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RELATIONSHIP BETWEEN TYPES OF PLASMODIUM FALCIPARUM AND PLASMODIUM VIVAX WITH THE DEGREE OF THROMBOCYTOPENIA IN MALARIA PATIENTS AT RSUD RATU AJI PUTRI BOTUNG PENAJAM PASER UTARA

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ABSTRACT

Malaria is a tropical infectious disease with high morbidity and mortality rates. In malaria, various kinds of haematological complications can arise, one of which is thrombocytopenia. Thrombocytopenia is most commonly encountered during acute malaria infection with varying degrees observed in both *Plasmodium falciparum* and *Plasmodium vivax* infections. The purpose of this study was to determine the relationship between the types of *Plasmodium falciparum* and *Plasmodium vivax* with the degree of thrombocytopenia in malaria patients at the Ratu Aji Putri Botung Penajam Paser Utara Hospital. This research is an observasional analytic study with cross sectional method. The data was taken by using purposive sampling method from the medical records of malaria patients hospitalized in Ratu Aji Putri Botung Penajam Paser Utara Hospital in the period of January 2013 - August 2018. Data analysis used the *Chi-square* test. Of the 310 malaria patients who were study subjects, 60,3% (n = 187) were infected with *Plasmodium falciparum* and 39,7% (n = 123) were infected with *Plasmodium vivax*. Most of the research subjects were male (95,8%) who were dominated by adults (56,5%). As many as 90% of malaria patients experienced thrombocytopenia with mild, moderate, and severe thrombocytopenia respectively 29,4% ; 56,6% ; 14,0%. Severe thrombocytopenia was more common in falciparum malaria patients (16,4%). The statistical test result for the type of Plasmodium with the degree of thrombocytopenia were p = 0,139. It was concluded that there was no relationship between the types of *Plasmodium falciparum* and *Plasmodium vivax* with the degree of thrombocytopenia in malaria patients.

Keywords: Malaria, Plasmodium, Degree of Thrombocytopenia

INTRODUCTION

The term malaria comes from two Italian words, namely “mala” means bad and “aria” means air because at that time this disease was often found in swampy areas that emitted a foul smell into the air in Rome. [1] The disease is caused by intracellular obligate protozoa in the blood of the genus Plasmodium. In humans, there are 5 types of Plasmodium that can cause malaria : *Plasmodium falciparum, Plasmodium vivax, Plasmodium ovale, Plasmodium malariae,* and *Plasmodium knowlesi*. [2]

Malaria is mostly a health problem in tropical and subtropical regions, especially countries in Africa and Asia. [3] World Malaria Report 2019 estimates that there were 228 million cases and 405.000 deaths related to malaria in the world in 2018. [4] Meanwhile, Penajam Paser Utara is the only area with high level of malaria endemicity outside the eastern region of Indonesia which is located in the Province of East Kalimantan. [5]

In malaria patients, there are frequent changes in their haematological status including anemia, thrombocytopenia, and leucopenia to leukocytosis as a result of the activity of the malaria parasite. [6] Thrombocytopenia is a condition in which the platelet counts is less than 150.000/µl of blood. [7] Thrombocytopenia is the most common haematological complication of malaria, especially in *Plasmodium falciparum* and *Plasmodium vivax* infections. So that some literature makes thrombocytopenia which is accompanied by fever, as an early indicator to increase the suspicion of an acute malaria diagnosis and lead to other, more specific check-up. [8-10] In general, thrombocytopenia in malaria is mild to medium and rarely symptomatic. [8,9] However, the emersion of severe thrombocytopenia needs to be watched out because it is a good predictor of a bad prognosis so that the effective management is needed to prevent complications that may arise. [9] One study stated that there was a 2.4-fold increased risk of hospitalized and a 4.7-fold increased risk of death in malaria patients with severe thrombocytopenia. [11]

The main mechanism of thrombocytopenia is not known for sure, but platelet damage caused by immunological and non-immunological processes is presumed to play a role in the occurrence of thrombocytopenia in malaria. [9] Several studies have also linked between thrombocytopenia to the infecting Plasmodium species. Devineni et al., (2015) found that *Plasmodium falciparum* infection often caused a decrease in amount of platelet to a severe degree than *Plasmodium vivax* infection, whereas another study by Kochar et al., (2010) found the opposite. [12.13]

MATERIAL AND METHOD

This type of research is an analytic observational study to find the relationship between two variables with a cross sectional design. Sampling was done by purposive sampling. The sample of this study were all malaria patients at the Ratu Aji Putri Botung Penajam Paser Utara Regional Hospital for the period January 2013 to August 2018 who met the inclusion and exclusion criteria of the study. The inclusion criteria of this study were patients diagnosed with malaria by an internist through confirmation of microscopic examination and undergoing hospitalization, and the results of routine blood tests at the time of arrival in the form of platelet counts. The study exclusion criteria were patients with mixed malaria, being pregnant, having other diseases that could affect routine hematological examinations such as chronic liver disease, bleeding disorders, HIV / AIDS, *dengue* hemorrhagic fever, chronic renal failure, malignancy, and patients who had received an anti-malaria treatment regimen before blood tests. Data sourced from the medical records of inpatient malaria patients at the Medical Record Installation of the Ratu Aji Putri Botung Penajam Paser Utara Hospital.

The independent variable of this study was the type of Plasmodium that causes malaria, namely *Plasmodium falciparum* and *Plasmodium vivax*. The dependent variable is the degree of thrombocytopenia. The degree of thrombocytopenia is grouped into three degrees, namely mild degrees (100,000 - 150,000 / µl), moderate degrees (50,000 - 100,000 / µl), and severe degrees (<50,000 / µl). The data were then analyzed by univariate and bivariate. Bivariate analysis was tested by Chi-square and was

considered significant if the *p* value was <0.05. The study was approved by the Health Research Ethics Commission of the Faculty of Medicine, Mulawarman University No. 13 / KEPK-FK / VIII / 2020.

RESULTS AND DISCUSSION

In this study, 310 patients became the research sample obtained from the medical record data of malaria patients at the Medical Record Installation of the Ratu Aji Putri Botung Penajam Paser Utara Hospital. The results of the univariate analysis of this study are shown in Table 1.

Tabel 1. Characteristics of Malaria Patients at Ratu Aji Putri Hospital, Botung Penajam Paser Utara

Characteristics	Percentage (%)	Frequency (n)
Plasmodium type		
P. falciparum	60,3	187
P. vivax	39,7	123
Sex		
Male	95,8	297
Female	4,2	13
Age (year)		
0 – 5	0,3	1
6 – 11	1,0	3
12 – 25	30,6	95
26 – 45	56,5	175
46 – 70	11,6	36

The majority of malaria patients at Ratu Aji Putri Botung Penajam Paser Utara hospital were infected with *Plasmodium falciparum* (60,3%) followed by *Plasmodium vivax* infection (39,7%). Similar to research by Dini et al., (2020) in Papua, where the most species that cause malaria is *Plasmodium falciparum* (54,4%) followed by *Plasmodium vivax* (32,5%). [14] The similar results were also reported by Patel et al., (2012) in Gujarat India, as many as 59% of malaria patients were infected with *Plasmodium falciparum* and 41% were infected by *Plasmodium vivax*. [15] In contrast to the study by Kustiah, Adrial, and Reza (2020) in Padang, West Sumatra, where the majority of malaria patients were infected with *Plasmodium vivax* (85%) compared to *Plasmodium falciparum* (13,3%). [16]

Differences in species that predominantly infect the population in an area can occur due to differences in geographical and ecological conditions for the breeding grounds for Plasmodium and Anopheles mosquitoes even though they are in the same country. [17] The high number of *P. falciparum* infection cases in the population in the Penajam Paser Utara area is in line with the report of the Indonesian Ministry of Health (2018), where 52% of malaria cases in Indonesia are caused by *P. falciparum* species infection. [5] The majority of malaria patients in this study were male (95.8%). This result is similar to research by Devineni et al., (2015) which states that the

percentage of male malaria patients is greater, namely 75.6% compared to female malaria patients, which is only 24.4%. [12] Similar results were also reported by Ghanchi et al., (2019) where 70.4% of malaria patients were male and 29.6% of female malaria patients. [18]

Men are more at risk of getting malaria because it is associated with high activities outside the home such as working. [16] The dominance of the types of work in the forestry, agriculture and fisheries sectors in the Penajam Paser Utara region also explains why malaria cases in male patients are so high in this region. [19] This is because their working environment is an ideal habitat for Anopheles mosquitoes to live and breed. [20] Women spend more time in the house doing household chores and their way of dressing is more closed than men so they have less contact with vectors. [21,22] The difference in malaria morbidity between men and women is also influenced by hormonal and genetic factors, where men produce chemicals that are more attractive to mosquitoes and the testosterone is known to suppress the anti-plasmodial immune response, on the other hand, the female hormone estrogen has been shown to increase the anti-plasmodial immune response. [22,23]

Table 1 shows that most of the malaria patients in the Ratu Aji Putri Botung Regional Hospital are in the age range 26 - 45 years (56.5%). This result is similar to Surve et al., (2017) in India, where 57% of malaria cases were in the 21-40 year age group. [24] Similar results were also reported by Afdhal et al., (2014) in West Sumatra where the majority of malaria patients were in the 20-40 year age group (44.8%). [6] High cases of malaria in the productive age group are related to their high mobility outside the home such as working, changing workplaces, or even traveling to malaria endemic areas, where this situation further increases their chances of contact with malaria vectors. [16,20,21] The high number of productive age malaria cases in Penajam Paser Utara is related to the working age of the population in this region, where the majority are in the age range 15 - 44 years. [19]

Table 2. Relationship between *P. falciparum* and *P.vivax* types with the degree of thrombocytopenia

Plasmodium type	Degree of Thrombocytopenia			P value
	Mild(%)	Moderate(%)	Severe(%)	
P. falciparum	44(25,7)	99(57,9)	28(16,4)	0,139
P. vivax	38(35,2)	59(54,6)	11(10,2)	
Jumlah	82(29,4)	158(56,6)	39(14,0)	

Based on table 2, moderate thrombocytopenia was found mostly in both types of Plasmodium infections (56.6%). Mild thrombocytopenia was more common in vivax malaria patients (35.2%) and severe thrombocytopenia was more common in falciparum malaria patients (16.4%). This result is similar to the research by Siagian et al., (2018) in East Kalimantan which found that 87% of malaria patients experienced thrombocytopenia with moderate thrombocytopenia occupying the largest percentage (45.65%). [7] Similar results were also obtained by Punnath et al., (2019) in Mangaluru India, of 627 malaria patients, 78.6% of them

experienced thrombocytopenia which was dominated by moderate thrombocytopenia (32.7%). [25] However, different results were reported by Bakhubaira (2013) in Yemen where mild thrombocytopenia was found to dominate in the amount of 57.6% followed by moderate thrombocytopenia at 24.2%. [26]

Thrombocytopenia in malaria is generally mild to moderate and is rarely symptomatic. [8,9] However, the emerge of severe thrombocytopenia needs to be watched out because it is a good predictor of poor prognosis. [9] The main mechanism of thrombocytopenia in malaria is not fully understood. [27-30] However, researchers hypothesized mechanisms that might play a role include coagulopathy, platelet sequestration in the spleen, platelet aggregation, immune-mediated platelet destruction, changes in bone marrow leading to impaired platelet production, oxidative stress, or perhaps even *P.falciparum*-induced peripheral destruction. [27,28,30]

During acute malaria infection, thrombocytopenia is associated with an increase in *platelet-associated IgG* (PAIgG). These antibodies can activate platelets by binding to parasite antigens attached to the platelet surface and forming immune complexes in situ and triggering platelet lysis. [9,31,32] Binding of platelets with PAIgG can also lead to removal of platelets by the reticuloendothelial (spleen) through phagocytosis of activated macrophages. [31] Hemolyzed infected erythrocytes produce *adenosine diphosphate* (ADP), a proaggregation factor that can play a role in triggering platelet activation and aggregation responses. [9,31] Platelet adherence and aggregation in malaria has also been associated with increased von Willebrand factor (vWF) levels and ADAMTS13 deficiency. [31,33] This results in an increased use of platelets which results in peripheral thrombocytopenia.[31] Macrophages are thought to play a role in causing thrombocytopenia in malaria. [31] In clinical trials of recombinant macrophage colony stimulating factors (M-CSF) it was found that an increase in M-CSF can trigger an increase in platelet destruction through increased macrophage activity. [8,32]

Platelet breakdown through oxidative stress is also known to be involved in the etiopathogenesis of thrombocytopenia. This is based on the finding of low levels of platelet *superoxide-dismutase* followed by an increase in *gluthathione-peroxidase* activity and high levels of platelet lipid peroxidase in malaria patients compared to healthy people. [32] In acute malaria infection, platelets are found to be more hypersensitive. [9,27] This is influenced by various factors such as immune complexes, the surface of the platelets in contact with infected erythrocytes, and damage to endothelial cells. [9] In addition, it was also found that there was an increase in the concentration of specific platelet-related proteins such as platelet factor 4 (PF4), beta thrombo-globulin (βTG), as well as an increase in the production of thromboxane A2 and prosycline. [27] This hypersensitivity of platelets is postulated to increase the hemostatic response and is the reason why bleeding is rare even in significant thrombocytopenia. [9]

Cytokines released during the inflammatory response of malaria are known to contribute to the severity of thrombocytopenia. [25] This situation is associated with increased levels of several cytokines such as TNF-α, IFNγ, IL-12, and IL10. Increased levels of TNF-α in malaria infection can play a role in the emergence of thrombocytopenia through trapping mechanisms and consumption of platelets in inflamed blood vessels. [25,34] IL-10 is an anti-inflammatory

cytokine as well as an immunoregulator that can suppress the production of pro-inflammatory cytokines by suppressing the activity of NK cells, macrophages, and Th-1. However, the presence of these cytokines can suppress platelet production. On the other hand, IL-6 is associated with its role in platelet production by promoting megakaryotopoiesis. [29] However, it is known that there is a decrease in plasma levels of these cytokines during severe thrombocytopenia. [25]

Based on table 2, the results of data analysis with the Chi-square test obtained *p* value = 0.139 ($p > 0.05$), which means there is no relationship between the types of *Plasmodium falciparum* and *Plasmodium vivax* with the degree of thrombocytopenia. These results are similar to a study by Martínez-Salazar & Tobón-Casta (2014) in Colombia of 862 malaria patients. The study showed that severe thrombocytopenia was found in 10.3% of falciparum malaria patients, 10.9% in vivax malaria patients, and 22.2% in mixed infections. The results of statistical analysis did not show an association between the type of *Plasmodium* infection and the severity of thrombocytopenia ($p > 0.05$). The study also stated that the platelet count did not differ based on the type of infecting species, indicating that there was a similar pathomechanism between *Plasmodium falciparum* and *Plasmodium vivax* infections. [35]

However, the results of this study are not in line with research by Arif et al., (2016) in India which states that there is a significant relationship between the types of *Plasmodium falciparum* and *Plasmodium vivax* with the degree of thrombocytopenia ($p < 0.001$). In that study, mild thrombocytopenia was generally associated with *Plasmodium vivax* (52.8%) than *Plasmodium falciparum* infection (10.71%), whereas severe thrombocytopenia was more common with *Plasmodium falciparum* infection (46.43%) than *Plasmodium vivax* infection (8.34%). [21] Although the results of this study statistically did not show a relationship between the types of infected species and the degree of thrombocytopenia, this study found that *Plasmodium falciparum* infection caused more severe thrombocytopenia when compared to *Plasmodium vivax* infection (16.4% vs 10.2%). This is not surprising given that malaria infection by *Plasmodium falciparum* is often associated with severe malaria pathogenesis. [36]

Plasmodium falciparum has the ability to modify the surface of infected erythrocytes so that they appear knobs. [37] In this knob, various kinds of proteins are expressed that can bind to surrounding erythrocytes, especially uninfected erythrocytes, blood vessel endothelium, and platelets. One of the proteins that play an important role in sitoadherens is *Plasmodium falciparum Erythrocyte Membrane* Protein (PfEMP-1) which can bind to several receptors, one of which is the CD36 receptor in the endothelium and platelets. The CD36 receptor which is expressed by platelets itself has a major role in mediating the clotting of parasite-infected erythrocytes. [31] The main proportion of total platelets in malaria patients is found in the platelet-erythrocyte complex so that this condition contributes greatly to the occurrence of thrombocytopenia. [38]

In India, Punnath et al. reported that there was an increase in levels of cytokines TNF-α and IL-10 and insignificant changes and even tended to decrease IL-6 levels in patients with falciparum malaria who experienced thrombocytopenia when compared to patients with vivax

malaria. These cytokines are known to play a role in the severity of thrombocytopenia during the malaria inflammatory response. [25] A meta-analysis study conducted by Naing & Whittaker (2018) actually found that vivax malaria patients and even severe falciparum malaria patients had the same risk of developing severe and even very severe thrombocytopenia. [28] Research by Dayanand et al., (2019) showed that there was no significant difference in platelet counts between falciparum malaria patients and vivax malaria sufferers. [39] This suggests that the two types of Plasmodium species have an equal chance of causing a decrease in the number of platelets.

In other studies that analyzed the relationship between Plasmodium type and the degree of thrombocytopenia, there was often a significant relationship, but in this study, the results were not related. This can occur considering that clinical manifestations in malaria patients can be influenced by various factors such as host factors, parasitic factors, and environmental factors. The clinical manifestations between individuals can be very diverse, ranging from asymptomatic malaria to severe and deadly malaria. The difference in morbidity patterns is thought to be related to the age of the host, the cumulative exposure of parasite clones with different virulence, to the host's immunity and genetic polymorphisms which ultimately determine the onset of severe malaria symptoms, including thrombocytopenia. Whereas in parasites, factors believed to play a role include resistance to antimalarial drugs, the ability of parasites to avoid immune responses through antigenic variation and polymorphism, parasite multiplication rates, *sitoadherens* and *rosetting*, and malaria toxins. [40]

The difference in these results with other studies is also thought to be due to variations in the time of infection onset with the patient arrival time to health facility. In a study conducted by Hasugian et al., (2018) in Timika Papua, found that the incidence of thrombocytopenia in malaria patients began to occur within 1-7 days after illness. [34] Another study even reported a decrease in platelet counts that occured within 7-9 days after being bitten by an infected Anopheles mosquito. [41] These findings suggest that the longer the time a patient arrives at a health facility, the heavier the reduction in platelet counts will be compared to patients who arrive earlier since the first onset. The variation in time between infection and arrival to the health facility results in variation in the degree of thrombocytopenia despite the infection of the same species.

CONCLUSION

In this study, most malaria patients experienced moderate thrombocytopenia and severe thrombocytopenia were more common in patients with *P. falciparum* infection. The results of statistical analysis stated that there was no relationship between *P. falciparum* and *P. vivax* with the degree of thrombocytopenia.

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