COMORBIDITIES AND PREGNANCY COMPLICATIONS AS DETERMINANTS OF COVID-19 SEVERITY IN PREGNANT WOMEN: A RETROSPECTIVE STUDY AT A NATIONAL MATERNAL REFERRAL CENTER

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Abstract. Background: *Pregnant women are considered people at risk in the context of COVID-19 due to physiological changes in immunity, cardiopulmonary function, and metabolic status. These changes may increase susceptibility to infection and lead to progression to severe diseases. In particular, maternal comorbidities and pregnancy-related complications have been identified as potential risk factors for worsened clinical outcomes. However, data from low- and middle-income countries remain scarce, limiting the generalizability of global evidence to these findings. Indonesia, one of the most populous countries in Asia, had high maternal morbidity during the pandemic, yet few studies have focused on determinants of COVID-19 severity among pregnant women.* **Objective:** *This study aimed to assess the association between maternal comorbidities, pregnancy-related complications, and the severity of COVID-19 in a national maternal referral hospital.* **Materials and methods:** *A retrospective observational study was conducted, involving 252 pregnant women with confirmed COVID-19 admitted to Harapan Kita Women and Children Hospital, Jakarta, between 2020 and 2022. COVID-19 severity was categorized as moderate or severe based on the World Health Organization (WHO) classification. Logistic regression was used to calculate odds ratios (OR) with 95% confidence intervals (CI) for associations between clinical variables and disease severity.* **Results:** *Maternal comorbidities were significantly associated with severe COVID-19 (OR 3.2; 95% CI 1.08-9.26). Diabetes mellitus (DM) was the strongest independent predictor of severe disease (OR 5.0; 95% CI 1.28-19.88). Hypertension (OR 2.8; 95% CI 0.59-13.60) and preeclampsia (OR 1.2; 95% CI 0.40-3.75) were not statistically significant. These findings align with global reports that metabolic dysfunction exacerbates inflammation and immune dysregulation.* **Conclusions:** *Comorbidities, particularly diabetes mellitus, significantly increase the risk of severe COVID-19 in pregnancy. Targeted screening and early intervention are essential, especially in resource-limited countries, in order to improve maternal outcomes.*

Key words: *comorbidity, COVID-19, disease severity, pregnancy*

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INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a highly transmissible virus, caused a global pandemic primarily through human-to-human transmission [1]. As of May 2023, the World Health Organization (WHO) declared COVID-19 no longer a Public Health Emergency of International Concern (PHEIC), after recording 765,020,162 confirmed cases and 7,049,617 deaths globally [2]. In Indonesia, the largest country in South-East Asia and the fourth most populous worldwide, there were 6,787,354 confirmed cases and 259,200 reported deaths during the same period [3-4]. At the pandemic's peak in October 2020, Indonesia had the second-highest COVID-19 death toll in Asia [5].

Although the state of emergency has ended, COVID-19 continues to impact populations at risk, such as the elderly, people with disabilities, and pregnant women [6]. The presence of comorbidities significantly contributes to adverse outcomes in infected individuals. National data from Indonesia indicate that the most prevalent comorbidities among COVID-19 patients include hypertension (49.1%), diabetes mellitus (34.9%), heart disease (16.9%), pregnancy complications (8.6%), and pulmonary disease (6%), along with other chronic conditions, such as chronic obstructive pulmonary disease, kidney disease, cancer, liver disease, asthma, and tuberculosis [7-8]. Jakarta, the nation's capital, reported the highest cumulative case count (22.2%), followed by West Java (18.4%) and Central Java (9.9%) [4].

COVID-19 symptoms range from mild to life-threatening, commonly presenting as fever (> 38 °C), cough, shortness of breath, fatigue, and diarrhea [9]. Severe cases may escalate quickly, resulting in septic shock, acute respiratory distress syndrome (ARDS), coagulopathy, or multi-organ failure [10-11]. The presence of comorbid conditions increases the likelihood of severe disease [12]. Among pregnant women with comorbidities, the risk of mortality is 3.2 times higher than among those without [13-14], and a meta-analysis has shown that around 20% of COVID-19-related maternal deaths occur in women with underlying health conditions [15].

Compared to the general population, pregnant women are more susceptible to severe COVID-19, maternal death, and complications during pregnancy [16, 17]. In Mexico, for instance, SARS-CoV-2 became the leading cause of maternal death from July 2020, accounting for over half of all maternal fatalities in 2021 [13]. Infection during pregnancy has also been linked to increased risks of preeclampsia, eclampsia, and preterm delivery [19, 20], with pneumonia devel-oping in up to 61.5% of infected pregnant patients [23]. Despite these global insights, there is limited evidence on the impact of maternal comorbidities and pregnancy complications on COVID-19 severity in Indonesia. This study was designed to assess the association between comorbidities, pregnancy complications, and COVID-19 severity among pregnant women receiving care at a national maternal referral hospital in Indonesia.

MATERIALS AND METHODS

This retrospective observational study included pregnant women diagnosed with COVID-19 who received care at Harapan Kita Women and Children Hospital (RSABHK) in Jakarta. Ethical approval was obtained from the RSABHK Ethics Committee. Data were collected from patient medical records from January 2020 to December 2022. A total of 252 confirmed COVID-19 cases in pregnant women were analyzed. As a national referral center for maternal health, RSABHK provides specialized antenatal and postnatal services for high-risk populations. All pregnant women with laboratory-confirmed COVID-19, regardless of trimester, were eligible for inclusion, irrespective of the presence or absence of comorbid conditions. All patients received treatment following national COVID-19 clinical management protocols.

Study Variables

The primary outcome in this study was the severity of COVID-19, classified into moderate and severe categories based on the World Health Organization (WHO) clinical management guidelines. Moderate disease was defined as the presence of pneumonia symptoms, such as fever, cough, dyspnea, or rapid breathing without signs of severe pneumonia, and with an oxygen saturation (SpO_2) of 90% or higher at room air temperature. Severe disease was characterized by pneumonia accompanied by at least one of the following: a respiratory rate greater than 30 breaths per minute, signs of severe respiratory distress, or a SpO_2 below 90% at room air temperature. Independent variables included gestational age, the presence of comorbidities, such as diabetes mellitus, hypertension, anemia, and obesity, as well as pregnancy-related complications, particularly preeclampsia. When available, data allowed for the differentiation between pre-existing diabetes mellitus and gestational diabetes.

Data analysis

Statistical analysis was performed using IBM SPSS Statistics version 27. Continuous variables were presented as means and ranges, while categorical variables were summarized using frequencies and

percentages. Associations between variables and disease severity were assessed using logistic regression to estimate odds ratios (OR) with corresponding 95% confidence intervals (CI). Statistical significance was defined as a p-value less than 0.05 and a 95% CI that did not include the value of 1.

RESULTS

The frequency distribution of key research variables is presented in Table 1. The participants had a mean age of 31.75 years (range 19-49 years). Most were ≤ 35 years old (180; 71.4%), while 72 (28.6%) were >35 years old. Regarding gestational age, 14 women (5.6%) were in the first trimester, 22 (8.7%) in the second trimester, and the majority, 216 (85.7%), were in the third trimester at the time of their COVID-19 diagnosis.

Comorbidities were common: 174 women (69.0%) had at least one comorbid condition, while 78 (31.0%) had none. More specifically, 11 women (4.4%) had diabetes mellitus (DM), 9 (3.6%) had hypertension, 70 (27.8%) had anemia, 52 (20.6%) were obese, and 35 (13.9%) had preeclampsia. A total of 91 women (36.1%) had both comorbidities and pregnancy-related complications. Regarding disease severity, 216 patients (85.7%) had moderate COVID-19, and 36 (14.3%) developed severe disease.

Table 1. Frequency Distribution of Research Variables (n = 252)

Variables	n (%)
Mean age (Min-Max)	**31.75 (19-49)**
Age ≤ 35 years old	180 (71.4)
Age > 35 years old	72 (28.6)
Gestational Age (weeks)	
First trimester (0-13)	14 (5.6)
Second trimester (14-27)	22 (8.7)
Third trimester (28-42)	216 (85.7)
Comorbidities	
No	78 (31.0)
Yes	174 (69.0)
Diabetes Mellitus	
No	241 (95.6)
Yes	11 (4.4)
Hypertension	
No	243 (96.4)
Yes	9 (3.6)
Anemia	
No	182 (72.3)
Yes	70 (27.8)
Obesity	
No	200 (79.4)
Yes	52 (20.6)
Preeclampsia	
No	217 (86.1)
Yes	35(13.9)
Comorbidities with complication	
No	161 (63.9)
Yes	91 (36.1)
COVID-19 severity	
Intermediate	216 (85.7)
Severe	36 (14.3)

Table 2 summarizes bivariate and multivariate analyses. Most pregnancies with COVID-19 reached the third trimester, but gestational age was not significantly associated with severity. The presence of any comorbidity significantly increased the odds of severe disease (OR 3.2; 95% CI 1.080-9.255; p = 0.036). Among the individual factors, diabetes mellitus was the only significant predictor of severe COVID-19 (OR 5.0; 95% CI 1.281-19.880; p = 0.021). Other factors, including hypertension (OR 2.8; 95% CI 0.586-13.597), preeclampsia (OR 1.2; 95% CI 0.402-3.752), anemia (OR 0.4; 95% CI 0.141-1.072), and obesity (OR 0.6; 95% CI 0.209-1.586), did not have any relevance to the disease severity in this cohort.

Existing comorbidities are generally associated with a significantly increased risk of severe COVID-19 (OR 3.2; 95% CI 1.080-9.255). Diabetes mellitus, for example, is one of these comorbidities (OR 5.0; 95% CI 1.281-19.880). In contrast, maternal hypertension (OR 2.8; 95% CI 0.586-13.597) and maternal preeclampsia (OR 1.2; 95% CI 0.402-3.752) were not symptoms of severe disease.

DISCUSSION

In this study, most COVID-19 cases among pregnant women were confirmed during the late third trimester. This observation aligns with previous reports indicating that most pregnant patients hospitalized with SARS-CoV-2 infection are in the late second or third trimester [24, 25]. Although gestational age was not significantly linked to disease severity in our analysis, physiological changes that occur in late pregnancy, such as decreased functional residual capacity, heightened oxygen demand, and modified immune function, may reduce tolerance to hypoxia and increase susceptibility to infection, thus potentially worsening clinical outcomes [26].

Studies show that pregnant women with one or more comorbid conditions had over three times the odds of experiencing severe COVID-19 symptoms compared to those without such conditions [13, 15, 27, 28]. While the estimated prevalence of DM in pregnant women in Indonesia ranges from 1.9% to 3.6% [29, 30], its clinical implications are significant. DM contributes to immune dysregulation and a pro-inflammatory environment characterized by elevated cytokines, including IL-6, TNF-α, and CRP, which are implicated in cytokine storm pathogenesis [31, 32]. Additionally, DM is associated with adverse pregnancy outcomes, such as preeclampsia, abnormal fetal growth, and increased perinatal mortality [33, 35]. The coexistence of DM & COVID-19 further amplifies the risk of maternal death [36-38].

Variables		n	Degree of Severity		Bivariate		Multivariate	
			Intermediate n (%)	Severe n (%)	p-value	OR (95% CI)	p-value	OR (95% CI)
Gestational Age (weeks)	First Trimester	14	11 (78.6)	3 (21.4)	1.0	1.0	1.0	1.0
	Second Trimester	22	17 (77.3)	5 (22.7)	0.927	1.1 (0.213-5.449)	0.970	1.0 (0.168-5.555)
	Third Trimester	216	188 (87.0)	28 (13.0)	0.375	0.5 (0.143-2.079)	0.319	0.5 (0.111-2.048)
Comorbidities	No	78	71 (91.0)	7 (9.0)	1.0	1.0	1.0	1.0
	Yes	174	145 (83.3)	29 (16.7)	0.107	2.0 (0.847-4.856)	0.036	3.2 (1.080-9.255)
Diabetes Mellitus	No	241	210 (87.1)	31 (12.9)	1.0	1.0	1.0	1.0
	Yes	11	6 (54.5)	5 (45.5)	0.011	5.6 (1.625-19.611)	0.021	5.0 (1.281-19.880)
Hypertension	No	243	210 (86.4)	33 (13.6)	1.0	1.0	1.0	1.0
	Yes	9	6 (66.7)	6 (33.3)	0.122	3.1 (0.759-13.345)	0.196	2.8 (0.586-13.597)
Anemia	No	182	153 (84.1)	29 (15.9)		1.0		1.0
	Yes	70	63 (90.0)	7 (10.0)	0.228	0.6 (0.244-1.408)	0.068	0.4 (0.141-1.072)
Obesity	No	200	172 (86.0)	28 (14.0)	1.0	1.0	1.0	1.0
	Yes	52	44 (84.6)	8 (15.4)	0.799	1.1 (0.476-2.620)	0.286	0.6 (0.209-1.586)
Preeclampsia	No	217	188 (86.6)	29 (13.4)	1.0	1.0	1.0	1.0
	Yes	35	28 (80.0)	7 (20.0)	0.301	1.6 (0.649-4.050)	0.718	1.2 (0.402-3.752)
Comorbidities & Complications	No	161	140 (87.0)	21 (13.0)	1.0	1.0	1.0	1.0
	Yes	91	76 (83.5)	15 (16.5)	0.454	1.3 (0.641-2.701)	0.630	0.8 (0.292-2.107)

Gestational diabetes mellitus (GDM) shares many of the same pathophysiological features as pre-existing DM. In 2021, the global prevalence of GDM was reported at 13.4% [29], with risk factors including obesity, advanced maternal age, and a family history of diabetes [39]. GDM promotes systemic inflammation and oxidative stress, potentially impairing immune function and worsening viral infections [40, 41]. Findings from Kleinwechter et al. indicated that overweight pregnant women with GDM were at higher risk for severe COVID-19 [41, 42], reinforcing the conclusion that metabolic dysfunction is a key determinant of disease severity.

Although hypertension is one of the most frequently reported comorbidities in patients with COVID-19 [43-47] it was not significantly associated with severe illness in our cohort. Biologically, hypertension may exacerbate disease through mechanisms such as endothelial dysfunction, oxidative stress, and the activation of pro-inflammatory pathways [42-47]. However, the limited number of hypertensive cases in our sample and potential confounders may have reduced our ability to detect a statistically significant relationship.

Preeclampsia has also been proposed as a potential risk factor for severe COVID-19. SARS-CoV-2 infection can trigger placental hypoxia, endothelial injury, and coagulation abnormalities – mechanisms that overlap with the pathophysiology of preeclampsia [48-52]. However, in our study, no significant association was found. Differences in diagnostic criteria, population demographics, and treatment approaches may explain this discrepancy. Nevertheless, both preeclampsia and COVID-19 independently contribute to worsened maternal outcomes [19, 53, 54].

This study has several limitations that should be acknowledged. The relatively modest sample and the single-center design may limit the generalizability of the findings to other populations or healthcare settings. Key variables, such as vaccination history, socioeconomic status, and the specific SARS-CoV-2 variant, were not recorded, although they may have significantly influenced patient outcomes. Despite these constraints, the findings emphasize the urgent need for early screening and proactive management of comorbidities, particularly diabetes, in pregnant women with COVID-19.

Future studies should aim to include larger, multi-center cohorts to enhance the generalizability and statistical power of findings. Prospective data collection is recommended to improve data completeness and accuracy. In addition, capturing key variables such as vaccination status, viral variants, and social determinants of health will allow for a more comprehensive understanding of the factors influencing maternal outcomes. Exploring the effectiveness of tailored interventions for high-risk groups, such as early glycemic control protocols and integrated antenatal COVID-19 care pathways, may further optimize clinical management. Such research would contribute to a more nuanced understanding of risk profiles and support the development of targeted strategies to improve both maternal and fetal outcomes during and beyond the COVID-19 pandemic.

CONCLUSION

The study concludes that pregnant women with underlying health conditions, especially diabetes mellitus, are at a markedly increased risk of experiencing severe COVID-19. Conversely, hypertension and preeclampsia did not emerge as significant predictors of disease severity in this population. These results emphasize the need for early detection and targeted management of diabetes in pregnant women to enhance clinical outcomes and mitigate the impact of severe COVID-19 during pregnancy.

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