients with thrombocytopenia and without raised thrombopoietic activity was 5.6% (CI for 95%: 3.4–7.8.) and the average IPF in 38 thrombocytopenia subjects with raised thrombopoietic activity was 14.4% (CI for 95%: 9.4-19.4) with p<0.00. In the study by Ashraf et al (2019) patients were grouped into two categories; Group 1 with central thrombocytopenia and Group 2 with peripheral thrombocytopenia. Group 1 (n=44) showed a IPF median interquartile range (IQR) of 8.2 (4.6-16.7), which was significantly lower (p<0.001) than Group 2 (n=14) whose median IPF IQR was 25.5 (15.2-39.3). Jeon et al (2020) reported significantly higher IPF values in the raised destruction and coagulative consumptive group compared to the dropped platelets production group with p<0.001. Goel G et al (2021), the IPF standard range among healthy controls was estimated to be 0.7% to 5.7%. The IPF mean was significantly greater in patients with raised platelet destruction (13.4%) compared to patients with dropped bone marrow platelet production (4.6%). The optimal IPF cutoff value to differentiate patients with raised destruction from patients with dropped production is 5.95% with a sensitivity of 88% and a specificity of 75.9% (13-16)

Asghar et al.'s study (2023), significantly showed higher IPF values in the median (IQR) raised destruction and coagulative consumptive group, 21% (14.4-26.2) compared to 6.5% (4.6-8.9) in dropped platelet production (p <0.001). The cutoff value with the greatest sensitivity and

specificity for IPF vs. the healthy population was 7.95% with a sensitivity of 97.7% and a specificity of 86%. The study of Meskini et al. (2024) also found that the IPF average in the peripheral thrombocytopenia group was significantly greater than in the central thrombocytopenia (15.71 ± 12.02% vs. 5.51 ± 3.04%) with p <0.001, and also determined the ROC curve of specificity and sensitivity, which showed that IPF has a very good diagnostic value to distinguish patients based on their etiology, with an area under the curve of 0.914. They also set a discriminatory cutoff value of 8.5% with a sensitivity of 77.8% and a specificity of 86.4% to determine the thrombocytopenia etiology. Thus, an IPF value more than 8.5% reports peripheral thrombocytopenia with raised platelet reconstruction (17,18)

Dropped production of platelet occurs due to megakaryocyte hypoplasia or inappropriate thrombopoiesis. This disorder can be caused by congenital or acquired factors. Megakaryocyte hypoproliferation can happen due to hematopoietic cells damage in the bone marrow through chemotherapy and radiotherapy that affect DNA, thereby disrupting cell separation and development. Extensive suppression of bone marrow can involve the erythrocyte, leukocyte and platelet series. Megakaryocyte hypoplasia is caused by bone marrow substitution by leukemia cells and infiltration of malignant cells in metastasis of cancer or lymphoma, which will reduce the number of platelets due to dropped bone marrow megakaryocytes. Bone marrow can also be replaced by fibrotic tissue such as in myelofibrosis. Increased apoptosis of abnormal cells and decreased production of normal cells result in a decrease in the number of blood cells, one of which is thrombocytopenia (2,4).

The etiology of increased platelet destruction due to immunological disorders such as immune thrombocytopenic (ITP) occurs due to platelet sensitization by autoreactive antibodies, usually IgG against platelet membrane components. The most frequently affected membrane epitope is the glycoprotein IIb/IIIa complex. Platelets that have been affected by IgG will be digested by splenic macrophages. While the etiology of increased platelet consumption includes disseminated intravascular coagulation (DIC) and sepsis resulting in increased consumption in the periphery which is influenced by a high inflammatory process (4,19).

CONCLUSION

IPF parameters can be used to determine the cause of thrombocytopenia because they have been shown to significantly differentiate thrombocytopenia patients based on their etiology.

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Ethics Committee Approval

The Ethics Commission of the Faculty of Medicine, Hasanuddin University Makassar, South Sulawesi, Indonesia. Based on recommendation letter Number: 920/UN4.6.4.5.31/PP36/2024, with protocol number: UH24100816, approved the study protocol and informed consent. Before data collection, all subjects were provided signed informed consent.

Conflict of Interest:

The author has no conflicts of interest associated with the material presented in this paper.

Authors' Contributions:

KS conducted the conceptualization, methodology, measurement, data analyzing, and original draft and manuscript writing.

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