The Influence of COVID-19 Severity on Maternal and Perinatal Outcomes: Evidence from a Cohort Study in Indonesia

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Abstract

Objective: This study aimed to assess the association between COVID-19 severity and maternal and neonatal outcomes at Dr. Hasan Sadikin General Hospital, Bandung, Indonesia.

Methods: A retrospective cohort study was conducted among pregnant women with confirmed COVID-19 who delivered between March 1, 2020, and March 31, 2022. Patients were categorized by disease severity (asymptomatic, mild, moderate, severe, or critical). Demographic, clinical, maternal, and neonatal data were collected. Statistical analyses included Fisher's exact and Kruskal-Wallis tests for bivariate analysis and Poisson regression for multivariate analysis (significance level $\alpha = 0.05$).

Results: Among 199 pregnant women, most were asymptomatic (42.7%) or had mild symptoms (37.2%). Higher COVID-19 severity was significantly associated with increased ICU/semi-ICU admission and oxygen therapy, as well as neonatal complications. After adjustment, moderate to critical cases showed significantly increased risks for ICU/semi-ICU care ($p = 0.012$, aRR 14.6; 95% CI: 1.8–118.2) and oxygen therapy ($p = 0.001$, aRR 12.2; 95% CI: 2.7–55.3). Mild cases were not linked to adverse outcomes.

Conclusion: Moderate to critical COVID-19 during pregnancy is associated with higher risks of adverse maternal and neonatal outcomes, emphasizing the importance of early detection and close monitoring.

Keywords: *pregnant women, COVID-19, disease severity, pregnancy outcomes, neonatal outcomes, Indonesia*

Dampak Keparahan COVID- 19 pada Luaran Kehamilan: Studi Kohort di Indonesia

Abstrak

Tujuan: Penelitian ini bertujuan mengevaluasi hubungan antara tingkat keparahan COVID-19 dan luaran kehamilan serta neonatal di RSUP Dr. Hasan Sadikin, Bandung.

Metode: Metode yang digunakan pada penelitian ini adalah kohort retrospektif pada ibu hamil dengan konfirmasi COVID-19 yang melahirkan antara 1 Maret 2020 hingga 31 Maret 2022. Pasien dikelompokkan berdasarkan tingkat keparahan (asimtomatik, ringan, sedang, berat, kritis). Data demografi, klinis, serta luaran ibu dan bayi dikumpulkan. Analisis statistik dilakukan menggunakan SPSS, dengan uji Fisher's exact dan Kruskal-Wallis untuk bivariat, serta regresi Poisson untuk multivariat (α=5%).

Hasil: Hasil penelitian menunjukkan dari 199 ibu hamil yang dianalisis, mayoritas bersifat asimtomatik (42,7%) atau ringan (37,2%). Keparahan penyakit yang lebih tinggi secara signifikan berhubungan dengan peningkatan kebutuhan perawatan ICU/semi-ICU dan terapi oksigen, serta komplikasi neonatal. Setelah penyesuaian, COVID-19 sedang–kritis berkorelasi dengan peningkatan risiko ICU/semi-ICU (p=0,012, aRR 14,6; 95% CI 1,8–118,2) dan terapi oksigen (p=0,001, aRR 12,2; 95% CI 2,7–55,3). Kasus ringan tidak menunjukkan hubungan dengan luaran buruk.

Kesimpulan: Keparahan COVID-19 sedang hingga kritis pada kehamilan meningkatkan risiko luaran buruk sehingga diperlukan identifikasi dini dan pemantauan ketat.

Kata kunci: COVID-19; Ibu hamil; Indonesia; luaran kehamilan, luaran neonatal; tingkat keparahan penyakit

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Introduction

Since first being identified in December 2019 in China, Coronavirus Disease 2019 (COVID-19) has spread rapidly across the globe. By March 2020, the World Health Organization (WHO) officially declared it a pandemic.[1,2] As of January 2023, over 600 million confirmed cases and more than 6 million deaths have been reported worldwide.[1]

COVID-19 presents with a broad spectrum of clinical manifestations, ranging from asymptomatic infection to critical, life-threatening illness.[2] Concerns regarding its impact on pregnancy have emerged, as earlier strains of the coronavirus family—such as severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV)—have been associated with adverse maternal and neonatal outcomes.[3]

Pregnancy-related alterations in immune function and physiological adaptations may increase susceptibility to infections and the risk of developing more severe illness.[4–7] These changes, combined with pre-existing comorbidities, can contribute to worse maternal outcomes and obstetric complications.[7,8]

Current data suggest that most pregnant women with COVID-19 experience mild to moderate flu-like symptoms. In fact, systematic reviews and meta-analyses based on universal screening have shown that a significant proportion of pregnant women infected with SARS-CoV-2 are asymptomatic.[9–11] Nevertheless, some studies indicate that COVID-19 during pregnancy may be associated with an increased risk of adverse outcomes, although generally less severe than those observed with SARS and MERS.[3,10,12,13]

Several studies have linked the severity of COVID-19 to poor maternal and neonatal outcomes. These include an increased incidence of cesarean delivery, hypertensive disorders of pregnancy, preterm birth, thromboembolic complications, intensive care unit (ICU) admission, low birth weight, neonatal COVID-19 infection, and admission to the neonatal intensive care unit (NICU).[14–16] Addressing these risks is critical for developing effective management strategies for pregnant women during the pandemic.

In this study, we investigated the association between COVID-19 disease severity and pregnancy as well as neonatal outcomes among pregnant women with laboratory-confirmed infection at Dr. Hasan Sadikin General Hospital, Indonesia. We hypothesized that the increasing severity of COVID-19 in pregnant women would be significantly associated with a higher risk of adverse maternal and neonatal outcomes. Additionally, we would also describe the clinical characteristics and maternal comorbidities among this population.

Methods

This was an analytical observational study employing a retrospective cohort design. The study included women with laboratory-confirmed COVID-19 infection during pregnancy who delivered at Dr. Hasan Sadikin General Hospital, a tertiary referral center in West Java, Indonesia, between March 1, 2020, and March 31, 2022. Ethical approval was granted by the Research Ethics Committee of Padjadjaran University (No. 1294/UN6.KEP/EC/2022) and by the Ethics Committee of Dr. Hasan Sadikin General Hospital (No. 13199/UN6.C.1/PT.00/2022).

A total sampling approach was used. All pregnant women with a positive COVID-19 diagnosis confirmed by reverse transcription polymerase chain reaction (RT-PCR) test, following national guidelines, were eligible. Exclusion criteria included multiple gestation pregnancies and incomplete data regarding

maternal or neonatal outcomes.

Data were extracted from hospital medical records by trained research assistants using a standardized data collection form. To ensure data reliability, two independent reviewers conducted a random cross-check of 20% of the records. Any discrepancies were resolved through consensus with a senior obstetrician. For missing data, a complete-case analysis was conducted. Variables with >10% missingness were reported, and sensitivity analyses were conducted to assess their potential impact.

Maternal characteristics collected included age, gestational age at admission, parity, and comorbidities.

The severity of COVID-19 was classified at admission based on WHO Clinical Management Guidelines.[2] Severity definitions:

- Mild: Non-specific symptoms without pneumonia or hypoxia
- Moderate: Clinical pneumonia, $SpO_2 \geq 90\%$
- Severe: Pneumonia with $SpO_2 < 90\%$ or respiratory distress
- Critical: Respiratory failure, ARDS, sepsis, or multi-organ failure

Pregnancy outcomes: maternal death, intensive care unit (ICU)/semi-ICU admission, oxygen therapy, premature rupture of membrane (PROM)/ preterm premature rupture of membrane (PPROM), and delivery method.

Neonatal outcomes: stillbirth, birth weight, low birth weight (<2500g), 1-minute and 5-minute Apgar scores <7.

All analyses were performed using IBM® SPSS® Statistics (version XX). Descriptive statistics were calculated for all variables. The Fisher's Exact test was used to analyze categorical variables, particularly when expected cell counts were small. The Kruskal-Wallis test was used for continuous or ordinal variables that did not follow a normal distribution, as determined by the Shapiro-Wilk test.

Assumptions for these tests include:

- For Fisher's Exact test: categorical variables with small sample sizes; assumes independence between groups.
- For Kruskal-Wallis test: independent observations and ordinal or continuous outcome variables with non-normal distribution.

Variables found significant in the bivariate analysis ($p < 0.05$) were included in Poisson regression analysis to estimate the relative risk (RR) of outcomes associated with increasing disease severity. This model was chosen over logistic regression because the outcome variables had high prevalence (>10%), and Poisson regression with robust error variance provides more accurate estimates of relative risk under such conditions. Covariates adjusted in the multivariable model included maternal age, gestational age, parity, and pre-existing comorbidities.

A power analysis was conducted using G*Power software to determine the minimum required sample size. Assuming an alpha level of 0.05, 80% power, and an effect size of 0.3 (moderate), a minimum of 88 participants was required for valid comparisons across three or more severity groups. The significance level was set at 5% (two-tailed), consistent with standard epidemiological research practice to balance Type I and Type II error rates.

Results

Between 1 March 2020 and 31 March 2022, 4933 pregnant women delivered at Dr. Hasan Sadikin General (flowchart in **Figure 1**). Among whom, 659 pregnant women had

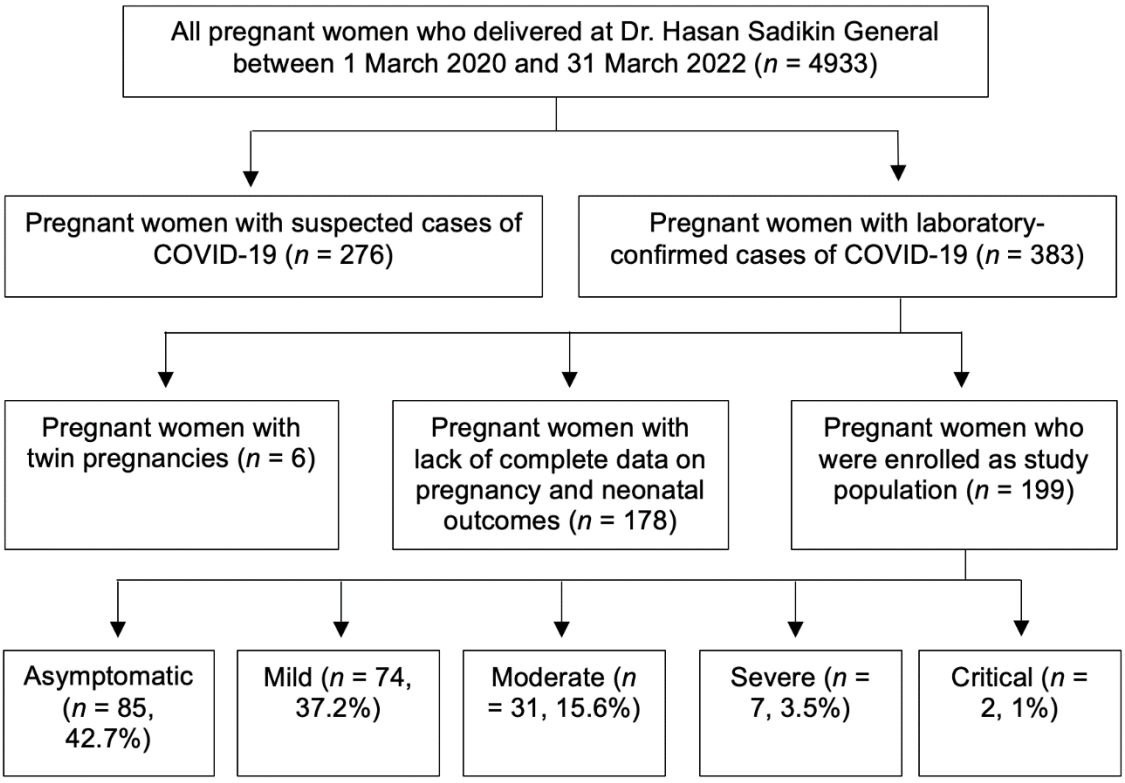

Figure 1 Study Flowchart.

suspected or confirmed cases of COVID-19. Out of this, 282 women did not meet the inclusion criteria, and 178 women met the exclusion criteria. Thus, 199 women with laboratory-confirmed COVID-19 cases were included in this study.

Demographic and clinical characteristics of pregnant women with COVID-19 infection are presented in **Table 1**. The majority of women presented with either asymptomatic infection (n = 85, 42.7%) or mild disease (n = 74, 37.2%), while only a small proportion experienced moderate (n = 31, 15.6%), severe (n = 7, 3.5%), or critical illness (n = 2, 1%) at the time of hospital admission. These findings suggest that, in this cohort, most pregnant women infected with COVID-19 did not develop clinically severe illness, which is consistent with global data indicating that pregnancy is not uniformly associated with severe COVID-19 symptoms.

The mean maternal age was 29.4 years (SD = 6.0), reflecting a relatively young obstetric population, which may partially explain the predominance of mild or asymptomatic cases, as younger maternal age has been associated with better outcomes in COVID-19. The mean gestational age at hospital admission was 36.6 weeks (SD = 2.8), indicating that most women were in late pregnancy. This is clinically relevant, as advanced gestation may influence the decision-making process regarding timing of delivery and respiratory support in the context of worsening maternal respiratory status.

In terms of parity, nulliparous women comprised 34.7% of the cohort (n = 69), followed by multiparous women (2–4 previous pregnancies) at 32.7% (n = 60), and primiparous women (one prior pregnancy) at 30.1% (n = 65). This fairly even distribution suggests that parity was not strongly associated with disease severity at baseline in this population, although further analysis is required to confirm this.

Approximately 20.4% of women (n

Table 1 Relationship between COVID-19 disease severity and pregnancy and neonatal outcomes

Variable	Categories COVID-19	aRR	95% CI	P value
ICU/semi-ICU	Moderate-Severe	14.6	1.8–118.2	0.012
Oxygen Therapy	Moderate-Severe	12.2	2.7–55.3	0.001
Caesarean Section	Moderate-Severe	1.0	0.5–1.9	0.994
APGAR <7 (5 Minutes)	Moderate-Severe	2.6	1.0–6.8	0.057

Table 2 Poisson regression to assess the relationship between COVID-19 disease severity and ICU/semi-ICU admission

Parameter	ß	SE	Wald Chi-Square	*P* Value	Adjusted-RR	95% CI
Mild COVID-19	1.289	1.158	1.238	0.266	3.6	0.4, 35.1
Moderate, severe, or critical COVID-19	2.678	1.068	6.284	0.012	14.6	1.8, 118.1
Maternal age	-0.009	0.073	0.016	0.900	1.0	0.9, 1.1
Gestational age at the time of admission	-0.186	0.088	4.480	0.034	0.8	0.7, 1.0
Parity	-0.199	0.376	0.279	0.597	0.8	0.4, 1.7
Any underlying medical conditions[a]	0.455	0.626	0.529	0.467	1.6	0.5, 5.4
Intercept	2.629	3.730	0.497	0.481	13.9	0.0, 20,719.2

Notes: [a]Includes asthma, tuberculosis, cardiovascular disease, chronic hypertension, gestational hypertension, morbid obesity, HIV infection, SLE, neurological disorder, and hyperthyroidism.
Abbreviations: SE, standard error; CI, confidence interval.

= 41) had at least one underlying medical condition, with chronic hypertension being the most frequently reported comorbidity. The presence of comorbidities such as hypertension is clinically important, as it may predispose patients to more severe maternal outcomes, including complications related to COVID-19 and hypertensive disorders of pregnancy. This finding underscores the importance of early identification and close monitoring of high-risk pregnant women infected with SARS-CoV-2.

Table 1 discusses the demographic and clinical characteristics of pregnant women infected with COVID-19 revealed that the majority were either asymptomatic or had mild symptoms at the time of hospital admission, with a mean maternal age of approximately 29 years and an average gestational age of nearly 37 weeks. The distribution of parity was relatively even, while chronic hypertension and obesity were among the most common comorbidities. In terms of pregnancy outcomes, the severity of COVID-19 was positively correlated with increased maternal complications. Women with moderate to critical disease had higher rates of ICU/semi-ICU admission and oxygen therapy compared to those with mild or no symptoms. Although caesarean section rates appeared to increase with severity, this was not statistically significant after adjusting for confounders.

Regarding neonatal outcomes, there was a notable increase in adverse outcomes such as low birth weight and low APGAR scores at both 1 and 5 minutes, particularly among women with more severe COVID-19. Stillbirths were also more frequently observed in the moderate to critical group. However,

Table 3 Poisson regression to assess the relationship between COVID-19 disease severity and oxygen therapy

Parameter	ß	SE	Wald Chi-Square	*P* Value	Adjusted-RR	95% CI
Mild COVID-19	0.588	0.915	0.512	0.414	1.8	0.3, 10.8
Moderate, severe, or critical COVID-19	2.502	0.771	10.547	0.001	12.2	2.7, 55.3
Maternal age	-0.010	0.057	0.028	0.867	1.0	0.9, 1.1
Gestational age at the time of admission	-0.120	0.071	2.894	0.089	0.9	0.8, 1.0
Parity	0.081	0.265	0.094	0.759	1.1	0.6, 1.8
Any underlying medical conditions[a]	0.100	0.585	0.029	0.864	1.1	0.4, 3.5
Intercept	0.735	2.979	0.061	0.805	2.1	0.0, 715.7

Notes: [a]Includes asthma, tuberculosis, cardiovascular disease, chronic hypertension, gestational hypertension, morbid obesity, HIV infection, SLE, neurological disorder, and hyperthyroidism.
Abbreviations: SE, standard error; CI, confidence interval.

Table 4 Poisson regression to assess the relationship between COVID-19 disease severity and cesarean section

Parameter	ß	SE	Wald Chi-Square	*P* Value	Adjusted-RR	95% CI
Mild COVID-19	-0.325	0.304	1.142	0.285	0.7	0.4, 1.3
Moderate, severe, or critical COVID-19	0.002	0.332	0.000	0.994	1.0	0.5, 1.9
Maternal age	0.065	0.029	5.136	0.023	1.1	1.0, 1.1
Gestational age at the time of admission	-0.053	0.046	1.332	0.248	0.9	0.9, 1.0
Parity	-0.252	0.146	2.986	0.084	0.8	0.6, 1.0
Any underlying medical conditions[a]	0.680	0.272	6.231	0.013	2.0	1.2, 3.4
Intercept	-0.999	1.829	0.298	0.585	0.4	0.0, 13.3

Notes: [a]Includes asthma, tuberculosis, cardiovascular disease, chronic hypertension, gestational hypertension, morbid obese, HIV infection, SLE, neurological disorder, and hyperthyroidism.
Abbreviations: SE, standard error; CI, confidence interval.

Table 5 Poisson regression to assess the relationship between COVID-19 disease severity and low APGAR score at 5 minutes

Parameter	ß	SE	Wald Chi-Square	*P* Value	Adjusted-RR	95% CI
Mild COVID-19	0.047	0.560	0.007	0.934	1.0	0.4, 3.1
Moderate, severe, or critical COVID-19	0.946	0.496	3.633	0.057	2.6	1.0, 6.8
Maternal age	-0.012	0.046	0.068	0.795	1.0	0.9, 1.1
Gestational age at the time of admission	-0.209	0.060	12.206	<0.001	0.8	0.7, 0.9
Parity	0.070	0.180	0.151	0.698	1.1	0.8, 1.5
Any underlying medical conditions[a]	-0.034	0.510	0.005	0.946	1.0	0.4, 2.6
Intercept	5.228	2.438	4.598	0.032	186.4	1.6, 22,172.5

Notes:
[a]Includes asthma, tuberculosis, cardiovascular disease, chronic hypertension, gestational hypertension, morbid obese, HIV infection, SLE, neurological disorder, and hyperthyroidism.
Abbreviations: SE, standard error; CI, confidence interval.

after adjusting for potential confounding factors, only ICU/semi-ICU admission and the need for oxygen therapy remained significantly associated with higher disease severity (adjusted relative risk [aRR] 14.6 and 12.2, respectively) showed in **Table 2-Table 5**. These findings underscore that while mild COVID-19 may not significantly impact maternal and neonatal outcomes, moderate to critical illness poses a substantially greater risk, highlighting the need for close monitoring and resource preparedness in this patient population.

Discussion

The present retrospective cohort study showed that most pregnant women with COVID-19 in Dr. Hasan Sadikin General Hospital had uncomplicated clinical manifestations at the time of admission, most were asymptomatic (*n* = 85, 42.7%) or had a mild COVID-19 (*n* = 74, 37.2%). The rest of this study's population had moderate (*n* = 31, 15.6%), severe (*n* = 7, 3.5%), or critical COVID-19 (*n* = 2, 1%). This proportion can be attributed to the fact that the Indonesian national recommendation for pregnant women with suspected or confirmed COVID-19 cases who are about to deliver requires them to be referred to a referral hospital, such as the one in this study; thus, pregnant women with uncomplicated disease were also referred, rather than just those with complicated disease.[9,18]

Similar to the present study, a previous cohort study on pregnant women with COVID-19 infection examined 47% of asymptomatic cases, 27% of mild cases, 14% of moderate cases, 8% of severe cases, and 4% of critical cases of COVID-19.[14] Other previous research found that most pregnant women with COVID-19 infection had mild to moderate COVID-19.[9,10,15] However, a systematic review and meta-analysis showed that in the context of universal screening strategy, an estimated 73% of women with COVID-19 had asymptomatic disease (95% CI 62—82%).[11] A previous prospective cohort study on pregnant women admitted for labor and delivery found similar results, demonstrating an estimated 86% of asymptomatic pregnant women were infected with COVID-19.[19]

In this study, the mean maternal age of mothers with COVID-19 infection was 29.4 years (SD = 6.0). Consistently, a previous study based in the UK reported that most pregnant women with COVID-19 were in the age range of 20—34 years, followed by women aged ≥35 years, and women aged <20 years.[20] The mean gestational age on admission was 36.6 weeks (SD = 2.8). This distribution was influenced by the fact that the study's population consisted of pregnant women who gave birth within the same time frame as their admission date, so they are more likely to be in the third trimester. However, it is also worth noting the result from previous study that stated pregnant women in the third trimester are more likely to be infected with SARS-CoV-2 and may experience more complications than those infected earlier in the pregnancy. The distribution of the number of parities of women in this study was almost even, with nulliparous, primiparous, and multiparous (2—4 previous pregnancies) each having percentages of 34.7% (*n* = 69), 30.1% (*n* = 65), and 32.7% (*n* = 60), respectively. Other studies indicated comparable result, with the percentages of nulliparous and multiparous being 37.4% and 61.3%, respectively.[21] Nearly a fifth of women (*n* = 41, 20.4%) had any underlying medical conditions, with chronic hypertension being the most common. A systematic review and meta-analysis reported that compared to pregnant women without COVID-19, pregnant women with COVID-19 were more likely to have comorbidities.[11] A national cohort study in the UK also stated that the percentage of pregnant women with symptomatic COVID-19 infections that have

relevant comorbidity were higher compared to the historical comparison group (22% *vs* 13%).[20] The comorbidities referred to included asthma (*n* = 49. 7%,), hypertension (*n* = 24.3%,), diabetes (*n* = 22.3%), heart disease (*n* = 13.2%,), liver disease (*n* = 12.1%), kidney disease (*n* = 9.1%,), and other diseases, with asthma and hypertension in particular increased the risk of hospital admission on symptomatic case of SARS-CoV-2 infection.[20]

Similar findings have also been reported in several low- and middle-income countries (LMICs), which suggest that the majority of pregnant women with COVID-19 present with asymptomatic or mild disease. For example, a retrospective cohort study in India found that 72% of pregnant women diagnosed with COVID-19 were either asymptomatic or had only mild symptoms at presentation. Likewise, a study in Brazil revealed that most pregnant women had mild symptoms (63.6%), with only a minority developing severe outcomes requiring intensive care.[22] These similarities may reflect shared factors among LMICs, including late presentation, universal referral policies for pregnant women, and possibly underreporting of symptoms due to stigma or access barriers. Nonetheless, differences in health system capacity and resource allocation might influence maternal and neonatal outcomes in more severe cases across these settings.

This study highlights a significant association between COVID-19 severity and adverse pregnancy outcomes. Moderate to critical COVID-19 in pregnant women substantially increased the likelihood of ICU/semi-ICU admission and the need for oxygen therapy, compared to asymptomatic individuals. Mild cases, however, did not show a significant risk increase. Several contributing factors for ICU admission were identified, including pulmonary disease, respiratory symptoms, and gestational age at admission. Similarly, oxygen therapy requirements were significantly higher among women with moderate to critical disease.[23] Although a significant relationship between COVID-19 severity and cesarean section was observed in previous studies, this study found that after adjusting for maternal age and underlying conditions, disease severity was no longer independently associated with cesarean delivery. Moreover, COVID-19 severity was initially linked with low APGAR scores at 5 minutes, but this association lost significance after adjusting for confounders. Gestational age at admission, however, remained a key factor in APGAR outcomes. These findings suggest that while COVID-19 severity does influence maternal and neonatal care requirements, other variables—such as maternal comorbidities and gestational age—play a crucial role in determining final pregnancy outcomes. Understanding these relationships is critical in managing pregnant women with COVID-19 to reduce complications.[23]

The biological mechanisms linking COVID-19 severity with adverse pregnancy outcomes are multifactorial and largely involve the dysregulation of the maternal immune and cardiovascular systems. SARS-CoV-2 infection can trigger an exaggerated maternal inflammatory response, characterized by elevated levels of pro-inflammatory cytokines such as IL-6, IL-1β, and TNF-α. This hyperinflammatory state may disrupt placental function, leading to placental insufficiency, impaired fetal oxygenation, and an increased risk of preterm birth or fetal distress.[24] Additionally, COVID-19-associated endothelial injury and coagulopathy can contribute to the development of complications such as preeclampsia-like syndromes, thrombosis, and placental abruption.[25] Moreover, hypoxemia in severe cases compromises maternal oxygen delivery, which may affect fetal well-being and increase the need for emergency interventions such as cesarean

delivery. These mechanisms help explain the observed association between moderate to critical COVID-19 and higher rates of ICU admission, oxygen therapy, and altered neonatal outcomes.

This study has several strengths. First, it included only pregnant women with confirmed COVID-19 infection based on PCR testing, ensuring diagnostic accuracy. Second, the analysis stratified data according to disease severity, allowing for meaningful comparisons of outcomes across severity levels.

However, some limitations must be acknowledged. The retrospective design relying on medical records led to the exclusion of cases with incomplete data. Additionally, the sample was restricted to women who delivered during the same hospitalization period, resulting in overrepresentation of third-trimester pregnancies and potentially limiting generalizability. Lastly, vaccination status was not included in the analysis, which may have influenced disease severity and maternal or neonatal outcomes.

Conclusion

The increase in COVID-19 disease severity may contribute to several adverse outcomes, including an increase in the rate of ICU/ semi-ICU admission and the rate of oxygen therapy. The outcomes of this study could be taken into consideration for the management principle of pregnant women with COVID-19. In the post-pandemic era, moderate to severe COVID-19 in pregnancy remains linked to adverse outcomes, including ICU admission and oxygen therapy. Clinical management should emphasize early identification, referral, and multidisciplinary care. Policymakers must maintain maternal health infrastructure, ensure access to ICU and oxygen support, and integrate COVID-19 screening and vaccination into antenatal care to protect vulnerable pregnant populations and enhance system preparedness for future health threats.

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