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THE ASSOCIATION BETWEEN INTERLEUKIN-6 AND C-REACTIVE PROTEIN IN COVID-19 PATIENTS

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Abstract
Background: Coronavirus Disease 2019 (COVID-19), caused by Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2), is characterized by an excessive inflammatory response that may lead to cytokine storm and worsening clinical outcomes. Interleukin-6 (IL-6) is a major pro-inflammatory cytokine that stimulates the production of C-reactive protein (CRP), making both biomarkers useful for assessing the inflammatory response in patients with COVID-19. Objective: This study aimed to determine the association between serum IL-6 and CRP levels in patients with COVID-19. Methods: This retrospective observational study analyzed medical record data from 30 patients with COVID-19 confirmed by reverse transcription polymerase chain reaction (RT-PCR). Serum IL-6 and CRP levels were obtained from laboratory results recorded in hospital medical records. Statistical analysis was performed using IBM SPSS Statistics version 22. The association between serum IL-6 levels as the independent variable and CRP levels as the dependent variable was assessed using simple linear regression analysis. The results were reported as the regression coefficient (β), correlation coefficient (R), coefficient of determination (R^2), and p-value. Results: Simple linear regression analysis demonstrated a significant positive association between serum IL-6 and CRP levels ($\beta = 0.335$; $R = 0.538$; $R^2 = 0.290$; $p = 0.002$). The positive regression coefficient indicated that higher serum IL-6 levels were associated with higher CRP levels. The R^2 value indicated that serum IL-6 explained 29.0% of the variation in CRP levels. Elevated IL-6 and CRP levels were observed in 90% and 93% of patients, respectively. Conclusion: Serum IL-6 levels were significantly and positively associated with CRP levels in patients with COVID-19. These findings suggest that IL-6 and CRP may provide complementary information for assessing the inflammatory response in patients with COVID-19.
***Keywords**: Biomarkers; COVID-19; C-Reactive Protein; Cytokine Storm; Inflammation; Interleukin-6*

Abstrak
Latar Belakang: Coronavirus Disease 2019 (COVID-19) yang disebabkan oleh Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) ditandai dengan respons inflamasi berlebihan yang dapat menyebabkan badai sitokin dan memperburuk kondisi klinis pasien. Interleukin-6 (IL-6) merupakan salah satu sitokin proinflamasi utama yang menstimulasi produksi C-reactive protein (CRP), sehingga kedua biomarker tersebut dapat digunakan untuk menggambarkan respons inflamasi pada pasien COVID-19. Tujuan: Penelitian ini bertujuan untuk mengetahui hubungan antara kadar IL-6 serum dan CRP pada pasien COVID-19. Metode: Penelitian ini merupakan penelitian observasional retrospektif yang menganalisis data rekam medis 30 pasien COVID-19 yang terkonfirmasi melalui reverse transcription polymerase chain reaction (RT-PCR). Data kadar IL-6 serum dan CRP diperoleh dari hasil pemeriksaan laboratorium yang tercatat dalam rekam medis rumah sakit. Analisis statistik dilakukan menggunakan IBM SPSS Statistics versi 22. Hubungan antara kadar IL-6 serum sebagai variabel independen dan kadar CRP sebagai variabel dependen dianalisis menggunakan regresi linear sederhana. Hasil analisis dilaporkan dalam bentuk koefisien regresi (β), koefisien korelasi (R), koefisien determinasi (R^2), dan nilai p. Hasil: Analisis regresi linear sederhana menunjukkan adanya hubungan positif dan signifikan antara kadar IL-6 serum dan CRP ($\beta = 0{,}335$; $R = 0{,}538$; $R^2 = 0{,}290$; $p = 0{,}002$). Koefisien regresi positif menunjukkan bahwa peningkatan kadar IL-6 serum berhubungan dengan peningkatan kadar CRP. Nilai R^2 menunjukkan bahwa kadar IL-6 menjelaskan sebesar 29,0% variasi kadar CRP. Kadar IL-6 dan CRP yang meningkat ditemukan masing-masing pada 90% dan 93% pasien. Kesimpulan: Kadar IL-6 serum berhubungan positif dan signifikan dengan kadar CRP pada pasien COVID-19. Hasil ini menunjukkan bahwa IL-6 dan CRP dapat memberikan informasi yang saling melengkapi dalam menggambarkan respons inflamasi pada pasien COVID-19.
Kata Kunci: Badai Sitokin; Biomarker; COVID-19; Inflamasi; Interleukin-6; Protein C-Reaktif

INTRODUCTION

Coronavirus disease 2019 (COVID-19), caused by Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2), was first identified in Wuhan, China, at the end of 2019 and

rapidly evolved into a global pandemic (World Health Organization, 2020). SARS-CoV-2 is a positive-sense, single-stranded RNA virus belonging to the family Coronaviridae and the order Nidovirales (Wang et al., 2020). The diagnosis of COVID-19 is confirmed by reverse transcription polymerase chain reaction (RT-PCR), which remains the gold standard for detecting SARS-CoV-2 infection (Korsman et al., 2020).

COVID-19 presents with a broad spectrum of clinical manifestations, ranging from asymptomatic infection and mild respiratory symptoms to severe pneumonia, acute respiratory distress syndrome (ARDS), multiple organ dysfunction, and death (Korsman et al., 2020; Perhimpunan Dokter Paru Indonesia, 2020). Disease severity is strongly associated with an exaggerated immune response characterized by excessive production of pro-inflammatory cytokines, commonly referred to as a cytokine storm (Callaway, 2020; Schett et al., 2020). This dysregulated inflammatory response contributes to extensive tissue damage, endothelial dysfunction, and multiorgan failure in patients with severe COVID-19 (Schett et al., 2020).

Among the inflammatory mediators involved in COVID-19, interleukin-6 (IL-6) is one of the most important cytokines. IL-6 stimulates the hepatic synthesis of acute-phase proteins, particularly C-reactive protein (CRP), making both biomarkers valuable indicators of systemic inflammation (Jones & Hunter, 2021; Kishimoto & Kang, 2022). Elevated serum IL-6 and CRP levels have consistently been associated with disease severity, respiratory failure, thrombotic complications, and poor clinical outcomes in patients with COVID-19 (Samprathi & Jayashree, 2021; Stringer et al., 2021; Gorog et al., 2022).

Several studies have suggested that IL-6 and CRP are complementary inflammatory biomarkers because CRP production is largely regulated by IL-6 during the acute inflammatory response (Jones & Hunter, 2021; Kishimoto & Kang, 2022). Simultaneous assessment of these biomarkers may improve the evaluation of inflammatory status and facilitate early identification of patients at risk of severe disease progression (Samprathi & Jayashree, 2021; Stringer et al., 2021). However, despite numerous international studies, evidence regarding the relationship between serum IL-6 and CRP levels among Indonesian patients with COVID-19 remains limited. Therefore, this study aimed to investigate the association between serum IL-6 and CRP levels in patients with COVID-19 and to evaluate whether these biomarkers could serve as complementary indicators for assessing inflammatory status and monitoring disease severity in patients with COVID-19.

METHODS

This retrospective observational study was conducted between November and December 2020 at the clinical laboratory of a private hospital in Central Jakarta, Indonesia. The study utilized secondary data obtained from the medical records of hospitalized patients with laboratory-confirmed COVID-19. The study population consisted of hospitalized patients with confirmed COVID-19. A purposive sampling technique was applied to select patients who met the predefined inclusion criteria. Eligible participants had elevated serum interleukin-6 (IL-6) levels (>12.5 pg/mL), elevated C-reactive protein (CRP) levels (>11 mg/L), and clinical manifestations of dyspnea. Medical records containing demographic information (age, date of examination, and clinical symptoms) as well as laboratory results for IL-6 and CRP were reviewed. Based on a commonly used rule of thumb in quantitative research, which considers 30 observations as a minimum initial threshold for statistical analysis, a total of 30 patients who fulfilled the predefined inclusion criteria were included in the study.

The IL-6 and CRP laboratory results were extracted from the medical records using a standardized data collection form. All data were anonymized prior to analysis to ensure patient confidentiality. Statistical analyses were performed using IBM SPSS Statistics version 22.0. Descriptive statistics were used to summarize the study variables. The relationship between IL-

6 and CRP levels was analyzed using simple linear regression analysis. The strength and direction of the association were determined using the correlation coefficient (r) and regression coefficient (β), respectively. Statistical significance was established at a two-sided p value of <0.05. This study was conducted using anonymized secondary data obtained from patients' medical records. No direct contact or intervention involving human participants was performed. Patient confidentiality was maintained throughout the study by removing all personal identifiers prior to data analysis.

RESULTS AND DISCUSSION

A total of 30 patients with confirmed COVID-19 were included in this study. Serum IL-6 levels ranged from 5.12 to 87.00 pg/mL and the reference range for normal IL-6 levels was 0.7–12.5 pg/mL. Serum CRP levels ranged from 10.00 to 54.00 mg/dL and the reference range for normal CRP levels was 1–11 mg/dL. The descriptive statistics of IL-6 and CRP levels are presented in Table 1.

Table 1. Descriptive Statistics of Interleukin-6 and C-Reactive Protein Levels

Parameter	Mean±SD	Shapiro-Wilk (W)	P-value
IL-6 (ρg/mL)	32.32±22.54	0.892	0.006
CRP (mg/dL)	27.69±14.05	0.910	0.015

Source: data proceed

Prior to further statistical analysis, the normality of the data was assessed using the Shapiro-Wilk test. The results indicated that both IL-6 and CRP levels were not normally distributed, with p-values of 0.015 and 0.006, respectively. The mean ± standard deviation was 27.69 ± 14.05 mg/dL for CRP and 32.32±22.54 ρg/mL for IL-6. Therefore, non-parametric statistical methods were considered for further analysis.

The results also showed that the majority of patients with COVID-19 had elevated IL-6 and CRP levels. Elevated IL-6 levels were observed in 90% of patients, while elevated CRP levels were found in 93% of patients, as shown in Figure 1.

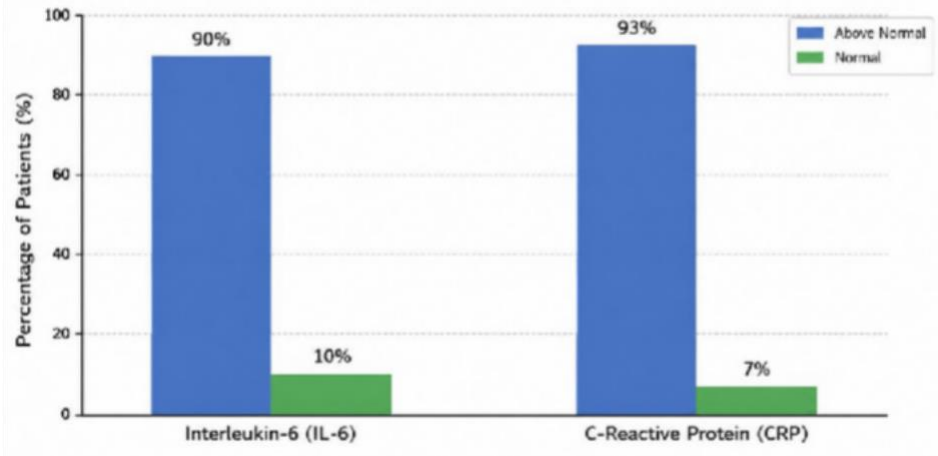

Figure 1. Distribution of IL-6 and CRP Levels According to the Normal Reference Range

Source: data proceed

Simple linear regression analysis demonstrated a statistically significant positive association between serum IL-6 and CRP levels in patients with COVID-19 (p = 0.002), as presented in Table 2. The correlation coefficient was 0.538, indicating a moderate positive correlation between the two biomarkers. The regression equation was y = 16.850 + 0.335x, indicating that each 1 pg/mL increase in IL-6 was associated with an increase of 0.335 mg/dL in CRP levels. The positive regression coefficient indicates that higher IL-6 levels were

accompanied by higher CRP levels.

Table 2. Simple Linear Regression Between IL-6 and CRP

Outcome Variable	Predictor	Regression Coefficient (β)	Correlation Coefficient (R)	R^2	p-value
CRP	IL-6	0.335	0.538	0.290	0.002

Source: data proceed

Discussion

The present study demonstrated a significant positive association between serum IL-6 and CRP levels in hospitalized patients with COVID-19. This finding supports the hypothesis that IL-6 and CRP are closely related inflammatory biomarkers reflecting the host immune response to SARS-CoV-2 infection. IL-6 is a key pro-inflammatory cytokine that stimulates hepatocytes to synthesize acute-phase proteins, particularly CRP. Therefore, increased IL-6 production is generally accompanied by elevated CRP concentrations during systemic inflammation (Jones & Hunter, 2021; Sproston & Ashworth, 2018; Stringer et al., 2021).

The elevation of IL-6 and CRP observed in this study is biologically plausible because SARS-CoV-2 infection induces an exaggerated inflammatory response through activation of macrophages, monocytes, neutrophils, and T lymphocytes. These immune cells release excessive amounts of pro-inflammatory cytokines and chemokines, leading to immune dysregulation, pulmonary inflammation, and tissue damage. Similar inflammatory mechanisms have previously been reported in COVID-19, where persistent cytokine production contributes to progressive pulmonary involvement, thrombotic complications, and disease severity (Gorog et al., 2022; Ragab et al., 2020). Likewise, studies have demonstrated that excessive inflammatory responses play a central role in disease progression and multiple organ dysfunction (Moore & June, 2020; Zhong et al., 2020).

The findings of the present study are consistent with previous reports showing that elevated IL-6 and CRP levels are associated with severe COVID-19. Chen et al. (2020) reported that patients with severe COVID-19 exhibited significantly higher circulating IL-6 concentrations than patients with moderate disease, indicating that IL-6 is closely associated with disease progression. Del Valle et al. (2020) further demonstrated that inflammatory cytokine signatures, particularly IL-6, accurately predicted disease severity and survival among hospitalized patients with COVID-19. Similarly, Santa Cruz et al. (2021) identified IL-6 as an important biomarker associated with fatal SARS-CoV-2 pneumonia, supporting its clinical value in identifying patients at high risk of adverse outcomes. Several systematic reviews and meta-analyses have also confirmed the prognostic significance of IL-6. Coomes and Haghbayan (2020) reported that elevated IL-6 levels were consistently associated with severe COVID-19 across multiple studies. Likewise, Aziz et al. (2020) demonstrated that patients with severe COVID-19 had significantly higher IL-6 concentrations than those with non-severe disease, further supporting the use of IL-6 as a biomarker of disease severity. Zhong et al. (2020) also emphasized that dysregulated immune responses mediated by excessive cytokine production contribute substantially to the pathogenesis of COVID-19 and may represent potential therapeutic targets.

A moderate positive correlation between IL-6 and CRP was observed in the present study. Although IL-6 is the principal cytokine responsible for inducing CRP synthesis, CRP production is also influenced by additional inflammatory mediators and clinical conditions. Consequently, IL-6 alone cannot completely explain variations in CRP concentrations. A positive correlation between IL-6 and CRP has also been reported in patients with COVID-19, suggesting that IL-6 stimulates the hepatic acute-phase response (Samprathi & Jayashree,

2021). McElvaney et al. (2020) likewise demonstrated that combining IL-6 and CRP improved prediction of adverse clinical outcomes compared with either biomarker alone, indicating that these biomarkers provide complementary prognostic information. Liu et al. (2020) further reported that IL-6, CRP, and procalcitonin were significant predictors of disease progression in patients with COVID-19, emphasizing the importance of interpreting IL-6 together with other inflammatory biomarkers.

From a clinical perspective, simultaneous assessment of IL-6 and CRP may facilitate early identification of patients at risk of developing hyperinflammation and cytokine release syndrome. Cytokine release syndrome is characterized by uncontrolled production of pro-inflammatory cytokines, particularly IL-6, resulting in diffuse alveolar damage, vascular endothelial injury, acute respiratory distress syndrome, and multiple organ dysfunction (Moore & June, 2020; Ragab et al., 2020). Herold et al. (2020) demonstrated that elevated IL-6 and CRP levels were strong predictors of the need for mechanical ventilation in hospitalized patients with COVID-19, highlighting the clinical usefulness of these biomarkers for patient monitoring and early therapeutic intervention. Despite the significant association observed in this study, several limitations should be acknowledged. The relatively small sample size and the use of secondary data from a single private hospital may limit the generalizability of the findings. In addition, only IL-6 and CRP were evaluated, whereas other inflammatory biomarkers such as ferritin, D-dimer, lactate dehydrogenase (LDH), and procalcitonin were not included in the analysis. Future multicenter studies involving larger populations and comprehensive inflammatory biomarker panels are warranted to further validate the prognostic value of IL-6 and CRP in patients with COVID-19.

CONCLUSION

This study demonstrated a significant positive association between serum interleukin-6 (IL-6) and C-reactive protein (CRP) levels in hospitalized patients with COVID-19. The findings indicate that increased IL-6 levels are accompanied by increased CRP levels, reflecting the systemic inflammatory response associated with SARS-CoV-2 infection. Although the correlation was moderate, both biomarkers may provide complementary information for assessing inflammatory status and identifying patients at risk of severe disease progression. Simultaneous measurement of IL-6 and CRP may therefore support early clinical assessment and monitoring of COVID-19 patients. Further multicenter studies with larger sample sizes and additional inflammatory biomarkers are recommended to validate these findings and to better establish the prognostic value of IL-6 and CRP in COVID-19.

Implication

The findings of this study provide additional evidence that serum interleukin-6 (IL-6) and C-reactive protein (CRP) are complementary inflammatory biomarkers associated with the immune response in patients with COVID-19. Simultaneous assessment of these biomarkers may assist clinicians in the early identification of patients at risk of developing severe inflammatory complications and support clinical decision-making during patient monitoring. Furthermore, these findings contribute to the growing body of evidence regarding inflammatory biomarkers in COVID-19 and may serve as a reference for future studies investigating the prognostic value of IL-6, CRP, and other inflammatory markers in larger and more diverse populations.

Strengths and Limitation

This study provides valuable evidence regarding the relationship between IL-6 and CRP in hospitalized patients with COVID-19 using routinely collected laboratory data from real-world clinical practice. The use of standardized laboratory measurements and objective biomarkers enhances the reliability of the findings. However, several limitations should be

acknowledged. First, the study included a relatively small sample size from a single private hospital, which may limit the generalizability of the results. Second, the retrospective design based on secondary medical record data limited the availability of clinical variables and prevented longitudinal assessment of biomarker changes. Finally, only IL-6 and CRP were analyzed, whereas other inflammatory biomarkers, such as ferritin, D-dimer, lactate dehydrogenase (LDH), and procalcitonin, were not included.

Conflict of Interest

The authors declare no conflict of interest.

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