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RELATIONSHIP BETWEEN LEUKOCYTE COUNT AND PROTEINURIA IN COVID-19 PATIENTS

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ABSTRACT

Background: Coronavirus Disease 2019 (COVID-19) is caused by SARS-CoV-2 with flu-like symptoms that could be serious in high-risk individuals. The use of laboratory parameters is determined as a predictor in improving the quality of care and thereby reducing mortality and morbidity. One of the laboratory parameters itself is a hematological examination, including leukocyte count. Several studies have shown that an increase in WBC count was independently associated with an increased risk of proteinuria. **Aim:** To determine the relationship between leukocytes and proteinuria in COVID-19 patients. **Method:** This cross-sectional study with retrospective data collection had a sample of patients with COVID-19 at Diponegoro National Hospital aged 19-60 years. The independent variable in this study was leukocyte count, while the dependent variable in this study was proteinuria. The type of data used was secondary data obtained by examining the medical records of COVID-19 patients. Data analysis between leukocyte count and proteinuria variables in patients with COVID-19 was tested using a bivariate chi-square analysis. **Results:** Samples that met the inclusion criteria were 34 samples with confirmed COVID-19. From the results of the chi square test, it was found that leukocytes to proteinuria had a p-value of 0.601 (p>0.05), which meant that there was no significant relationship between the number of leukocytes and proteinuria. **Conclusion:** There was no significant relationship between leukocyte count and proteinuria in patients with COVID-19.
Keywords: COVID-19, Leukocytes, Proteinuria

INTRODUCTION

Coronavirus Disease 2019 (COVID-19) is a disease caused by SARS-CoV-2 with flu-like symptoms that can be serious in high-risk individuals.[1] In Indonesia, it was recorded that until April 5, 2020, there were 2,273 confirmed cases of COVID-19; 164 people recovered, and 198 people died with a mortality percentage of 9.11%, and one of them was Semarang City. Semarang City was designated as one of the COVID-19 Red Zones by the end of February 2020.[2]

Latest research has shown that the process of entry of SARS-CoV-2 into cells is similar to that of SARS. This is based on the 76% structural similarity between SARS and SARS-CoV-2. This virus targets Angiotensin Converting Enzyme 2 (ACE2) as an entry receptor. The protein (S) facilitates the entry of the SARS-CoV-2 virus into target cells. This process relies on binding of protein S to cellular receptors and priming of protein S to cellular proteases.[3]

COVID-19 is characterized by dysregulation of multiple biological pathways, mirrored by an abnormal immune response and an exaggerated pro-inflammatory state, which finally converge to trigger the development of a profound hemostasis disturbance.[4] Several laboratory tests were abnormal in hospitalized patients.[5] The use of laboratory parameters is set as predictor in improving the quality of care, thereby reducing mortality and morbidity.[6] One of the laboratory parameters is a hematological examination, including an examination of the leukocyte count.

The presence of infection or inflammation in the patient could detect by Leukocyte count. Leukocytes play an essential role in helping the body fight infection or other diseases. Leukocytes are a vital part of the immune system that produces antibodies that fight viruses, fungi, bacteria, and disease-causing parasites that enter the body. The problem in fighting the SARS CoV-2 virus is that our bodies do not yet have antibodies or an adaptive immune system. If the immune system cannot stop the virus from replicating, these pathogens will go into overdrive, increase inflammation, especially in the lungs, and causes pneumonia.[7]

At the beginning of damage to organs and respiratory tract, after exposure to SARS CoV-2, they would experience inflammation or inflammation. This inflammation would cause an

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inflammatory reaction against the inflamed organ. This inflammatory response results in leukocytosis and neutrophilia. The body would produce more white blood cells to increase immunity in maintaining the body's condition. Neutrophils are one type of white blood cell marker of inflammation or inflammation. Neutrophils would work when they get a signal from cytokine hormones that indicate the location of inflammation in the body so that there is an increase in neutrophils in the peripheral blood.[8]

Several studies have shown that an increase in WBC count is independently associated with an increased risk of proteinuria. Proteinuria is a consequence of two mechanisms, abnormal transglomerular protein pathways due to increased permeability of the glomerular capillary wall and subsequent impaired reabsorption by proximal tubular epithelial cells. Several serine proteases derived from neutrophils could cause glomerular capillary wall injury. Impaired reabsorption could trigger the activation of genes encoding cytokines, which contribute to interstitial inflammation. This indicates that proteinuria is a low-grade inflammatory process. Thus, the inflammatory response may in part contribute to proteinuria.[9]

Based on the background above, this study would discover the relationship between leukocyte count and proteinuria in COVID-19 patients.

METHOD

This cross-sectional study with retrospective data collection had samples of patients with COVID-19 at the Diponegoro National Hospital Semarang aged 19-60. Patients with a history of CKD, leukemia, nephrotic syndrome, and pregnancy were excluded. Research subjects were taken by consecutive sampling.

The independent variable in this study was leukocyte count, while the dependent variable was proteinuria. The type of data used was secondary data obtained by examining the medical records of COVID-19 patients. The Chi-square test was used to analyze the variable number of leukocytes and proteinuria in patients with COVID-19. The significance value was $p < 0.05$.

RESULTS

Data was taken based on medical records at Diponegoro National Hospital from December 2019 - August 2021. Samples that met the inclusion criteria were 34 samples with confirmed COVID-19. Age was categorized into two, with the age category ≤ 55 years being 25 (73.5%) and > 55years being 9 (26.5%). The youngest was 26 years old, and the oldest was 60. Of the research subjects, 11 (32.4%) patients were male and 23 (67.6%) patients were female. The characteristics of the research subjects were presented in table 1.

Table 1. Distribution of Research Subject Characteristics

Variable	Frequency	%
Age		
≤ 55 years	25	73.5
> 55 years	9	26.5
Gender		
Male	11	32.4
Female	23	67.6
Leukocyte		
Leukopenia	1	2.9
Normal	20	58.8
Leukocytosis	13	38.2
Hematocrit		
Low	15	44.1
Normal	19	55.9
High	0	0
Thrombocyte		
Thrombocytopenia	2	14.7
Normal	25	73.5
Thrombocytosis	4	11.8
Hemoglobin		
Low	13	38.2
Normal	21	61.8
High	0	0
Blood Sugar Level		
Hypoglycemia	0	0
Normal	3	8.8
Hyperglycemia	31	91.2
Proteinuria		
Positive	15	44.1
Negative	19	55.9

Leukocyte count was categorized into three; leukopenia was 1 (2.9%), normal leukocytes were 20 (58.8%), and leukocytosis was 13 (38.2%). Hematocrit was categorized into three, with the result obtained for low hematocrit being 15 (44.1%), normal hematocrit being 19 (55.9%), and no high

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hematocrit. Platelet counts fall into three categories. The result obtained for thrombocytopenia was 5 (14.7%), normal platelet was 25 (73.5%), and thrombocytosis was 4 (11.8%). Hemoglobin was categorized into three; low hemoglobin was 13 (38.2%), normal hemoglobin was 21 (61.8%), and no high hemoglobin. When blood glucose was categorized into three, the results showed no hypoglycemia, normal blood sugar was 3 (8.8%), and hyperglycemia was 31 (91.2%). Proteinuria variables were divided into two groups as follows: 19 (44.1%) negative proteinuria and 15 (55.9%) positive proteinuria.

Table 2. Relationship between Leukocyte Count and Proteinuria

Variable	Proteinuria		p
	Positive	Negative	
Leukocyte			
Leukocytosis	5 (38.5%)	8 (61.5%)	
Normal	10 (50%)	10 (50%)	0.601
Leukopenia	0 (0%)	1 (100%)	

There was no significant relationship between the number of leukocytes and proteinuria (p =0.601).

DISCUSSION

COVID-19 patients are declared confirmed if they have conducted a Polymerase Chain Reaction (RT-PCR) examination showing positive results. Meanwhile, to assess the course of the disease, supporting examinations such as chest imaging and blood laboratory would be carried out. A laboratory examination, one of the available general examinations, could support the diagnosis of COVID-19, with hematology as one of its types. . Complete blood counts in COVID-19 patients could show leukopenia, leukocytosis, thrombocytopenia, normal hematocrit, and normal hemoglobin.

There was 1 (2,9%) patient with leukopenia, 20 (58.8%) patients with normal leukocytes, and 13 (38.2%) patients with leukocytosis. . This study's results were from previous research conducted by Fadhilah Amalia Rahman, et al., who concluded that the general description of the leukocyte count was normal. It showed an increase in the number of leukocytes along with the worsening clinical severity.[10] The research held by Zabaneh *et al.* found an increase in the number of leukocytes, a decrease in the number of lymphocytes, and the occurrence of cytokine storms. The mechanism that occurred started from viral invasion of the respiratory tract through ACE2 receptors in the respiratory tract and then attacked target cells through the CD147 protein. The more viruses that enter, the S protein from SARS-CoV-2 encodes an IL-6 amplifier which causes an increase in pro-inflammatory cytokines so that inflammation occurs in organs, especially the lungs, causing more clinical manifestations. This could be what caused an increase in the number of leukocytes to be positively related to the clinical severity of COVID-19 patients.[11]

Laboratory examinations for COVID-19 patients other than hematology were urine protein examinations to assess the amount of protein in the urine. Suppose it was known that there was excess protein in the urine. In that case, this could indicate certain diseases, especially kidney disorders. In this study, there were positive proteinuria results, as much as 15 (44.1%) and negative with 19 (55.9%) out of 34 patients. COVID-19 patients can experience various degrees of kidney damage. In a study conducted by Cheng, *et al.* reported that COVID-19 patients experienced hematuria and proteinuria. In addition, research conducted by Li, Z also concluded that COVID-19 patients experienced massive albuminuria and showed proteinuria during hospitalization.[12]

This study resulted in the absence of a significant relationship between the number of leukocytes and proteinuria in COVID-19 patients. The results of this study were correlated with previous research conducted by Andreas in 2019, where there was no relationship between leukocytes and urine protein in third-trimester pregnant women.[13] This could be due to the failure to divide the severity of COVID-19. Previous studies showed that proteinuria in moderate, severe, and critical COVID-19 was 4.7%, 27.6%, and 63.2%, respectively. Based on these results, the milder the degree ofCOVID-19 a person was, the less likely the patient was to experience proteinuria.[14] Insignificant results could be sourced from the severity of patients who tended to be mild and moderate, which resulted in a majority of negative proteinuria results. In addition, proteinuria detection tools were not

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disclosed in the laboratory examination. Previous studies had noted that urine dipstick tests were insensitive to non-albumin proteinuria. Non-albumin proteinuria itself was the most common type of proteinuria found at admission and follow-up. More detectable non-albumin proteinuria was found on spot urine analysis than on the dipstick test.[15]

The discrepancy in the study results could also be caused by the respondent's age related to proteinuria levels because the elasticity of blood vessels decreases in old age. Organ functions decreased and body cells could no longerregenerate like youths. The older a person was, the more the condition of the organs tended to decline and became more susceptible to complications of other diseases. Negative proteinuria could occur due to other factors, such as most respondentsdid not smoke nor consume alcohol, had a healthy lifestyle, exercising regularly, and maintaining a good diet.[16]

The limitations of this study were incomplete medical record data. Not all COVID-19 patients were examined for urinalysis and proteinuria. Hence limited data was included.

CONCLUSION

Based on the results of the research and discussion above, this study concluded that there was no significant relationship betweenthe leukocyte count and proteinuria in patients with COVID-19.

In further research, it should be necessary to do similar research with a larger sample. Further research also could differentiate the severity of COVID-19 from patients who are research subjects andanalyze the relationship between leukocyte count and proteinuria based on each degree.

ETHICAL APPROVAL

This study has been approved by The Health Research Ethics Committee of Faculty of Medicine of Diponegoro University with the certificate number of No. 357/EC/KEPK/FK-UNDIP/IX/2021.

CONFLICTS OF INTEREST

There is no conflict of interest related to the materials, methods, and findings in this study.

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AUTHOR CONTRIBUTION

Conseptualization, Anggar Setiorini; methodology, Anggar Setiorini; writing- drafting, Anggar Setiorini; writing-editing, Anggar Setiorini, Indranila Kustarini Samsuria, and Dwi Retnoningrum; supervision, Indranila Kustarini Samsuria, Dwi Retnoningrum, and Ariosta.

RECOGNITION

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