

ORIGINAL ARTICLE

## The Association of Laboratory Parameters with COVID-19 Severity in Pregnancy

### Hubungan Parameter Laboratorium dengan Derajat Klinis COVID-19 pada Kehamilan

Rully Ayu Nirmalasari<sup>1</sup>, Lily Marliany Surjadi<sup>1</sup>, Laksmi Maharani<sup>1</sup>, Yuyun Lisnawati<sup>2</sup>, Dhea Mangun<sup>3</sup>

<sup>1</sup>Department of Obstetrics and Gynaecology, Faculty of Medicine, Universitas Trisakti, Indonesia

<sup>2</sup>Persahabatan General Hospital, Jakarta, Indonesia

<sup>3</sup>Medical Profession Program, Faculty of Medicine, Universitas Trisakti, Indonesia

 dr.rully@trisakti.ac.id

 <https://doi.org/10.18051/jbk.291-299>

#### ABSTRACT

##### Background

Pregnant women were one of the most susceptible groups because they are vulnerable to respiratory infection. They may get more severe symptoms due to their physiological changes during pregnancy including the immunological response. This study was performed to find whether there is an association between laboratory parameters (Hb, leukocytes, platelet, neutrophils, lymphocyte, monocyte, NLR, PLR and CRP) and the severity of Covid-19 infection in pregnant women.

##### Methods

This study is a retrospective cohort study using secondary data from patient's medical records at Persahabatan General Hospital, Jakarta from March to June 2021.

##### Results

Pregnancy cases with COVID-19 in this study were in the mean of 29 year age. Most of them are in the third trimester of pregnancy. 80.5% from 67 patients have no- mild symptom while 19.5% have moderate to severe symptom. There are no difference in vital sign nor oxygen saturation at first admission. Lower level was found in the parameter of leukocyte, lymphocyte and monocyte. Neutrophil, neutrophil-to-lymphocyte ratio and C-reactive Protein increase as the degree of severity increase. The mean neutrophil in pregnant women with moderate to severe COVID-19 symptom was  $80.49 \pm 7.47$  while median NLR value was of 6.76 (2.73-18.71).

##### Conclusions

Neutrophil, neutrophil-to-lymphocyte ratio and C-reactive Protein has associate significantly to severity symptoms of COVID-19 in pregnancy.

**Keywords:** COVID-19; pregnancy; symptom; severity; laboratory

## ABSTRAK

### Latar Belakang

Ibu hamil merupakan salah satu kelompok yang paling rentan terhadap infeksi saluran pernapasan. Mereka mungkin mengalami gejala yang lebih parah karena adanya perubahan fisiologis selama kehamilan termasuk perubahan pada respons imunologis. Penelitian ini dilakukan untuk mengetahui adanya hubungan antara parameter laboratorium (Hb, leukosit, trombosit, neutrofil, limfosit, monosit, NLR, PLR dan CRP) dengan derajat klinis Covid-19 pada ibu hamil.

### Metode

Penelitian ini merupakan penelitian kohort retrospektif dengan menggunakan data sekunder berupa rekam medis pasien di RSUP Persahabatan Jakarta pada bulan Maret sampai Juni 2021.

### Hasil

Pasien hamil dengan COVID-19 pada penelitian ini berada pada rerata usia 29 tahun. Kebanyakan dari mereka berada pada trimester ketiga kehamilan. Sebanyak 80,5% dari 67 pasien tidak mengalami gejala hingga gejala ringan, sedangkan 19,5% mengalami gejala sedang hingga berat. Tidak ada perbedaan tanda vital dan saturasi oksigen pada saat masuk RS pertama kali. Kadar yang lebih rendah di kelompok gejala berat terdapat pada parameter leukosit, limfosit dan monosit. Sedangkan neutrofil, rasio neutrofil-limfosit, dan Protein C-reaktif meningkat seiring dengan meningkatnya derajat keparahan. Rerata neutrofil pada ibu hamil dengan gejala COVID-19 sedang hingga berat adalah  $80,49 \pm 7,47$  sedangkan nilai median NLR adalah 6,76 (2,73-18,71).

### Kesimpulan

Nilai Neutrofil, rasio neutrofil terhadap limfosit, dan Protein C-reaktif berhubungan secara signifikan dengan gejala keparahan COVID-19 pada kehamilan.

**Kata Kunci:** COVID-19; hamil; gejala; keparahan; laboratorium

## INTRODUCTION

COVID-19 infection was first found in Wuhan China in early December 2019.<sup>1-3</sup> In January 2020 with a declaration from the World Health Organization (WHO), it became a Public Health Emergency of International Concern. Until now, multiple SARS-CoV-2 variants have been circulating globally due to its ability to mutate.<sup>4-5</sup> Pregnant women were one of the most susceptible groups because they were vulnerable to respiratory infection.<sup>2</sup> They may get more severe symptoms due to their physiological changes during pregnancy, including in their immune and cardiopulmonary systems. One of the factors contributing to the less morbid nature of COVID-19 as compared with SARS-CoV-2 infections in pregnant women is the immunological response. The immune response to SARS CoV-2 infection is activation of both proinflammatory (Th-1) and anti-inflammatory (Th-2) mediators.<sup>6</sup> Many concerns emerged about the possible effects on pregnant women with catastrophic outcomes.<sup>7</sup>

In the beginning, not so many studies about the effects of COVID-19 infection in pregnancy. One of study has been performed by Zhu et al in China to compare the effect of the disease in 35 non-pregnant and 31 pregnant women. They found that fever was less found in pregnant women ( $p=0.006$ ), but shorter intervals from the onset of the disease to hospitalization ( $p=0.005$ ), and a higher proportion of severe and critical cases ( $p=0,039$ ).<sup>8</sup> A systematic review of 29 studies showed the effects of COVID-19 in mothers and neonates. They found that the preterm birth rate was 34.2% and the cesarean section rate was 82.7%. Among all laboratory tests, elevated neutrophils, elevated CRP, and low hemoglobin levels were prominent (71.4%, 67.7%, and 57.3% respectively).<sup>9</sup>

Many studies performed later showed that the effects of COVID-19 infection in pregnancy were not as bad as was presumed. A systematic review of 18 studies showed that the clinical characteristics of pregnant women with COVID-19 infection were similar to non-pregnant adults, and neonatal outcomes were also good in most cases.<sup>10</sup> Another study in the first 60 pregnant women with COVID-19 infection in Madrid got the result that, most of them had a favorable clinical course, with only one-third of them developing pneumonia, and 5% of whom showed critical clinical status. They also found that CRP levels were positively correlated with severe pneumonia and as the patient improved clinically, the neutrophil/ lymphocyte ratio was decreased.<sup>11</sup>

Based on many controversies as a result of COVID-19 infection in pregnant women. We want to explore the disease in Indonesian pregnant women, especially in Jakarta. Since the first case in 2019 was considered over, there were many variants of the COVID-19 virus have been detected, for example, alpha, beta, gamma, delta, epsilon, and many others. This study was performed to find whether there is an association between laboratory parameters and the severity of Covid-19 infection in pregnant women. So that we can do common supporting examinations to help establish a working diagnosis and the course of COVID-19.

## METHODS

This was a retrospective cohort study of 67 pregnant patients in Persahabatan General Hospital. Data was taken from patient medical records collected from March to June 2021, consisting of maternal characteristics (age, parity, gestational age, vital signs), severity of disease, and laboratory parameters. The inclusion criteria used were pregnant women infected with COVID-19 as a result of polymerase chain reaction (PCR) test and complete laboratory data on routine hematology, leucocyte count, and C-reactive protein (CRP).

According to the Indonesian Ministry of Health, the severity of symptoms was classified into: no symptoms, mild symptoms, moderate symptoms, severe symptoms, and critical. Mild Symptom is patients with symptoms with no evidence of viral pneumonia or hypoxia. Symptoms that appear include fever, cough, fatigue, anorexia, shortness of breath, myalgia, or non-specific conditions such as sore throat, nasal congestion, headache, diarrhea, nausea and vomiting, and loss of smell or taste that occur before symptoms. SpO<sub>2</sub> > 95% with room air. Moderate symptoms in patients with clinical signs of pneumonia (fever, cough, shortness of breath, rapid breathing) but no signs of severe pneumonia including SpO<sub>2</sub> > 93% with room air. Severe symptoms are patients with clinical signs of pneumonia (fever, cough, shortness of breath, rapid breathing) with one respiratory frequency > 30 x/minute, severe respiratory distress, or SpO<sub>2</sub> < 93% in room air. Critical is patients with Acute Respiratory Distress Syndrome (ARDS), sepsis and septic shock, or other conditions that require mechanical ventilation or vasopressor therapy.

The severity of symptoms was divided into two groups. First consists of patients with no to mild symptoms, the others were included in the moderate to severe groups.

Data that have been collected were then tabulated and analyzed using Statistical Package for the Social Science (SPSS) version 25. The normality test was taken using the Kolmogorov-Smirnov test. Mann Whitney test was performed to find the differences among data with abnormal distribution, contrarywise is analyzed using an unpaired T-test.

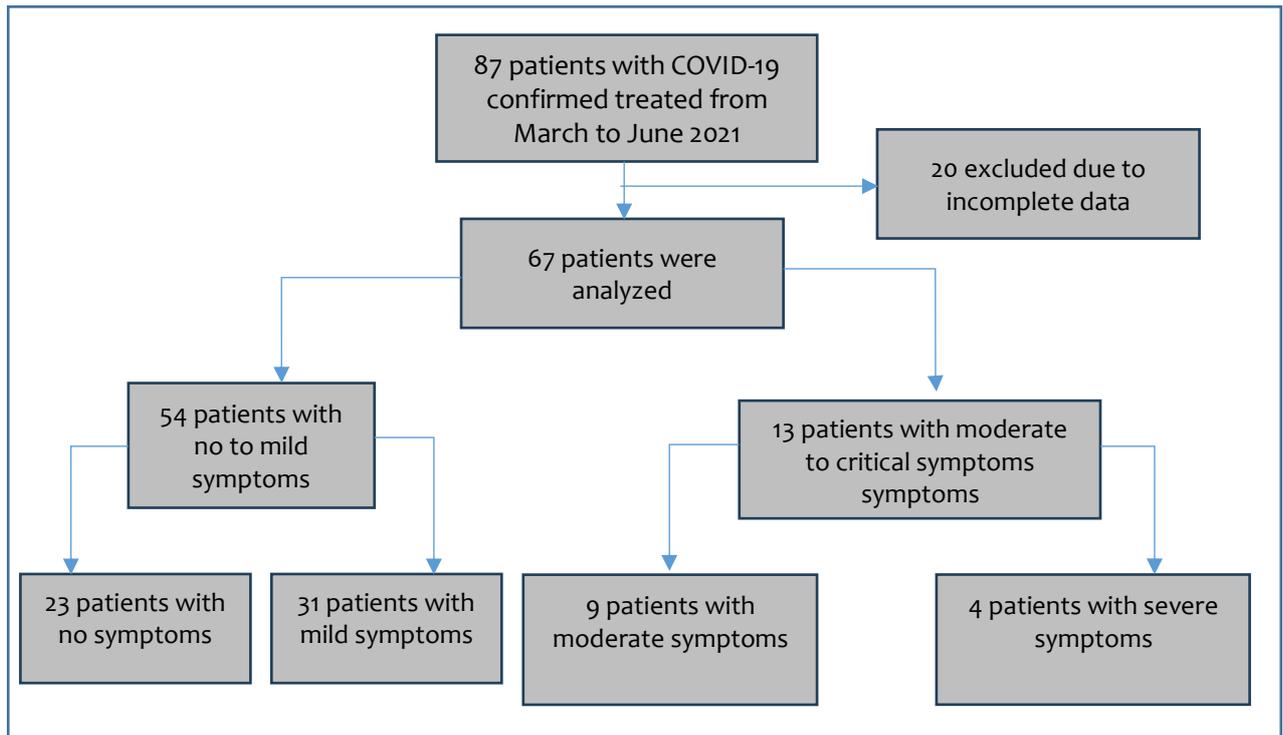


Figure 1. Flowchart of Research Subject

## RESULTS

There were 87 pregnant patients with COVID-19 treated at Persahabatan Hospital from March to June 2021. Of the total, 20 patients were excluded due to incomplete data 13 patients were treated with moderate to critical symptoms, and 54 others with no to mild symptoms whom mostly treated due to obstetric reasons (Figure 1).

### Maternal Characteristics

The mean and median of maternal age, parity, and vital signs between the two groups have the same number and characteristics. Regards to gestational age, most COVID-19 patients were in the third trimester of pregnancy, occurring earlier in the moderate severe group. A thorough report of maternal characteristics can be seen in Table 1.

Table 1. Characteristics of Research Subject

Characteristic	Asymptomatic – mild symptoms (n=54)	Moderate – severe symptoms (n=13)
Maternal age (year)	29±5	29±5
Parity	2 (1-2)	2 (1-2)
Gestational age (weeks)	38 (8-41)	32 (8-38)
Trimester (n)		
First	2	1
Second	2	3
Third	50	9
First vital sign		
Temperature	36.6 (36-37.5)	36.5 (36-38.8)
Systolic	118 (100-154)	120 (105-141)
Diastolic	80 (60-104)	71 (54-87)
Pulse rate	87 (63-123)	106 (48-128)
Respiratory rate	20 (16-24)	20 (18-30)
Oxygen saturation (%)	99 (97-100)	98 (73-100)

### Laboratory Parameters Related to Maternal COVID-19 Severity of Symptoms

In laboratory parameters, there was a statistically significant relationship ( $p < 0.05$ ) between neutrophils, neutrophil to lymphocyte ratio (NLR), and C-Reactive Protein (CRP) to severity of symptoms. Moderate-severe symptoms group has a slightly higher Platelet-to-Lymphocyte ratio and lower level of lymphocytes than the other group. Comparison of other laboratory parameters to COVID-19 severity is shown in Table 2

Table 2. Maternal with COVID-19 Laboratory Results and Its Relationship to Severity of Symptoms

Laboratory parameters	Asymptomatic-mild symptoms (n=54)	Moderate-severe symptoms (n=13)	p-value
Hemoglobin	11.45 (7.5-14.1)	10.78 (8.1-13.5)	0.22*
Leukocytes	8,370 (4310-18360)	7,370 (5040-16600)	0.912*
Platelets	276,759±80379.51	242,769±69124.47	0.139**
Neutrophils	74.64±7.35	80.49±7.47	0.013**
Lymphocyte	15.6(7.1-33.6)	11.7(4.9-23.8)	0.05*
Neutrophil-to-Lymphocyte ratio	4.90 (1.79–10.16)	6.76 (2.73-18.71)	0.017*
Platelet-to-lymphocyte ratio	190.67 (93.25-548.15)	212.65 (139.19-369.23)	0.145*
Monocytes	6.82±2.46	6.06±2.94	0.34**
C-Reactive Protein	4.34 (0.70-88)	7.89 (2.73-118.7)	0.007*

\*Mann Whitney

\*\*Unpaired T-test

## DISCUSSION

COVID-19 has different symptoms that could differ from one person to another.<sup>12</sup> Here we showed that a few laboratory parameters were related to the severity of symptoms in pregnant patients with COVID-19. First, the neutrophils, the major type of leucocytes on differential counts decrease in pregnancy due to impaired neutrophilic apoptosis and phagocytic activity.<sup>13,14</sup> Here

We confirmed a statistically significant rise of neutrophils in patients as the severity of COVID-19 symptoms increased. It showed an upward trend in moderate to critical patients.

The increase in neutrophil-lymphocyte ratio was consistent with other studies involving pregnant COVID-19 patients.<sup>15-29</sup> Our study shows the same result significantly. Increased neutrophil count and neutrophils-to-lymphocytes ratio were predominant in severe cases.<sup>30</sup> According to Yang et al, the optimal threshold at 3.3 for NLR showed a superior prognostic possibility of clinical symptoms to change from mild to severe.<sup>16</sup>

C-reactive proteins were significantly related to the severity of symptoms in pregnant patients. Non-survivors of COVID-19 patients kept a high level or showed an upward trend for C-reactive protein.<sup>15,30</sup> Research results conducted by Sahin O et al found the use of combined CRP and ferritin appears to have higher sensitivity and negative predictive value than using other tests alone.<sup>15</sup> According to Wardika et al, there was a significant difference in CRP, IL-6, and D-dimer levels between severity symptoms of COVID-19. So, CRP can be used as a prognostic predictor in COVID-19 patients with severe symptoms.<sup>31</sup>

In this study, we also found decreasing values of Platelets, lymphocytes, and monocytes but not statistically significant. A hypothesis suggested that impairment to the lung tissue and pulmonary endothelial cells by virus infection would increase consumption of platelets/megakaryocytes, and reduce the production of platelets in the lungs.<sup>32</sup> Despite the physiology of thrombocytopenia due to pregnancy, infection by COVID-19 escalates the decline. According to Chen R et al, thrombocytopenia was identified as a significant risk factor for disease severity and mortality in patients infected with COVID-19.<sup>30</sup> PLR was significantly higher in the severe disease group. PLR more than NLR was useful in detecting pregnant patients with COVID-19 severe disease. with a 221 PLR cut-off point, the sensitivity was 90% and the specificity 83%.<sup>33</sup> Compared with mild/moderate, severe and critical patients showed a higher incidence of abnormal leukocytes, neutrophils, NLR, and PLR.<sup>30</sup>

Lymphocyte count decreases during pregnancy through the first and second trimesters but increases during the third trimester. Chen R et al show that lymphocyte levels in COVID-19 pregnant patients decrease in contrast to the increasing severity of the disease, with the lowest in critical survivors.<sup>15,30,34</sup> Our result is the same as a systematic review involving 50 studies found that also monocyte level was significantly decreased in patients with COVID-19 infection: (35) The decrease of Leukocytes in more severe symptoms is contrary to most of the studies. Regarding the lower level of leukocytes in the moderate-severe group, this result is similar to one study in China that stated that leukocyte numbers did not remarkably change in patients with severe disease.<sup>36</sup>

## CONCLUSION

Patients with moderate to severe symptoms of SARS-COV2 infection have a slightly higher Platelet-to-Lymphocyte ratio than the mild symptoms group. This study also shows that common laboratory parameters such as neutrophils, NLR, and CRP have a significant relationship with the severity of COVID-19 in pregnant women in Indonesia. Increased neutrophil count, neutrophils-to-lymphocytes ratio, and upward trend for C-reactive protein were predominant in severe cases. For now that SARS-CoV-2 variants still exist and appear in less severe symptoms, these findings

can be a supporting examination to determine the worsening of Covid disease in pregnant patients.

## ACKNOWLEDGEMENT

The authors want to thank all the staff of Persahabatan General Hospital, all respondents, as well as the Faculty of Medicine, Universitas Trisakti.

## AUTHORS CONTRIBUTION

YL contributes to the data collection. RAN and LMS contribute to processing and analyzing the data. DM contributed to collecting references. RAN and LMS contributed to the writing of the manuscript. LM contributed to the improvement of the manuscript.

## FUNDING

These research funds are received from the Universitas Trisakti research grant.

## CONFLICT OF INTEREST

The authors have no conflicts of interest.

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