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Correlation of Interleukin-6 And Hs-Crp Value in Covid 19 Patients With Severe Symptoms in Makassar Prodia Clinical Laboratory

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ABSTRACT

Corona Virus Disease 2019 (COVID-19) is a new infectious disease caused by a novel coronavirus known as Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2).Patients with severe symptoms of Coronavirus disease-19 (Covid-19) experience hyperinflammation and also a cytokine storm which contributes to the high mortality rate. A useful clinical parameter is needed for risk stratification of Covid-19 patients. This study aims to determine the relationship between Interleukin-6 and Hs-CRP values in Covid-19 patients with severe symptoms at the Prodia Makassar Clinical Laboratory. This research is an observational analytic study with a cross sectional approach. The subjects of this study were 30 patients with Covid-19 with severe symptoms, the time of the study was December 2021 - April 2022. Interleukin-6 and Hs-CRP examinations were carried out on the Roche Cobas 6000 automatic device. Analysis of the data using the Pearson-Product Moment Correlation Test using the help of the Statistical Product and Service Solution program. The results of the research analysis showed a significance value of 0.000 < 0.005. The conclusion of this study is that there is a relationship between Interleukin-6 and Hs-CRP in Covid-19 patients with severe symptoms at the Prodia Makassar Clinical Laboratory. The relationship between the two variables is strong and positive so that as HS-CRP increases, IL-6 will also increase.

Keywords: interleukin-6; hs-crp; COVID-19, severe symptoms, patient

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INTRODUCTION

Coronavirus Disease 2019 (COVID-19) is a disease caused by the coronavirus, initially known as a respiratory disease and believed to have been initially transmitted from bats. The coronavirus in humans was first discovered in the noses of patients with the common cold. This virus has a high virulence rate, making it highly contagious. The virus was first detected in Wuhan in 2019. From the time it was first discovered until October 2021, hundreds of millions of people worldwide have been infected, with a total of 243,561,596 confirmed cases and a mortality rate of 2.0% (4,947,777) in 204 countries, including 151 countries with community transmission. According to data from the COVID-19 Task Force in Indonesia, 4,257,489 people have been exposed to COVID-19. Specifically, in Sulawesi, Maluku, and Papua, the numbers are recorded as 34,721 in North Sulawesi, 47,158 in Central Sulawesi, 109,926 in South Sulawesi, 20,160 in Southeast Sulawesi, 11,833 in Gorontalo, 12,354 in West Sulawesi, 14,589 in Maluku, and 34,346 in Papua (COVID Task Force Data, 2021).

Coronavirus transmission can occur through various means such as droplets from coughing and sneezing, as well as personal contact like touching and shaking hands. Touching objects or surfaces with the virus on them and then touching the mouth, nose, or eyes before washing hands can also spread the virus (WHO, 2020). Additionally, it has been reported that coronavirus can be transmitted through the fecal-oral route (WHO, 2021).

The coronavirus generally attacks the human respiratory system and shows a clinical picture that varies between 5-20%, potentially causing disturbances in several human organs. COVID-19 infections can vary significantly in causing clinical symptoms in infected patients. If COVID-19 is not promptly treated, it can lead to complications in the human organ systems, such as inflammation in most of the body's organs. Inflammation symptoms are marked by changes in Hs-CRP levels. This condition can develop into severe cases requiring intensive care. COVID-19 patients with severe clinical symptoms often progress to pneumonia, Acute Respiratory Distress Syndrome (ARDS), and multi-organ failure, primarily due to increased pro-inflammatory cytokines. One of the acute pro-inflammatory cytokines, interleukin-6, has a strong correlation with the occurrence of ARDS (Kerget et al., 2020).

Interleukin-6 is a pro-inflammatory cytokine that plays a role in the body's host defense against infections. However, excessive IL-6 synthesis can lead to a severe systemic inflammatory response known as a cytokine storm. The pathophysiology of COVID-19 with severe clinical symptoms is characterized by an imbalance in the immune response, resulting in negative effects such as the overproduction of pro-inflammatory cytokines, impacting the prognosis. A cytokine storm is associated with the severity and mortality of patients infected with SARS-CoV-2 through increased vascular permeability and multi-organ failure (Cruz et al., 2020). Interleukin-6 modulates host immunity through various mechanisms, such as the control of monocytes and differentiation into macrophages, modulation of antigen-dependent B cell differentiation, increased IgG production by B cells, and promotion of the Th2 cell response (Kim et al., 2021).

C-Reactive Protein (CRP) is an acute-phase protein found in normal serum, although in very low concentrations, and is a pro-inflammatory mediator secreted in large amounts during inflammation (Anisa Nur Azizah, 2016). High sensitivity C-Reactive Protein (Hs-CRP) is a quantitative measurement of CRP concentration, which can measure levels from < 0.2 – 300 mg/L (Handojo, 2004). According to research, Hs-CRP testing can detect inflammation more quickly. Hs-CRP testing has been standardized in various laboratories (Agustin, 2016).

Currently, clinical laboratories have an effective and efficient contribution to the management of COVID-19 patients, particularly

in aiding diagnosis. Additionally, clinical laboratories play a role in assisting with screening, management, and prevention of serious complications (Kerboua, 2021). With the increasing demand for Hs-CRP testing and the introduction of new Interleukin-6 tests at Prodia Clinical Laboratory in Makassar as a supplementary examination for COVID-19 patients with severe symptoms, we are interested in conducting this research.

MATERIAL AND METHODE

This study is an observational analytic study with a cross-sectional approach, which is a type of research used to study the correlation between risk factors by collecting data simultaneously at a specific point in time. The study was conducted in the Immunoserology section of the Prodia Clinical Laboratory in Makassar. The subjects of this study were COVID-19 patients categorized as having severe symptoms, while the objects of this study were interleukin-6 and Hs-CRP.

The study population consisted of all patients from Eastern Indonesia whose samples were referred to Prodia Makassar and who had been diagnosed by clinicians as having severe COVID-19. The sample for the study was collected from various Prodia branches in Eastern Indonesia (Prodia Manado, Prodia Kendari, Prodia Sorong, Prodia Jayapura, Prodia Palu, Prodia Ternate, Prodia Ambon, Prodia Gorontalo) and referring hospitals in Makassar that conducted clinical tests for IL-6 and Hs-CRP.

The sampling technique used was accidental sampling, which involves selecting samples by taking cases or respondents who happen to be present or available at a particular place according to the research context. The minimum sample size required for this study is 30 samples. The sample size was calculated using the formula for the correlation coefficient with a sample. The instrument used is the Roche Cobas 6000. The data obtained from the examination results will be analyzed using the statistical data processing application SPSS version 25.0. The data analysis used is Pearson Product Moment correlation analysis.

The steps for data analysis include:

1. Normality Test The normality test is conducted using the Kolmogorov-Smirnov test for sample sizes ≥ 50, while for sample sizes < 50, the Shapiro-Wilk test is used. If the significance value is > 0.05 ($\alpha = 0.05$), the data is normally distributed; if the significance value is ≤ 0.05, the data is not normally distributed.
2. Statistical Test After conducting the normality test, hypothesis testing is carried out using the Pearson Product Moment correlation method. The Pearson Product Moment correlation is used to test the relationship between two variables with numerical data. Conclusions can be drawn by comparing the calculated r value with the table r value at $\alpha = 0.05$. If the calculated r > table r, it means Ho is rejected, indicating a relationship between the two variables tested. The test results are interpreted based on the significance value (p) compared to $\alpha = 0.005$; if $p < 0.005$, Ho is rejected, indicating a relationship between the two variables tested. If an asterisk (*) appears next to the correlation coefficient in the SPSS table results, it indicates a significant or meaningful test result. The relationship between two variables can be either positive or negative. A positive relationship occurs when an increase in one variable is followed by an increase in the other variable, while a negative relationship occurs when an increase in one variable is followed by a decrease in the other variable. The strength of the relationship between the two variables can be divided into four areas:
    1. 0.00 - 0.25: No relationship/weak
    2. 0.26 - 0.50: Moderate relationship
    3. 0.51 - 0.75: Strong relationship
    4. 0.76 - 1: Very strong/perfect relationship

RESUTS AND DISCUSIONS

The results from Table 1 show that out of 30 samples of severe COVID-19 patients, 16 individuals (53.3%) had non-comorbid COVID-19, while 14 individuals (46.7%) had COVID-19 with comorbidities. For the IL-6 and Hs-CRP tests, all 30 patients (100%) exhibited abnormal results. IL-6 levels are considered normal if they are below 7 pg/mL, and Hs-CRP levels are normal if they are below 10 mg/L. A univariate analysis of IL-6 and Hs-CRP in severe COVID-19 patients was conducted. Table 2 shows that for Hs-CRP, the mean value was 46.38 mg/L, with a minimum of 10.80 mg/L, a maximum of 90.76 mg/L, and a standard deviation of 24.70 mg/L. For IL-6, the mean was 36.85 pg/mL, with a minimum of 9.85 pg/mL, a maximum of 86.47 pg/mL, and a standard deviation of 19.68 pg/mL. The Shapiro-Wilk normality test results indicate that the significance values for Hs-CRP and IL-6 were 0.076 and 0.108, respectively. Since these values are greater than the significance level of 0.05 ($\alpha = 0.05$), it can be concluded that the data for both variables are normally distributed. The next step involved performing a Pearson Product Moment Correlation Test, yielding the following results (Table 2).

From the table above (Table 3), the Sig. (2-tailed) value for the correlation between Hs-CRP and IL-6 is 0.000, which is less than 0.005, indicating a significant correlation between the variables Hs-CRP and IL-6. Furthermore, the presence of an asterisk (*) next to the correlation coefficient indicates that the test result is significant. The Pearson correlation coefficient (r) value for the relationship between Hs-CRP and IL-6 is 0.740, which is greater than the critical value (r table) of 0.361. This indicates a significant positive correlation between Hs-CRP and IL-6. The positive nature of the correlation means that as Hs-CRP levels increase, IL-6 levels also increase, indicating a strong relationship between these two variables.

Tabel 1. Frequency Distribution of IL-6 and Hs-CRP Testing in Severe COVID-19 Patients

Variable	Frequency	Percent	Valid Percent	Cumulative Percent
Covid Non Komorbid	16	55,30%	55,30%	55,30%
Covid dengan Komorbid	14	46,70%	46,70%	46,70%
Total	30	100%	100%	100%
Hs-CRP Normal	0	0%		
Hs-CRP Abnormal	30	100%		
Interleukin-6 Normal	0	0%		
Interleukin-6 Abnormal	30	100%		

Table 2. Analysis of IL-6 and Hs-CRP Results in Severe COVID-19 Patients

Variable	Mean	SD	Min-Max	N
Hs-CRP	46.38 mg/L	24.70 mg/L	10.80 mg/L - 90.76 mg/L	30
Interleukin-6	36.85 pq/mL	19.68 pq/mL	9.85 pq/mL– 86.47 pq/mL	30

Table 3. Shapiro-Wilk Normality Test Significance Values

Variable	Shapiro Wilk
Hs-CRP	0.076
IL-6	0.108

This study found that COVID-19 patients with severe symptoms are those infected with the COVID-19 virus, with some accompanied by comorbidities and others without. As we know, some factors that can exacerbate the condition when exposed to COVID-19 include the presence of comorbidities. In this study, it was found that 16 individuals (53.3%) were non-comorbid COVID-19 patients, while 14 individuals (46.7%) were COVID-19 patients with comorbidities. The involvement of comorbidities in the pathogenesis of COVID-19 plays a direct role as a predictor of disease progression, leading to ARDS (Acute Respiratory Distress Syndrome), a condition where alveolar damage occurs due to fluid leakage from the capillary blood vessels into the alveoli, and multi-organ failure. These results align with the study by Wibisana et al. (2021), which stated that individuals with chronic diseases are more susceptible to COVID-19 infection and are more likely to develop severe clinical manifestations, also linked to factors regarding the immune system. Individuals with weakened immune systems are more easily infected with COVID-19 and can experience severe clinical manifestations (Wibisana et al., 2021). Previous research suggests that comorbidities can worsen a disease and lead to very severe and critical clinical manifestations such as respiratory failure, pneumonia, and severe respiratory distress. According to Liu et al. (2020), hypertension is the most common comorbidity that can increase the severity of COVID-19 symptoms.

In COVID-19 patients with severe symptoms, an excessive immune response or hyperinflammation occurs, marked by elevated Hs-CRP levels in the patient's blood. Hs-CRP increases rapidly at the onset of inflammation and cell and tissue damage. This condition is consistent with the findings of this study, where the lowest Hs-CRP level was 10.80 mg/L, the highest was 90.76 mg/L, and the mean was 46.3820. This indicates that Hs-CRP levels in COVID-19 patients exceed the normal Hs-CRP level of <10 mg/L. Elevated Hs-CRP levels correlate with disease severity and are a predictor of progression to a worse condition. These findings are consistent with a retrospective cohort study by Sharifour et al. (2020), which found that median CRP levels correlate with COVID-19 severity and predict mortality. A study by Striger et al. (2021) determined that CRP levels at the time of admission can predict mortality in COVID-19 patients. CRP levels with a cutoff of 40 mg/L are associated with mortality in COVID-19 patients. This threshold can help clinicians use CRP measurements in monitoring, decision-making, and patient therapy planning.

Increased Hs-CRP levels in the first seven days of hospitalization can be used as a parameter to predict disease progression and the need for transfer to intensive care. A study by Liu et al. (2020) comparing groups of patients in disease progression stages with those in recovery showed that Hs-CRP levels significantly increased in the disease progression group, with the increase indicating a poor prognosis. An observational study by Liu et al. (2020) examining medical records of COVID-19 patients found that initial serum CRP levels upon hospital admission were useful as discriminators of COVID-19 infection severity.

Hyperinflammation in COVID-19 patients can lead to death. This hyperinflammation is characterized by excessive and uncontrolled cytokine release. Interleukin-6 is a cytokine involved in hyperinflammation and is used as a biomarker for hyperinflammation. This aligns with the findings of this study, where the average IL-6 level was 36.8557 pg/mL. The lowest IL-6 result was 9.85 pg/mL, and the highest was 86.47 pg/mL. These results exceed the normal IL-6 level of <7 pg/mL. This is similar to what Sayah et al. (2021) stated, that a cutoff of 42 pg/mL can predict >90% of patients at risk and is a strong predictor of death. In a meta-analysis study of 1,465 patients in China, the IL-6 level in the severe COVID-19 group was 56.8 pg/mL. Liu et al. (2020) found a lower median IL-6 level in

severe COVID-19 cases, at 17.6 pg/mL. Shi et al. (2020) found an even lower median IL-6 level of 10 pg/mL. In a meta-analysis study involving 1,357 COVID-19 patients, Mojtabavi et al. (2020) found that the average difference in IL-6 levels between mild-to-moderate and severe cases was 23.1 pg/mL (95% CI: 12.42-33.79).

The significant increase in IL-6 and Hs-CRP results is a marker of hyperinflammation or increased inflammatory cytokines. According to Liu et al. (2020), who studied the ability of IL-6 and CRP to predict mild and severe COVID-19 infection, Gubernatorova et al. (2020) stated that an IL-6 level >80 pg/mL can predict the likelihood of respiratory failure in COVID-19 patients. The proportion of patients with significant increases in IL-6 and Hs-CRP levels is higher in the severe COVID-19 group compared to the mild group. Patients with IL-6 levels >32 pg/mL and CRP levels >41.8 mg/L are at a higher risk of experiencing severe complications.

CONCLUSION

Based on the results of the study, the levels of IL-6 and Hs-CRP showed an increase beyond normal values. This indicates a strong correlation between Hs-CRP and Interleukin-6 in COVID-19 patients with severe symptoms at Prodia Clinical Laboratory in Makassar. In line with the above conclusion, it is recommended to increase the sample size in future studies to obtain a broader range of results and facilitate easier analysis. Additionally, it is suggested to include other variables, such as additional parameters involved in the inflammatory response in COVID-19, which may also influence various aspects of this research.

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