

Comparison of Clinical Characteristics between Pregnant Women Confirmed with Covid-19 With and Without Severe Preeclampsia

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Abstract

Background: Several clinical studies have reported that COVID-19 was associated with an increased risk of preeclampsia and preeclampsia-like syndrome in infected pregnant women, but the results are still controversial. This study aims to compare the clinical characteristics of pregnant women with confirmed COVID-19 with and without severe preeclampsia.

Methods: This retrospective study of pregnant women confirmed for COVID-19 was carried out at RSUP Dr. Hasan Sadikin from April 1st, 2020 to April 30th, 2022. Epidemiological data, clinical features, and laboratory results of subjects with and without severe preeclampsia in pregnant COVID-19 patients were collected and analyzed

Results: Eighty-six subjects were in our study, with 42 subjects with severe preeclampsia and 44 subjects without severe preeclampsia. The average age of mothers in this study was 26 years, with a more significant proportion at term. The proportion of primigravida with severe preeclampsia was significantly more than those without severe preeclampsia (71.42% vs 29.54%, $p=0.02$). There was no significant difference in clinical severity between patients with or without severe preeclampsia ($p>0.05$). Comparing laboratory parameters showed significant differences in the laboratory characteristics of hemoglobin (28.57% vs 2.2%, $p=0.03$) and platelets (33.33% vs 4.54%, $p=0.02$).

Conclusion: Our study showed that the clinical characteristics and disease severity were not significantly different. Laboratory markers correlate significantly with the severity of maternal disease, so they can be used as prognostic indicators.

Keywords: Characteristics, COVID-19, Pregnancy, Severe Preeclampsia

Perbandingan Karakteristik Klinis Ibu Hamil Terkonfirmasi Covid- 19 Dengan dan Tanpa Preeklamsia Berat

Abstrak

Latar Belakang: Beberapa studi klinis telah melaporkan bahwa Infeksi COVID-19 dikaitkan dengan peningkatan risiko preeklamsia dan sindroma yang mirip preeklamsia pada wanita hamil yang terinfeksi, tetapi hasilnya masih kontroversial. Penelitian ini bertujuan untuk mengetahui perbandingan karakteristik klinis ibu hamil yang terkonfirmasi COVID-19 dengan dan tanpa preeklamsia berat.

Metode: Penelitian secara retrospektif pada ibu hamil positif COVID-19 ini dilakukan di RSUP Dr. Hasan Sadikin dari tanggal 1 April 2020 sampai dengan 30 April 2022. Data berupa epidemiologi, gambaran klinis, hasil laboratorium subjek dengan dan tanpa preeklamsia berat pasien hamil COVID-19 dikumpulkan dan dianalisis

Hasil: Data yang berhasil dikumpulkan dalam penelitian ini adalah delapan puluh enam subjek yang terbagi atas 42 subjek dengan preeklamsia berat dan 44 subjek tanpa preeklamsia berat. Usia rata-rata ibu dalam penelitian ini 26 tahun, dengan proporsi yang lebih signifikan pada usia kehamilan cukup bulan. Proporsi primigravida dengan preeklamsia berat lebih signifikan dibandingkan dengan tanpa preeklamsia berat (71.42% vs 29.54%, $p=0.02$). Tidak ditemukan perbedaan signifikan pada keparahan klinis di antara pasien dengan atau tanpa preeklamsia berat ($p>0.05$). Perbandingan parameter laboratorium didapatkan perbedaan signifikan pada karakteristik laboratorium hemoglobin (28,57% vs 2,2%, $p=0.03$) dan trombosit (33,33% vs 4,54%, $p=0.02$).

Kesimpulan: Penelitian ini menunjukkan bahwa karakteristik klinis dan keparahan penyakit tidak berbeda secara signifikan pada kedua pasien. Penanda laboratorium berkorelasi signifikan dengan tingkat keparahan penyakit ibu sehingga dapat digunakan sebagai indikator prognostik.

Kata kunci: Karakteristik Klinis, COVID-19, Kehamilan, Preeklamsia Berat

Introduction

Coronavirus disease 2019 (COVID-19) is a severe acute respiratory syndrome caused by coronavirus-2 (SARS-CoV-2). The disease spread rapidly first throughout China, and then throughout Europe, the United States, and the rest of the world reaching a total of 3,435,894 confirmed cases worldwide as of May 5th, 2020.¹ The spread of the number of cases is quite fast and spread to various countries in a short time. As of May 1st, 2021, WHO reported that 223 countries had been affected by the spread of this virus, and as many as 150,989,419 people in the world had been confirmed with 3,173,576 deaths due to COVID-19.³ Indonesia reported its first case on March 2nd, 2020. Cases are increasing and spreading quickly throughout Indonesia. As of May 1st, 2021, the Ministry of Health reported that 1,672,880 people had been confirmed and 45,652 of them had died. Banten is ranked seventh in the province with the highest number of COVID-19 cases after DKI Jakarta as of September 9th, 2021 with a total of 130,191 (3.1%). Multidimensional strategies have been taken with various objectives ranging from preventing virus transmission to preventing disease complications.⁴

COVID-19 has a broad spectrum of severity and clinical manifestations of the disease.^{2,3} Although respiratory symptoms predominate among all clinical manifestations of COVID-19, COVID-19 can also be characterized by multiorgan failure and vascular effects leading to hypertension, kidney disease, anemia, thrombocytopenia, and liver injury.

Pregnant women are a population at high risk of being infected with COVID-19. According to data from the Indonesian Obstetrics and Gynecology Association (POGI) Jakarta, 13.7% of pregnant women are more susceptible to being infected with COVID-19 than non-pregnant people.⁴

In Indonesia, severe preeclampsia is the cause of 30% - 40% of maternal deaths. Apart from that, it is also known that preeclampsia has replaced maternal bleeding as the main cause of maternal death in several hospitals in Indonesia.⁵ The number of maternal deaths in 2018 based on district/city health profile reporting was 700 cases or 79.68 per 100,000 KH, an increase of 5 cases compared to 2017, namely 695 cases. The causes of maternal death are still dominated by 26% bleeding, 30% hypertension, 17% disorders of the circulatory system (heart), and 20% other causes. Therefore, attention and serious treatment are needed for women giving birth with this complication.

Several clinical studies report that COVID-19 is associated with an increased risk of preeclampsia and preeclampsia-like syndrome in infected pregnant women, but the results remain controversial.

Based on the case series, hypertensive disorders of pregnancy and preeclampsia were not higher in pregnant women with COVID-19 than in uninfected pregnant women.¹⁶ From a retrospective analysis of 2682 pregnant women who gave birth in one hospital in Sweden between March 25 and July 24, 2020, Ahlberg et al. reported that 156 women with preeclampsia (5.8%) were positive for SARS-CoV-2. The study found that pregnant women with SARS-CoV-2 infection had a higher prevalence of preeclampsia than pregnant women who were not infected (7.7% vs 4.3%; OR=1.84; 95% CI 1.004-3.36). Additionally, data from the study also showed that positive tests for SARS-CoV-2 in women in active labor have been associated with a higher prevalence of preeclampsia. The study concluded that COVID-19 is a complex respiratory tract infection with systemic effects that can mimic preeclampsia.¹⁶

The INTERCOVID study is a large research study completed in October 2020 among 2,130 pregnant women in 18

countries. The study found that pregnant individuals with COVID-19 had a nearly two-fold higher risk of preeclampsia, as well as other adverse outcomes including maternal death, severe infections, and premature birth compared with pregnant individuals without COVID-19. Specifically, 9 out of 100 women with COVID-19 in pregnancy experience preeclampsia, while 5 out of 100 women without COVID-19 experience preeclampsia.¹⁶ A July 2021 review of several studies found that the odds of developing preeclampsia, especially severe preeclampsia, eclampsia, and HELLP syndrome, were significantly higher among pregnant women with COVID-19 infection than among those without COVID-19 infection. Both asymptomatic and symptomatic COVID-19 infections significantly increased the odds of preeclampsia although it was higher among patients with symptomatic disease. Some research has mentioned that preeclampsia may be more common in pregnant women with COVID-19.⁶

Therefore we conducted a study to compare the clinical characteristics of pregnant women with confirmed COVID-19 with and without severe preeclampsia.

Methods

This research is a retrospective analytical study by taking secondary data from medical records at RSUP Dr. Hasan Sadikin from April 1st, 2020 – April 30th, 2022. A comparative analysis was carried out on several characteristics of pregnant patients who had confirmed COVID-19 with or without severe preeclampsia. The subjects of this study were pregnant patients who were confirmed positive for COVID-19 with or without severe preeclampsia and met the inclusion and exclusion criteria in this study and were then analyzed based on several characteristic variables. The inclusion criteria for this study were pregnant women

who were confirmed positive for COVID-19 with and without severe preeclampsia during the study. The criteria of Severe preeclampsia is defined as a blood pressure higher than 160/110 mmHg and more than 3+ urine protein after 20 weeks of gestational age. The exclusion criteria for this study were pregnant patients with confirmed COVID-19 but do not have complete medical records, patients with autoimmune disease, and other infectious diseases. The number of research subjects during the observation period was 86 pregnant women who were treated, consisting of 42 patients with severe preeclampsia, and 44 patients without severe preeclampsia. COVID-19 is confirmed by real-time reverse transcription-polymerase chain reaction (RT-PCR) or rapid antigen test (RAT).

Data were divided into two groups, namely patients with severe preeclampsia and those without severe preeclampsia. Subject characteristics included parity, maternal age, gestational age, contact history, maternal death, ventilator use, pulmonary edema, neutrophil value, neutrophil-lymphocyte ratio, hemoglobin, SGOT/SGPT, platelets, lymphocytes, leukocytes, and clinical severity.

Statistical analysis was carried out using IBM SPSS version 25. Descriptive data for continuous and categorical data are represented as mean \pm standard deviation and proportion in percentage (%). A comparison of maternal severity levels was analyzed using chi-square. Spearman's correlation was used to evaluate the relationship between maternal clinical severity and laboratory parameters. A p-value <0.05 was considered significant for all analysis results.

Results

There were 86 patients participating in the study, with 42 patients with severe preeclampsia and 44 patients without preeclampsia. The average age of mothers

Table 1 Clinical Characteristics of Patients

Variable	Severe Preeclampsia n(%)	Without Severe Preeclampsia n(%)	P-Value
Parity			
Primigravid	30 (71.42)	13 (29.54)	0.02
Multigravid	12 (28.57)	31 (70.45)	
Maternal Age			
Mean age (\pm SD)	26.71 \pm 4.76	26.69 \pm 4.68	0.74
Gestational Age			
<37 weeks	13 (30.95)	16 (36.36)	0.24
\geq 37 weeks	29 (69.04)	28 (63.63)	
Contact history			
Yes	33 (78.57)	34 (77.27)	0.97
No	9 (21.4)	10 (22.7)	
Maternal Death			
Yes	0 (0)	0 (0)	0.29
No	42 (100)	42 (100)	
Ventilator Using			
Yes	2 (4.7)	1 (2.2)	0.08
No	40 (95.3)	43 (97.72)	
Pulmonary Edema			
Yes	2 (4.7)	1 (2.2)	0.08
No	40 (95.3)	43 (97.72)	
Neutrophils (%)			
55-79	31 (73.80)	10 (22.72)	0.122
\geq 80	11 (26.19)	34 (77.27)	
Neutrophil Lymphocyte Ratio (NLR)			
<5.8	34 (80.9)	11 (25)	0.210
\geq 5.8	8 (19.04)	33 (75)	
Hemoglobin (Hb)			
<10	12 (28.57)	1 (2.2)	0.03
\geq 10	30 (71.42)	43 (97.72)	
SGOT / SGPT			
Normal	32 (76.19)	44 (100)	0.635
Abnormal	10 (23.80)	0 (00.00)	
Platelets			
<150	14 (33.33)	2 (4.54)	0.02
> 150	28 (66.6)	42 (95.45)	
Lymphocytes (%)			
<22	39 (92.85)	39 (88.63)	0.312
\geq 22	3 (7.1)	5 (11.3)	
Leukocytes			
4,000-10,000	26 (61.9)	12 (27.27)	0.140
> 10,000	16 (38.09)	32 (72.7)	

in this study was 26 years, with a more significant proportion at term. The proportion of primigravidas with severe preeclampsia was significantly more than those without severe preeclampsia (71.42% vs 29.54%, $p=0.02$). Of the total 86 patients, 3 patients (3.34%) required intensive oxygen via a ventilator. There are significant differences in characteristics of hemoglobin laboratory (28.57% vs 2.2%, $p=0.03$) and platelets (33.33% vs 4.54%, $p=0.02$).

Clinical Severity vs Laboratory Parameters

Comparison of maternal clinical severity with laboratory parameters resulted in positive significance for platelet count ($p=0.009$ vs 0.104), and hemoglobin ($p=0.001$ vs 0.503)

Correlation between maternal clinical severity and associated risks in pregnancy

Patients with SARS-CoV-2 infection can

experience a range of clinical manifestations, from no symptoms to critical illness. In general, adults with SARS-CoV-2 infection can be grouped into the following severity of illness categories; however, the criteria for each category may overlap or vary across clinical guidelines and clinical trials, and a patient’s clinical status may change over time.

Asymptomatic: Individuals who test positive for SARS-CoV-2 using a virologic test (i.e., a nucleic acid amplification test [NAAT] or an antigen test) but have no symptoms consistent with COVID-19.

Mild illness: Individuals who have any of the various signs and symptoms of COVID-19 (e.g., fever, cough, sore throat, malaise, headache, muscle pain, nausea, vomiting, diarrhea, loss of taste and smell) but do not have shortness of breath, dyspnea, or abnormal chest imaging.

Moderate illness: Individuals who show evidence of lower respiratory disease

Table 2 Correlation between Clinical Severity and Laboratory Parameters

Parameter Laboratory	Severe Preeclampsia		Without Severe Preeclampsia	
	Spearman'srho	p-value	Spearman'srho	p-value
NLR	- 0.051	0.686	0.423	0.002
Lymphocyte count	- 0.052	0.684	- 0.173	0.211
Leukocyte count	-0.045	0.142	-0.144	0.234
Platelet count	0.322	0.009	- 0.124	0.104
Hemoglobin Level	0.438	0.001	-0.085	0.503
Liver enzymes	0.262	0.037	0.244	0.075

Table 3 Comparison of COVID-19 Severity Levels

Clinical Severity	n (%)	n (%)	Chi-Square	p-value
	Severe Preeclampsia	Without Severe Preeclampsia		
Asymptomatic	22 (52.38)	24 (54.54)		
Mild	12 (28.57)	10 (22.72)		
Moderate	6 (14.28)	7 (15.90)	6.02	0.23
Severe	2 (4.75)	2 (4.54)		
Critical	0 (0)	1 (2.2)		

during clinical assessment or imaging and who have an oxygen saturation measured by pulse oximetry (SpO₂) $\geq 94\%$ on room air at sea level.

Severe illness: Individuals who have an SpO₂ $< 94\%$ on room air at sea level, a ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO₂/FiO₂) < 300 mm Hg, a respiratory rate > 30 breaths/min, or lung infiltrates $> 50\%$.

Critical illness: Individuals who have respiratory failure, septic shock, or multiple organ dysfunction.

There were 4 patients who developed serious disease, of which 2/4 (50%) experienced severe preeclampsia and 2/4 (50%) without severe preeclampsia. One of the patients suffered from critical illness COVID-19 due to chronic lung disease such as Tuberculosis. There was no significant difference in clinical severity between patients with and without severe preeclampsia ($p > 0.05$).

Discussion

In this study, there were no significant differences in clinical characteristics between Covid-19-positive pregnant women who experienced severe preeclampsia and those who did not experience severe preeclampsia.

Mechanism of preeclampsia. There are two phases, the first is the placental phase where there is dysfunction, ischemia, and hypoxia in the placenta which then causes the activation of the Renin Angiotensin System (RAS). This causes the second phase, namely the systemic phase, where systemic endothelial dysfunction occurs, causing damage to organs such as the kidneys, liver, and brain.

A similar phase is also found in COVID-19, where the first phase begins with alveolar ischemia and hypoxia due to SARS-CoV-2 infection which then activates the RAS. Then systemic endothelial dysfunction

also occurs which also causes systemic organ damage. This is what causes the symptoms of both to be similar and often overlap during pregnancy.⁷

Several clinical studies report that COVID-19 is associated with an increased risk of preeclampsia and preeclampsia-like syndrome in infected pregnant women, but the results remain controversial. COVID-19 is also associated with immune activation that results in increased levels of proinflammatory cytokines, including interleukin (IL)-2, IL-6, IL-7, and tumor necrosis factor- α . SARS-CoV-2 infection can also affect endothelial cells, and during pregnancy, can cause endothelium, microthrombus deposition, and microvascular dysfunction.

In patients with COVID-19, leukocyte counts can vary between leukopenia, leukocytosis, and lymphopenia, although lymphopenia appears to be more common. An important piece of information based on research results is that lymphocyte counts are associated with increased disease severity in COVID-19. Lymphopenia and lower lymphocyte counts indicate a poor prognosis in COVID-19 patients.

A study previously stated that pregnant women who were positive for COVID-19 would be more likely to be screened for preeclampsia, even though the symptoms and laboratory abnormalities found were not much different from Covid-19-negative patients who experienced preeclampsia.⁸ Because the symptoms found were similar, the prevalence of preeclampsia increased in patients with SARS-CoV-2 virus infection can be caused by misdiagnosis.⁹

Significant differences were only found in two variables, namely hemoglobin level and platelet count. In pregnant women infected with COVID-19, low hemoglobin levels are more common in mothers who experience severe preeclampsia than those who do not. In general, anemia can occur in inflammatory conditions, including in cases

of Covid-19.¹⁰ Apart from that, anemia is also associated with poor outcomes in cases of Covid-19.¹¹

Previous research also stated that the lower the hemoglobin level during pregnancy, the greater the risk of preeclampsia.¹² The current study also found that low platelet counts were more common in pregnant women with preeclampsia than those without preeclampsia. Covid-19 patients are often found to have mild thrombocytopenia and increased platelet consumption.¹³ In addition, thrombocytopenia in cases of preeclampsia occurs due to microangiopathy, where there is damage to the endothelium which then triggers platelet aggregation and thrombus formation in small blood vessels.¹⁴ However, mild thrombocytopenia cannot be a sign of organ damage indicating severe preeclampsia.¹

In this study, the severity of Covid-19 also did not differ significantly between patients with and without severe preeclampsia. This is in accordance with previous research on the INTERCOVID study population which stated that Covid-19 was independently associated with preeclampsia, and this association was not influenced by the severity of Covid-19.¹⁶

Conclusion

Our study showed that clinical characteristics and disease severity were not significantly different in the two groups. Laboratory markers correlate significantly with the severity of maternal disease, so they can be used as prognostic indicators.

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