Research Article

Inflammatory Marker and their Association with COVID-19 Severity in Pregnant Women

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Abstract

Objective: To analyze the correlation between blood markers; C-Reactive Protein (CRP), D-Dimer, Neutrophil-to-Lymphocyte Ratio (NLR) and the severity of COVID-19 in pregnant women during the 2020 pandemic at Persahabatan Hospital, Jakarta.

Methods: This cross-sectional study was conducted at Persahabatan Hospital, a National Respiratory Referral Center in Jakarta. A total of 525 pregnant women with confirmed COVID-19 who met the inclusion criteria were included in the study. Laboratory markers, including CRP, D-Dimer, and NLR, were analyzed and categorized as normal or elevated. Data were analyzed using the Chi-square test, and correlations were evaluated using Spearman's rank correlation coefficient.

Results: The results showed that elevated biomarkers were significantly correlated with increased disease severity. CRP (>10 mg/L), D-Dimer (>3333 mg/L), and NLR (≥5.8) were all associated with moderate to severe disease. All biomarkers demonstrated a significant correlation with disease severity ($p < 0.005$).

Conclusion: Elevated CRP, D-Dimer, and NLR levels are associated with increased disease severity in pregnant women with COVID-19, suggesting their potential role as practical indicators for disease severity assessment.

Keywords: Covid 19, CRP, D-Dimer, NLR, Pregnant.

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INTRODUCTION

Coronavirus disease (COVID-19) is characterized by a high level of transmissibility, having infected more than 6.3 million people in Indonesia and causing 157,000 deaths.[1] Globally, by January 19, 2021, more than 90 million cases had been confirmed, with 2 million deaths reported.[2] In Indonesia alone, by January 20, 2021, there were 939,948 confirmed cases, and 26,857 deaths had occurred.[3]

The risk of severe COVID-19 is increased in pregnant women due to physiological adaptations during gestation, including altered immune responses, compromised respiratory function, and enhanced coagulation activity.[2,4] These conditions predispose them to severe disease manifestations. For example, From the other study, total 11 hospital in 10 provinces in Indonesia, reporting 2018 pregnant women confirmed COVID-19.[5] Another study, reported there were 62 pregnant women confirmed COVID-19 with 6 maternal deaths.[6]

COVID-19 presents with a range of clinical symptoms such as fever (>38°C), cough, dyspnea, fatigue, myalgia, diarrhea, and anosmia. The severity of the disease is classified into asymptomatic, mild, moderate, and severe cases. Most patients have a good prognosis, but a minority may experience critical illness or death. [7]

Laboratory biomarkers, including CRP, NLR, and D-dimer, have been associated with disease severity and maternal outcomes. NLR, a biomarker of the systemic inflammatory response syndrome (SIRS), reflects the balance between neutrophil activation and lymphocyte suppression, which is often accompanied by endothelial dysfunction. This dysfunction is exacerbated by the release

of cytokines during the inflammatory process, further activating inflammatory cells and immune responses. Elevated NLR has been consistently associated with more severe COVID-19 manifestations.[7–10]

Pregnancy and COVID-19 are both conditions that enhance coagulation activity in the body. While increased D-dimer levels have been linked to poor prognosis in COVID-19 patients, the implications of this marker in pregnant women remain insufficiently explored. CRP is a plasma protein produced by the liver and generated in response to inflammatory mediators such as IL-6. It is a non-specific acute-phase reactant (CRP) used as a biomarker of inflammatory conditions. Increased CRP levels are associated with an increase in the severity of the disease.[9,11]

Despite significant advancements in understanding COVID-19, current evidence on the association between laboratory markers and the clinical severity of COVID-19 in pregnant women is limited, particularly in Jakarta. The Persahabatan Hospital, a COVID-19 referral center in Jakarta, has managed numerous cases of pregnant women with suspected, probable, and confirmed COVID-19 since the outbreak began. During 2020, 525 pregnant women with confirmed COVID-19 underwent treatment at the hospital.

The data from these cases provide an invaluable opportunity to analyze the correlation between biomarkers such as CRP, NLR, and D-dimer with disease severity and maternal outcomes. Understanding these correlations could improve management strategies for pregnant women affected by COVID-19 and contribute to improved outcomes for both maternal and neonatal.

METHODS

This cross-sectional study was conducted at Persahabatan Hospital, a National Referral Center located in a central pandemic area. This study was approved by the Ethics Committee of the Faculty of Medicine, Universitas Indonesia (No. KET-528/UN2.F1/ETIK/PPM.00.02/2021), which waived the requirement for informed consent due to the use of retrospective analysis. Data from all pregnant women who were hospitalized between March 1st, 2020 and February 30th, 2021 were evaluated according to the inclusion and exclusion criteria. The inclusion criteria comprised all pregnant women with confirmed COVID-19 during pregnancy or labor at Persahabatan Hospital.

Between March 2020 and February 2021, a total of 845 medical records of pregnant women admitted to RSUP Persahabatan were reviewed. Of these, 239 cases were excluded due to the absence of confirmed COVID-19 diagnosis. The remaining 606 records represented pregnant women with confirmed COVID-19 and were included in the periodic study.

A second exclusion was applied to 81 cases, consisting of 9 cases with gestational age below 24 weeks, 2 cases managed conservatively at less than 24 weeks of gestation, and 70 cases with incomplete data. After applying both exclusion criteria, a total of 525 medical records met the eligibility criteria and were included for final analysis. Clinical severity of COVID-19 was classified according to the Indonesian Ministry of Health guidelines and grouped into asymptomatic-mild and moderate-severe categories

We evaluate 525 subjects with fulfill the criteria. Characteristics of pregnant women with COVID-19 including age, gestational age, parity, education, occupation, and body mass index (BMI). Laboratory finding to evaluate includes CRP level, D-dimer level, and NLR. We categorize the data into normal and elevated levels.

The classification of symptoms follows the classification of symptoms according to the Indonesian Ministry of Health, symptoms are classified into four categories:[12] Asymptomatic cases refer to patients who exhibit no symptoms. Mild symptoms include patients who present with clinical complaints but show no evidence of viral pneumonia or hypoxia; such symptoms may include fever, cough, fatigue, shortness of breath, myalgia, sore throat, nasal congestion, diarrhea, nausea, and vomiting. Moderate symptoms are characterized by clinical signs of pneumonia such as fever, cough, shortness of breath, and rapid breathing without indications of severe pneumonia, and with oxygen saturation (SpO_2) greater than 93% on room air. Severe symptoms are defined by the presence of pneumonia signs accompanied by at least one of the following: respiratory rate exceeding 30 breaths per minute, severe respiratory distress, oxygen saturation below 93% on room air, septic shock, and or organ dysfunction.

In this study, cases were grouped into two categories: asymptomatic mild symptoms and moderate severe symptoms. Data were obtained through consecutive sampling of medical records in sequence until the minimum required sample

size was reached. The collected data were entered into Microsoft Excel for editing and coding. Statistical analyses were performed using SPSS version 23 for Macintosh. Data distribution was assessed, and the Chi-Square test was applied under the assumption of normal distribution.

RESULTS

A total of 525 pregnant women with confirmed COVID-19 were included in this study. The median maternal age was 30 years (range: 17-47), with a median gestational age of 38 weeks (27-41). The median parity was 1 (0-5), and all variables demonstrated non-normal distributions. Regarding educational background, the majority of participants had ≤ 12 years of education (88.9%), while 11.1% had more than 12 years of schooling. Most of the women were unemployed (77.8%), and 22.2% were employed. Based on the body mass index (BMI), 64,4% had a BMI < 30 kg/m^2, whereas 35,6% were classified as obese BMI > 30 kg/m^2).

Tabel 1. Demographic Characteristic in Pregnant Women with Confirmed COVID-19

Characteristic	
Demography	n (%)
Maternal age	30 (17–47)*
Gestational age	38 (27–41)*
Parity	1 (0 – 5)*
Education	
≤12	466 (88.9)
>12	58 (11.1)
Occupation	
Un-Employed	408 (77.8)
Employed	116 (22.2)
BMI	
Normal (< 30 kg/BB/m^2)	338 (64.4)
Obesity (≥ 30 kg/BB/m^2)	187 (35.6)

*Abnormal distribution

The most frequently reported clinical symptom was cough (42.8%), followed by nasal congestion (24.4%), fever (21.4%), and dyspnea (19.7%). Other symptoms included fatigue (16.3%), sore throat (9.8%), nausea/vomiting (3.2%), and diarrhea, which was the least common (1.5%). In terms of disease severity, 40.0% of participants were asymptomatic, 38.6% had mild disease, 14.5% had moderate disease, and 6.9% presented with severe/critical illness.

Table 2. Clinical Characteristic in Pregnant Women with Confirmed COVID-19

Clinical Characteristic	N (%)
Fever	
Yes	113 (21.4)
No	412 (78.6)
Cough	
Yes	225 (42.8)
No	300 (57.2)
Dyspnue	
Yes	103 (19.7)
No	422 (80.3)
Nasal Congestion	
Yes	128 (24.4)
No	397 (75.6)
Sore Throat	
Yes	53 (9.8)
No	472 (90.2)
Fatigue	
Yes	83 (16.3)
No	442 (83.7)
Nausea/Vomiting	
Yes	17 (3.2)
No	508 (96.8)
Diarrhea	
Yes	5 (1.5)
No	520 (98.5)
Severity of Disease	
Asymptomatic	211 (40.0)
Mild	202 (38.6)
Moderate	76 (14.5)
Severe/Critical	36 (6.9)

Median laboratory values included hemoglobin of 11.7 g/dL, leukocyte count of 10100/µL, and platelet count of 272000/µL, all of which exhibited non-normal distributions. Most participants demonstrated normal CRP levels were normal in 75.9% of subjects and elevated in 24.1%. D-Dimer levels were normal in 74.8% of subjects and elevated in 25.2%. For NLR, 72.9% of participants had elevated values (≥ 5.8), whereas 27.1% fell within the normal range. Elevated CRP, D-dimer, and NLR were significantly associated with moderate-to-severe COVID-19.

Table 3. Laboratory Characteristic in Pregnant Women with Confirmed COVID-19

Laboratory Characteristic	N (%)
Hemoglobin	11.7 (5.9 –16.1)*
Leucocyte	10100 (6120-28100)*
Platelet	272000 (12080 - 613000)*
C-Reactive Protein (CRP)	
Normal (< 10 mg/L)	401 (75.9)
Increased (10-30 mg/L)	73 (13.8)
Very Increased (≥ 30 mg/L)	51 (10.3)
D-dimer	
Normal (≤3333 mg/L)	392 (74.8)
Increased (> 3333 mg/L)	133 (25.2)
Neutrophil-Lymphocyte Ratio (NLR)	
< 5.8	143 (27.1)
≥ 5.8	382 (72.9)

All of the subject 525 pregnant women with normal CRP levels (< 10 mg/L), 343 cases were classified as asymptomatic to mild, and 55 cases were moderate to severe.[13] Meanwhile, among patients with elevated CRP levels (> 10 mg/L), 71 cases were asymptomatic to mild, and 56 cases were moderate to severe.

From total 525 subject with normal D-Dimer levels (≤ 3333 mg/L), 320 cases were classified as asymptomatic to mild, and 71 cases were moderate to severe.13 In contrast, among those with elevated D-dimer levels (> 3333 mg/L), 94 cases were asymptomatic to mild, and 40 cases were moderate to severe.

Among the 525 study subjects with normal NLR levels (< 5.8), 122 cases were classified as asymptomatic to mild, and 21 cases were moderate to severe.13 In contrast, among those with elevated NLR levels (≥ 5.8), 292 cases were asymptomatic to mild, and 90 cases were moderate to severe.

Table 4. Correlation between Laboratory Result with Severity of Disease

	Severity of Disease		*P-value*
	Asymptomatic Mild	**Moderate - Severe**	
CRP			
Normal (≤ 10)	343	55	< 0.005 (0.000)
Elevated (> 10)	71	56	
D-dimer			
Normal (≤3333 mg/L)	320	71	< 0.005 (0.004)
Elevated (> 3333 mg/L)	94	40	
NLR			
Normal (< 5.8)	122	21	< 0.005 (0.027)
Elevated (≥ 5.8)	292	90	

A significant association was observed between all evaluated laboratory biomarkers and COVID-19 severity. The C-reactive protein demonstrated a highly significant correlation with disease severity ($p<0.001$), with elevated CRP levels associated with a higher proportion of moderate-to-severe cases. D-dimer levels were also significantly associated with severity ($p=0.0004$), indicating the that elevated D-dimer is linked to more severe clinical presentation. The Neutrophil-to-Lymphocyte Ratio exhibited a statistically significant association with severity ($p=0.027$). Participants with elevated NLR values had a considerably higher number of moderate-to-severe cases compared with those with normal values.

DISCUSSION

The subjects of this study were pregnant women confirmed to have COVID-19, aged 17–47 years, who were treated at Persahabatan Hospital. The study, conducted from March 2020 to February 2021, involved 525 participants. Demographic data showed that the majority were at 38 weeks of gestation, had a normal BMI, and had given birth once (parity of 1).

C-Reactive Protein is synthesized by the liver in response to inflammatory signals, particularly interleukin-6 (IL-6). It acts as an early indicator of both infection and inflammation. Under normal conditions, CRP levels in the blood are below 10 mg/L, but they can increase quickly beginning within 6 to 8 hours and reaching their highest levels around 48 hours after the onset of illness. Its concentration decreases when the inflammatory

stages end and the patient is healing. Despite being non-specific, elevated CRP levels can indicate an increase in disease severity.[13,14] This study shows a significant association between elevated CRP levels (>10 mg/L) and the severity of COVID-19. These findings align with a study by Ali N, which reported a significant correlation between CRP levels >10 mg/L and COVID-19 disease severity.[15] A similar study conducted in Ethiopia classified asymptomatic-moderate cases as non-severe conditions and severe symptoms as severe cases, using a CRP level threshold >30 mg/L, demonstrating a significant correlation between increased CRP levels and disease severity.[16]

D-Dimer is a product of fibrin degradation that reflects increased coagulation and fibrinolysis activity, representing the activation of both systems. Both pregnancy and infection can elevate D-Dimer levels. Consequently, individuals with COVID-19 are at risk for deep vein thrombosis (DVT), venous thromboembolism (VTE), and possible pulmonary embolism (PE), with risks reported to be as high as 25%.[17] Several studies have examined the relationship between D-Dimer levels and disease severity. A systematic review in 2020 highlighted that monitoring D-Dimer levels is crucial in clinical practice for COVID-19 infection management. The mean D-Dimer level was recorded at 580 mg/L in patients with mild disease compared to 3550 mg/L in those with severe disease. Gutiérrez, demonstrated that D-Dimer levels increase during the third trimester, with intervals ranging from 551-3333 mg/L.[18] In this study, D-Dimer levels were assessed in 525 subjects; most showed normal D-Dimer levels (≤3333 mg/L). Among these, 320 cases were classified as asymptomatic to mild, while 71 cases were classified as moderate to severe. Conversely, among those with elevated D-Dimer levels (>3333 mg/L), 94 cases were asymptomatic to mild, and 40 cases were moderate to severe. The findings revealed a significant association between elevated D-Dimer levels and disease severity, consistent with the study by Uzel, which demonstrated a similar relationship.[19]

The Neutrophil-to-Lymphocyte Ratio is used as a marker of disrupted immune regulation in the context of viral infections.[20] In this study, NLR levels were analyzed across all subjects, revealing a predominance of elevated NLR levels (≥5.8). Among these, 292 cases were classified as asymptomatic to mild, while 90 cases fell into the moderate to severe category. Conversely, normal NLR levels (≤5.8) were identified in only 122 asymptomatic to mild cases and 21 moderate to severe cases. These findings are consistent with those reported by Yildiz, who demonstrated a significant association between elevated NLR levels and COVID-19 severity.[21]

The interconnected roles of CRP, D-Dimer, and NLR highlights their collective role in assessing disease severity among pregnant women with COVID-19. Elevated CRP indicates systemic inflammation driven by cytokine release during infection, which can lead to increased neutrophil activation reflected by higher NLR values.[21,22] Concurrently, elevated D-Dimer signifies coagulation disturbances that are particularly concerning in pregnant patients due to their predisposition to thrombotic events.[23] Thus, these biomarkers not only serve as indicators of individual pathological processes but also reflect broader physiological changes occurring during COVID-19 infection.[23,24]

The integration of these biomarkers into clinical practice can enhance risk stratification for pregnant women diagnosed with COVID-19. Recognizing elevated levels of CRP, D-Dimer, and NLR could guide healthcare providers in making timely decisions regarding patient management strategies aimed at mitigating adverse outcomes for both mothers and infants.

CONCLUSION

Biomarkers such as CRP, D-Dimer, and the NLR have demonstrated a strong correlation with the severity of COVID-19 in pregnant women. These quantitative markers reflect underlying pathological processes, including inflammation, coagulation disturbances, and immune dysregulation. Elevated levels of these biomarkers can serve as valuable adjuncts in clinical practice, aiding in the stratification of disease severity, guiding therapeutic interventions, and predicting maternal outcomes in affected patients. Further research is warranted to refine their predictive utility in obstetric care during infectious disease outbreaks.

STUDY of LIMITATION

The findings of this study provide insight into the impact of COVID-19 during the period when the alpha variant was predominant. However, it is important to acknowledge certain limitations. This research was limited to a one-year timeframe,

while the pandemic extended beyond that period. Data from subsequent waves involving the delta and omicron variants, which were associated with higher mortality rates, were not included. As a result, the findings may not fully capture the evolving dynamics and severity of COVID-19 across different variants. Future multicenter, longitudinal studies that encompass multiple viral variants are warranted to validate and expand upon these findings. Such studies could provide a more comprehensive understanding of the pandemic's impact and inform public health strategies more effectively.

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