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Leukocyte and Platelite Cell Counts With C-Reactive Protein (CRP) Values in Dengue Hemorrhagic Fever

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ABSTRACT
Dengue hemorrhagic fever is a health problem caused by infection with dengue viruses (DENVs). Hematological examination of the number of leukocyte and platelet cells is carried out because thrombocytopenia, leukopenia and leukocytosis are often found in this infection. Inflammation in Dengue Fever conditions can be detected using C-Reactive Protein (CRP) as an inflammation biomarker. This study aims to determine the correlation between the number of leukocyte and platelet cells with CRP values in Dengue Hemorrhagic Fever patients. The research methodology in this study is correlation analysis using a cross sectional approach. The sample size in this study was 40 blood samples infected with the dengue virus. This research was carried out at the Prima Main Clinic in Surabaya in February - March 2024. Routine hematological examination of leukocyte and platelet cell counts used the Sysmex XP-100 flow cytometer method and examination of CRP values using the Wondfo CRP test using the fluorescence immunoassay (FIA) method. The results of this study showed that 30% of patients experienced leukopenia, 37.5% leukocytosis, 100% thrombocytopenia, 77.5% of patients had high CRP results. The correlation in this study between leukocytes and CRP with a p value of 0.041 and the correlation of platelets with CRP with a p value of 0.00, meaning that there is a relationship between the number of leukocytes and platelets and the value of ¬C-Reactive Protein (CRP) in conditions of Dengue Hemorrhagic Fever infection because ($p < 0.05$).

Keywords: Leukocyte cells, thrombocyte cells, C-Reactive Protein, Dengue Fever

INTRODUCTION
According to data sources from the World Health Organization (WHO), since the beginning of 2023, there have been 2,997,097 cases recorded with a presentation of 45% confirmed and 0.13% severe Dengue Hemorrhagic Fever (DHF). America has the highest number of infections with 1,302 deaths and an overall infection rate of 305 cases per 100,000 people (WHO, 2023).The number of dengue virus infections in Indonesia up to the 40th week was reported at 68,996 incidents in 464 districts/cities in 34 provinces with 498 deaths found in 195 districts/cities in 32 provinces. (Fauzan, 2023).

Dengue hemorrhagic fever (DHF) describes a health disorder that arises due to infection by the Aedes aegypti mosquito with the dengue virus, which is often found in areas with moderate to high rainfall (Hartini & Pawenang., 2023). Clinical manifestations of DHF include fever that lasts 2-7 days, anorexia, dizziness, pain in the joints and reddish spots (Hidayani, 2020). Symptoms of this disease are often found in other diseases so that some people do not think of it as Dengue Hemorrhagic Fever (DHF), the risk of death can occur due to delays in diagnosis, routine hematology laboratory examinations can confirm the diagnosis of Dengue Hemorrhagic Fever (Tawakal & Azkiya, 2020).

On the other hand, Marsudi stated that the number of erythrocyte cells found in dengue virus infections tends to be

normal, an increase in the number of erythrocyte cells from normal values occurs if there is plasma leakage which also increases packet cell volume (PCV) levels. Complement activation that releases C3a and C5a will cause hemostatic disorders in the form of thrombocytoepia. Inflammation when the dengue virus enters will activate cytokines that increase body temperature so that leukopenia occurs which remains normal when entering the healing stage (Marsudi at al., 2022).

The possibility of a mild to moderate decrease in the number of leukocytes in DHF patients. A mild decrease in the number of leukocytes in the range of the first to third day of fever. A decrease in mature neutrophil cells and the formation of new cells causes leukopenia, resulting in lymphocytosis. Thrombocytopenia is in line with the occurrence of leukopenia and then occurs normally as body temperature decreases (Syafutra & Afrainin Syah, 2021). On the other hand, Nguyen Lam Vuong stated that a multi-country observational study obtained higher C-Reactive Protein (CRP) results in dengue fever patients compared to other viral infections, but the C-Reactive Protein (CRP) results were lower when compared to bacterial infections, resulting in a correlation between dengue fever examination and C-Reactive Protein (CRP) results. A positive correlation was formed between biomarkers of dengue virus infection and blood cell count results (Vuong at al., 2020). C-Reactive Protein (CRP) dengue fever infection has a positive impact on the occurrence of thrombocytopenia, where plasma leakage occurs in the body during the fever stage due to inflammation of macrophages and monocyte cells. The inflammatory process activates the liver and triggers liver cells to produce C-Reactive Protein (CRP), this causes a decrease in the number of platelet cells but an increase in the value of C-Reactive Protein (CRP) in the patient's body (Renowati & Sefridana, 2020). The increase in cytokines released by lymphocyte cells in the process of neutrophil cell migration during inflammation in the bone marrow at an increase in the temperature of Dengue Fever (DHF) patients goes hand in hand with an increase in body biomarker levels. Pathophysiological factors and differences in specific cytokines that cause variations in C-Reactive Protein production. Based on this, C-Reactive Protein (CRP) can be used as a laboratory examination for other examinations for Dengue Fever (DHF) (Ekawati at al., 2022).

Agglutination is a qualitative examination of C-Reactive Protein (CRP) which is interpreted by titer. The highest titer results in Ari's 2023 study in fever conditions on days 4-5 were with a titer of 1:32. CRP with agglutination examination cannot show the quantitative inflammation value that occurs in each patient (Kusnadi, 2023). Quantitative laboratory examination of C-Reactive Protein (CRP) using the fluorescence immunoassay (FIA) method has advantages including not requiring scan steps and using a small sample, making it simpler and providing fast results (Fukase at al., 2021).

RESEARCH METHOD

This type of research uses a cross-sectional analytical method conducted on January 2 - March 30, 2024 at the Prima Utama Clinic, Surabaya. The sample population is blood samples from 40 DHF patients, the sample criteria in this study are the results of the examination of the number of leukocytes and platelets and leukocytes below normal values with an age range of 10-35 years. The samples used in this study were obtained using a non-probability sampling technique or non-random sampling type of purposive sampling. Hematology examination of Dengue Fever patients at the Prima Utama Clinic, Surabaya. Then a C-Reactive Protein (CRP) examination was carried out using the fluorescence immunoassay (FIA) method to determine the relationship between the number of leukocytes and

platelets and the CRP value. Data processing was carried out using a non-parametric correlation test, namely the Spearman test to determine the relationship between the number of leukocytes and the C-Reactive Protein (CRP) value and the relationship between the number of platelets and the C-Reactive Protein (CRP) value in Dengue Fever patients.

RESULT AND DISCUSSION

The results of data collection are processed using SPSS, then edited, coded, tabulated and analyzed, which are presented in the form of tables with explanations.

Table 1. Spearman test table of leukocyte cells against CRP values in dengue fever patients at the Prima Utama Clinic, Surabaya

Korelasi				
			Leukocyte Cell Count	CRP Value
Spearman's rho	Leukocyte cell count	Correlation coefficient	1,000	-0,325*
		Sig. (2-tailed)	.	0,041
		N	40	40
	CRP value	Correlation coefficient	-0,325*	1,000
		Sig. (2-tailed)	0,041	.
		N	40	40

Based on the results above, the sig. (2-tailed) value is 0.041, because the sig. (2-tailed) value is less than 0.05 or p <0.05, it means that there is a significant relationship between the number of leukocyte cells and CRP values. Then the correlation coefficient number is obtained at -0.325, meaning that the level of correlation/relationship strength is a sufficient or strong enough relationship.

Table 2. Spearman test table of platelet cells against CRP values in dengue fever patients at the Prima Utama Clinic, Surabaya

Korelasi				
			Platelet cell count	CRP value
Spearman's rho	Platelet cell count	Correlation coefficient	1,000	-0,859**
		Sig. (2-tailed)	.	0,000
		N	40	40
	CRP value	Correlation coefficient	-0,859**	1,000
		Sig. (2-tailed)	0,000	.
		N	40	40

Based on the results above, the sig. (2-tailed) value is 0.000, because the sig. (2-tailed) value is less than 0.05 or p <0.05, it means that there is a significant relationship between the number of platelet cells and CRP values. Then the correlation coefficient number is -0.859, meaning that the level of correlation/relationship strength is a very strong relationship.

Based on the results above, the sig. (2-tailed) value is 0.000, because the sig. (2-tailed) value is less than 0.05 or p <0.05, it means that there is a significant relationship between the number of platelet cells and CRP values. Then the correlation coefficient number is -0.859, meaning that the level of correlation/relationship strength is a very strong relationship.

Based on the results of the distribution of blood tests on the number of leukocytes in 40 Dengue Fever patients at the Prima Utama Clinic in Surabaya, 13 samples (32.5%) were obtained with examination results below normal values or <4,000 cells/mm3 or called leukopenia. This occurs when the dengue virus that enters the bloodstream is captured by macrophages which then become APCs

(antigen presenting cells) which activate T-helper cells to phagocytose more viruses. Viremia by the dengue virus interferes with the formation of leukocyte cells in the bone marrow as a place of production by inhibiting the production of leukocyte cells, resulting in abnormalities in the bone marrow which cause the patient to experience fever and a decrease in leukocytes at the beginning of the infection (Devi, Affari Rahmawati Rima., et al. 2024). Based on the number of leukocyte cells in 12 samples (30%) in normal conditions with normal leukocyte values of 4,000-10,000 cells/mm3, while the remaining 15 samples (37.5%) experienced leukocytosis or leukocyte counts above normal values. The normal number of leukocyte cells in the test sample is likely due to the production of leukocyte cells in the bone marrow returning to normal because the dengue virus no longer infects the bone marrow, so that the regenerated leukocyte cells phagocytose viremia (Widarti, et al., 2023). Based on the results of the distribution of routine blood tests on the number of platelet cells in this study on Dengue Hemorrhagic Fever patients at the Prima Utama Clinic Surabaya, the results were 100% of patients with thrombocytopenia/decreased platelet count. Viral inhibition that occurs in the bone marrow causes abnormalities in progenitor cells, stromal cells that release cytokines as inflammatory activators that affect platelet cell aggregation. This causes fluid and plasma to shift/hemoconcentration due to dilation of blood vessels from intravascular to interstitial which causes a decrease in body fluids including the number of platelet cells (Putra, Rizky Ananda., 2024).

Based on the results of the distribution of C-Reactive Protein (CRP) examination using the Wondfo tool, the fluorescence immunoassay (FIA) method obtained normal results <0.05 mg/L for 9 samples (22.5%) and 31 samples (77.5%) had results above normal values with an average value of C-Reactive Protein (CRP) of 53 mg/L.

C-Reactive Protein (CRP) is part of a protein whose blood levels increase during inflammation (Renowati., 2020). Another function of C-Reactive Protein is to activate the movement of phagocyte cells such as granulocytes and monocytes (macrophages), and the attachment of T lymphocytes (Kusnadi, Adi., 2023).

C-Reactive Protein is used as a biomarker for Dengue Fever because C-Reactive Protein levels are higher in severe Dengue Fever with leukopenia and thrombocytopenia compared to non-severe Dengue Fever with a CRP threshold of 188.2 mg/L. This occurs because the binding of the virus and sample antibodies activates the work of cytokines that play a role in blood vessel vulnerability which causes hemostasis. CRP values vary even though infected with the dengue virus, meaning that the CRP increase factor is based on the characteristics of each cytokine and differences in congenital clinical conditions (Salsabila, Yaumi Tsu'a., et al. 2023). This study showed high CRP conditions in patients who had blood test results of thrombocytopenia and leukopenia.

Statistical testing with a normality test of graphic analysis validated with skewness with data results not normally distributed, then the test was continued with a non-parametric test, namely the Spearman test.

Based on the results of the study, the number of leukocyte cells against CRP obtained a sig. value. (2-tailed) of 0.041, because the sig. value (2-tailed) is less than 0.05 or $p < 0.05$, it means that there is a significant relationship between the number of leukocyte cells and the CRP value. Then the correlation coefficient figure of -0.325 is obtained, meaning that the level of correlation/relationship strength is a sufficient or strong enough relationship. The relationship between the number of leukocyte cells and CRP in DHF disease begins with the dengue virus that enters the host/human that enters the bloodstream and invades leukocytes which then replicate.

The dengue virus that enters will inhibit the work of the bone marrow as a place of leukocyte production which results in a decrease in the number of leukocyte cells or leukopenia which returns to normal values over time (Kusdianto., 2020). Leukocytes in the dengue virus infection process will respond to viremia by releasing cytokine proteins as activators of acute phase proteins such as C-Reactive Protein (CRP) (Djohan et al., 2023) and interferon which are involved in the migration process with neutrophil cells so as to stimulate the formation and increase of C-Reactive Protein (CRP) (Salsabila et al., 2023). Based on the results of the study, the number of platelet cells is known to have a sig. (2-tailed) value of 0.000. because the sig. (2-tailed) value is less than 0.05 or p <0.05, it means that there is a significant relationship between the number of platelet cells and the CRP value. Then a correlation coefficient figure of -0.859 is obtained, meaning that the level of correlation/relationship strength is a very strong relationship. The relationship between the number of platelet cells and the CRP value in DHF patients starts from the dengue virus infection that enters and can bind antibodies to activate complement and the coagulation system. The release of ADP (adenosine diphosphate) in this infection causes platelet aggregation to not work properly, resulting in thrombocytopenia and a high possibility of bleeding (Faradiana & Adimayanti, 2023). This also stimulates the formation and increase of C-Reactive Protein (CRP). The attachment of the virus to antibodies becomes an activator of cytokines in the liver, increasing the permeability of blood vessels which will cause plasma leakage. C3a and C5a will eliminate the number of platelet cells in the blood circulation (Salsabila et al., 2023).

CONCLUSION AND RECOMMENDATION

Based on the results of the study of the relationship between the number of leukocytes and platelets to CRP values in DHF patients at the Prima Utama Clinic Surabaya, it can be concluded that Analysis of the number of leukocytes in Dengue Hemorrhagic Fever (DHF) patients obtained patients with leukopenia conditions of 30% and patients with leukocytosis conditions of 37.5%[1]. Analysis of the number of platelets in Dengue Hemorrhagic Fever (DHF) patients obtained patients with thrombocytopenia conditions of 100%[2]. Analysis of the results of C-Reactive Protein (CRP) in Dengue Hemorrhagic Fever (DHF) patients obtained patients with high value results of 77.5%[3]. There is a relationship in the examination of the number of leukocytes and platelets to C-Reactive Protein (CRP) in Dengue Hemorrhagic Fever (DHF) patients[4].

For patients or families of patients who have fever to immediately check to the nearest health facility and provide sufficient fluids to prevent dehydration which can cause dengue shock syndrome (DSS)[1]. It is hoped that further researchers will conduct more specific research such as NS1 with a comparison of hematocrit or erythrocyte ratio index[2]. For the community to prevent Dengue Hemorrhagic Fever by carrying out 3M activities[3].

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