ORIGINAL ARTICLE

Characteristics, Risk Factors, and Maternal-Foetal Outcomes of Pregnant Women with COVID-19 Admitted to Hospital Sungai Buloh, Malaysia: A Single-Centre Retrospective Cohort Study

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ABSTRACT

INTRODUCTION: Malaysia was hit by one of the biggest waves of COVID-19 in year 2021, the worst-case morbidity and mortality since the pandemic started in 2020. Hospital Sungai Buloh (HSB), Selangor was the first hospital designed to treat COVID-19 cases only and was the referral centre for COVID-19 in the Klang Valley, hence all pregnant patients with COVID-19 in Selangor was referred here for treatment and care. This study aims to describe the characteristics and outcomes of pregnant women with COVID-19 admitted to HSB, and to identify the risk factors associated with severe outcomes. **MATERIALS AND METHODS:** This study is a single centre, retrospective cohort study whereby electronic records of pregnant patients with COVID-19 admitted to HSB from May to August 2021 were searched and data on sociodemographic and clinical characteristics, management, complication and outcomes of the mother and foetal were retrieved. **RESULTS:** Out of 282, 66 women had severe covid-19 (stage 4 &5) and 216 had non-severe COVID-19 (stage 1-3). We found that pregnant patients with severe COVID-19 infection are more likely to be obese, have lower absolute lymphocyte counts and higher C-reactive protein (>50) on admission, and higher day of illness on admission. **CONCLUSION:** Severe COVID-19 resulted in longer hospital stay, associated with higher disease related complications and adverse maternal and foetal outcomes. However, vertical transmission is rare although possible in COVID-19. Our study provides a valuable local data from a single COVID-19 centre in Malaysia

Keywords
COVID-19, Pregnancy, Maternal-fetal outcomes, Risk factors, Retrospective cohort study

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INTRODUCTION

Hospital Sungai Buloh (HSB) was the referral centre for COVID-19 in the Klang Valley, Selangor,Malaysia at the start of the pandemic. Between March to June 2021, 3396 pregnant women were diagnosed with COVID-19 in Malaysia and the number continued to rise.[1] Approximately 3-5.5% of these women required intensive care unit (ICU) admissions and as of 9th Aug 2021, a total of 70 maternal deaths due to COVID-19 had been reported in Malaysia.[2] Pregnant women are at slightly increased risk of becoming having severe illness when infected with COVID-19, as physiological adaptations during pregnancy may predispose them to a more severe course of pneumonia.[3]

Previous studies have identified obesity, pre-existing diabetes, and other cardiometabolic comorbidities as important risk factors for severe COVID-19 in pregnancy. Ethnic disparities in disease severity have also been reported globally, suggesting the influence of both biological and socio-economic factors.[4] Understanding the characteristics, risk factors, and outcomes can facilitate optimal resource allocation to address COVID-19-related concerns effectively. Despite numerous studies examining the effects of COVID-19 on maternal and neonatal outcomes,[5] there remains a scarcity of data from Malaysia on these aspects. This study aims to describe and compare the characteristics and outcomes of pregnant women with

COVID-19 admitted to HSB, and to identify risk factors associated with severe disease.

MATERIALS AND METHODS

This was a single-centre retrospective cohort study involving pregnant women with COVID-19 who were admitted to HSB between May and August 2021. Pregnant patients with SARS-CoV-2 infection confirmed by either polymerase chain reaction (PCR) testing or a rapid test kit (RTK) during this period were included. Data on sociodemographic characteristics, clinical variables, laboratory parameters, management, complication as well as pregnancy and neonatal outcomes were extracted from electronic records. Clinical severity of COVID-19 is as in Appendix 1. Clinical deterioration was defined as an increase in the World Health Organization (WHO) ordinal scale during hospitalisation (Appendix 2). Regarding foetal outcomes, miscarriage was defined as pregnancy loss at ≤20 weeks of gestation, while stillbirth was defined as pregnancy loss occurring after 20 weeks of gestation. Sample size was determined using the events per variable (EPV) principle. With an EPV of ≥10 and four predictors in the model, at least 40 pregnant women with severe COVID-19 were required.[6,7]

Statistical analysis

Variables were summarised as mean (SD) or median (IQR) for continuous data and frequencies (%) for categorical data. Clinically relevant variables were compared between non-severe and severe COVID-19 groups using independent t-test or Mann–Whitney U test for continuous variables and chi-square or Fisher's exact test for categorical variables.

Variables applicable only to patients with severe COVID-19 such as markers of disease progression during hospitalisation, oxygen therapy requirements, intensive care utilisation, and selected laboratory biomarkers measured during clinical deterioration were analysed descriptively. The pattern of missing data was assessed using Little's test for Missing Completely at Random (MCAR). A non-significant result (p>0.05) indicated consistency with the MCAR assumption.

To identify factors associated with severe COVID-19, multivariable logistic regression analysis was performed. Stepwise variable selection was applied to identify variables for inclusion in the final model. Adjusted odds ratios (ORs) with 95% confidence intervals (CIs) were reported to describe the associations between potential risk factors and severe COVID-19 outcomes. The discriminative performance of selected variables and the final multivariable model in identifying severe COVID-19 was evaluated using receiver operating characteristic (ROC) curve analysis.

Complete case analysis was used for the multivariable regression model. To assess the potential impact of exclusions due to missing data, baseline characteristics of participants included in the final regression model were compared with those excluded because of missing data. All statistical analyses were performed using Stata version 16,[8] and a two-sided p value <0.05 was considered statistically significant.

RESULTS

Sample Characteristics

A total of 282 pregnant patients admitted with COVID-19 to HSB from May to August 2021, out of which 66 (23.4%) were severe cases and 216 were non-severe. The mean age of all patients was 30.55 (5.53) with the average BMI of 28.21 (6.43) kg/m^2 (Table I). A total of 77.3% were Malays and the most common comorbidities were diabetes mellitus. Majority of the respondents were non-smokers and in third trimester with 37 as median week of gestation.

Characteristics by COVID-19 Severity

When comparing by severity status, severe patients were older, but the difference was not statistically significant. The percentage of patients with obesity was significantly higher in the severe group (p value=0.001).

The median gestation age at admission was lower among patients with severe COVID-19 A higher percentage of unvaccinated patients in the severe group (90.9%) compared to the non-severe group (81.0%) (p value= 0.026).

Patients with severe COVID-19 presented to hospital at day 6 of illness, compared to the non-severe patients who present at day 4 of illness (p value <0.001). Non-severe disease was defined as clinical stage 1-3 (needing no oxygen therapy), while severe disease comprised clinical stage 4-5 (pneumonia needing variable oxygen therapy). Out of 66 patients with severe COVID-19 (Stage 4 & 5), only 16 of them admitted initially with severe disease, whereas 50 of them came in with initial diagnosis of COVID-19 stage 1& 2 before becoming severely ill (Stage 4&5) afterwards (as depicted in table 1- stage on admission and table 3-highest stage achieved during hospitalisation).

Patients with severe COVID-19 had lower Absolute Lymphocyte Count (ALC) at admission, higher CRP and higher Neutrophil to Lymphocyte Ratio (NLR). About 45.9% of patients with severe COVID-19 has CRP of more than 50 mg/L at admission, compared to only 7.1% in the non-severe group (p value <0.001).

Clinical management and hospital course severe COVID-19 patients

Table II presents the clinical management, and hospital course of severe COVID-19 patients (n=66). More than half required ICU admission, occurred at a median of day 5 after hospitalisation and 9 days from illness onset with deterioration occurring around day 8 of illness.

Eight severe patients had positive blood culture. All of them were mechanically ventilated except for 1 patient who were just on NPO2 (she had CoNS). Meanwhile, among the mechanically ventilated, eleven had positive tracheal aspirate-9 had multi-resistant Acinetobacter baumannii, 1 Pseudomonas aeruginosa and 1 mixed growth.3

The median ICU stay of the patients was 11 days. Among severe cases, a substantial proportion required mechanical ventilation, while others received varying levels of oxygen support, including nasal prongs, face mask, and HFNC. In term of highest oxygen requirements among the patients with severe disease, 42.4% were mechanically ventilated, 33.3% received only NPO2, 13.7% received up to facemask oxygenation and 10.6% had up to HFNC. Median day of receiving oxygen support was 8 days and among the mechanically ventilated patients (n=28), median ventilation was 8 days. Mean D-dimer was highly elevated at 1198.5, however the mean ferritin was normal at 251.

Table I: Sociodemographic, Clinical, and Laboratory Characteristics at Admission and During Clinical Deterioration Among Pregnant Women with COVID-19 by Disease Severity

Variable	Total	Non-severe	Severe	P value
Age, years, mean (SD) (n=282)	30.55 (5.53)	30.20 (5.50)	31.70 (5.50)	0.054
Race				
Malay	218 (77.3%)	166 (76.9%)	52 (78.8%)	
Indian	14 (4.96%)	11 (5.1%)	3 (4.5%)	
Chinese	14 (4.96%)	12 (5.6%)	2 (3.0%)	0.930
Others	3 (1.06%)	2 (0.9%)	1 (1.5%)	
Non-Malaysian	33 (11.7%)	25 (11.6%)	8 (12.1%)	
BMI, mean (SD) (n=200)	28.21 (6.43)	27.34 (±5.90)	30.82 (7.27)	<0.001
Obesity	71 (25.2%)	46 (21.3%)	25 (37.9%)	0.007
Diabetes Mellitus	102 (36.2%)	77 (35.6%)	25 (37.9%)	0.740
Bronchial asthma	14 (5%)	10 (4.6%)	4 (6.1%)	0.640
Pulmonary disease	2 (0.7%)	2 (0.7%)	0 (0.0%)	0.430
Cardiac disease	1 (0.4%)	1 (0.5%)	0 (0.0%)	0.580
Renal disease	4 (1.4%)	4 (1.9%)	0 (0.0%)	0.270
Smoking status (n=157)				
Current	3 (1.9%)	0 (0%)	3 (5%)	0.040
Never	154 (98.1%)	91 (100%)	63 (95%)	
Vaccination status (n=192)				
Not vaccinated	162 (84.4%)	102 (81.0%)	60 (90.9%)	
One dose	17 (8.8%)	11 (8.7%)	6 (9.1%)	0.026
Two doses	13 (6.8%)	13 (10.3%)	0 (0.0%)	
Trimester (n=279)				
First trimester	7 (2.5%)	6 (2.8%)	1 (1.5%)	
Second trimester	15 (5.3%)	6 (2.8%)	9 (13.6%)	0.002
Third trimester	260 (92.2%)	204 (94.4%)	56 (84.8%)	
Gestation week	37 (4)	37 (2)	34 (7)	<0.001
Day of illness	4 (3)	4 (3)	6 (3)	<0.001
COVID-19 Stage at admission				
Stage 1	102 (36.2%)	98 (45.4%)	4 (6.1%)	
Stage 2	156 (55.3%)	112 (51.9%)	44 (66.7%)	
Stage 3	8 (2.8%)	6 (2.8%)	2 (3.0%)	<0.001
Stage 4A	14 (5%)	0 (0%)	14 (21.2%)	
Stage 5A	1 (0.4%)	0 (0%)	1 (1.5%)	
Stage 5B	1 (0.4%)	0 (0%)	1 (1.5%)	
ALC at admission (n=250)	1.38 (1.02- 1.78)	1.5 (1.15-1.93)	1.00 (0.79-1.29)	<0.001
NLR at admission (n=249)	4.15 (3.0-6.1	3.80 (2.73-5.2)	5.93 (4.85-7.3)	<0.001
CRP at admission, No (%), (n=230)				
≥ 50 mg/L	40 (17.4%)	12 (7.1%)	28 (45.9%)	<0.001
CRP at deterioration (n=69)	6.6 (4.7- 9.5)	3.35 (3.2-4.7)	7.80 (6-11)	<0.001
NLR at deterioration (n=69)	6.2 (3.7 – 9.1)	3.66 (3.1-4.4)	6.6 (4.9-9.7)	0.008
Highest creatinine (n=4)	154.5 (82.5- 243.5)	82.5 (58-107)	243.5 (202 -285)	0.120
Highest ALT (n=22)	157 (138- 356)	153 (127 - 433)	159 (140-323)	0.857

Note: Data are presented as median (Q1-Q3) unless stated. ALC: Absolute Lymphocyte Counts, NLR: Neutrophils to Lymphocyte Ratio, ALT: Alanine transaminase

Disease progression during hospitalisation and maternal–foetal outcomes

Among severe cases, dexamethasone was the most commonly used and only 7 patients received Tocilizumab, and none had Baricitinib. Antibiotic use was more frequent in severe than non-severe cases. Overall, in patients with severe COVID-19, most of them were in stage 4A and 5B.

Table II: Clinical management and hospital course among pregnant women with severe COVID-19 (n=66)

Variable	Statistics
Ferritin on deterioration (n=47)	251 (161-406)
D-dimer on deterioration (n=50)	1198.5 (848 -1614)
Highest level of oxygen requirement	
NP	22 (33.3%)
FM	9 (13.7%)
HFNC	7 (10.6%)
MV	28 (42.3%)
Total days on oxygen support (n=66)	8 (4-15)
Total days on HFNC (n=29)	2 (2-3)
Total days on MV (n=28)	8 (3 - 14.5)
Day of illness on deterioration into higher stage (n=59)	8 (7- 9)
ICU admission	35 (53%)
ICU length of stay (days) (n=35)	11 (6 -15)
Day of illness at ICU admission (n=36)	9 (7- 10)
Day of hospitalisation at ICU admission (n=35)	5 (3 - 6)
Positive blood culture (n=8)	
Acinetobacter baumanii (ACBM)	1 (12.5%)
Multi-drug resistant ACBM	3 (37.5%)
Coagulase Negative Staphylococcus	3 (37.5%)
Enterococcus faecium	1 (12.5%)
Positive tracheal aspirate culture (n=11)	
Group 1 beta lactamase pseudomonas	1 (9.1%)
Multi-drug resistant ACBM	9 (81.8%)
Mixed growth	1 (9.1%)

Note: Data are presented as median (Q1-Q3) or number (%), as appropriate. MV: Mechanical Ventilation, HFNC: High Flow Nasal Cannula, NP: Nasal Prongs, FM: Face Mask, O2: Oxygen, ICU: Intensive Care Unit

In terms of complications 50% had Pulmonary Embolism (PE) confirmed by Computed Tomography Pulmonary Angiography (CTPA) 25.8% had liver impairment, 6.1% had pneumothorax and pneumomediastinum, respectively. Only one patient needed Renal Replacement Therapy (RRT), had ACS and pericardial effusion respectively. A total of 40 (60.7%) patients with severe COVID-19 had Organizing Pneumonia (OP), based on CTPA and/or HRCT. A total of 13 (19.7%) patients had mild OP, 7 (10.6%) moderate OP and 20 (30.3%) had severe OP. Surprisingly, 4 (1.9%) patients with non-severe COVID-19 had OP reported on their CT scans.

Severe disease was significantly associated with prolonged hospitalisation and all maternal deaths occurred in the severe group. Among seven maternal death, their foetuses survived except for one stillbirth. In the non-severe group, two miscarriages in early pregnancy, the rest were delivered alive. Obstetric and neonatal outcomes also differed by disease severity.

Table III: Disease progression during hospitalisation and maternal–foetal outcomes

Variable	Total (n=282)	Non-severe (n=216)	Severe (n=66)	P value
Treatment received				
Dexamethasone	61 (21.6%)	6 (2.8%)	55 (83.3%)	
Antibiotics	82 (29.1%)	36 (16.7%)	46 (69.7%)	
Prednisolone	39 (13.8%)	0 (0%)	39 (59.1%)	
Methylprednisolone	38 (13.5%)	0 (0%)	38 (57.6%)	
Hydrocortisone	31 (11%)	1 (0.5%)	30 (45.5%)	
Tocilizumab	7 (2.5%)	0 (0%)	7 (10.6%)	
Highest COVID-19 stage reached				
Stage 1	85 (30.1%)	85 (39.4%)	-	
Stage 2	113 (40.1%)	113(52.3%)	-	
Stage 3	18 (6.4%)	18 (8.3%)	-	
Stage 4A	32 (11.3%)	-	32 (48.5%)	
Stage 5A	6 (2.1%)	-	6 (9.1%)	
Stage 5B	28 (9.9%)	-	28 (42.4%)	
Maternal Complications				
Needing RRT	1 (0.4%)	0 (0%)	1 (1.5%)	
Renal impairment	4 (1.4%)	1 (0.5%)	3 (4.5%)	
Liver impairment	21 (7.4%)	4 (1.9%)	17 (25.8%)	
Pneumothorax	4 (1.4%)	0 (0%)	4 (6.1%)	
Pneumomediastinum	4 (1.4%)	0 (0%)	4 (6.1%)	
Pulmonary embolism	35 (12.4%)	2 (0.9%)	33 (50%)	
Cardiac complications				
ACS	1 (0.4%)	0 (0%)	1 (1.5%)	
Pericardial Effusion	1 (0.4%)	0 (0%)	1 (1.5%)	
Organising pneumonia diagnosed on CTPA/HRCT	44 (15.6%)	4 (1.9%)	40 (60.6%)	
Mild	17 (6%)	4 (1.9%)	13 (19.7%)	
Moderate	7 (2.5%)	0 (0%)	7 (10.6%)	
Severe	20 (7.1%)	0 (0%)	20 (30.3%)	
Total days of hospitalisation, median (Q1-Q3)	8 (6-10)	7 (5.5-8.5)	16 (9-21)	<0.001
Obstetric and foetal outcomes				
Maternal outcome (n=282)				<0.001
Alive	275 (97.5%)	216 (100%)	59 (89.4%)	
Death	7(2.5%)	0 (0%)	7 (10.6%)	
Mode of delivery (n=160)				0.020
Vaginal delivery	35 (21.9%)	31 (26.5%)	4 (9.3%)	
LSCS	125 (78.1%)	86 (73.5%)	39 (90.7%)	
Apgar score, median (Q1-Q3) (n=155)	9 (9-9)	9 (9 – 9)	9 (4.5-9)	<0.001
Gestational age at birth, week, median (Q1-Q3) (n=165)	38 (37-39)	38 (37 - 39)	37 (34-38)	<0.001
Foetal birthweight, kg, mean (SD) (n=153)	2.82 (0.58)	2.89 (0.53)	2.61 (0.68)	0.058
Foetal death (n=212)				
Miscarriage	2 (0.9%)	2 (1.3%)	0 (0%)	
Stillbirth	1 (0.5%)	0 (0%)	1 (1.6%)	
Alive	209 (98.6%)	148 (98.7%)	61 (98.4%)	
Foetal COVID status (n=151)				
Positive	1 (0.6%)	0 (0%)	1 (2.6%)	

Women with severe COVID-19 were more likely to undergo caesarean delivery (p=0.020) and delivered at a significantly earlier gestational age (p<0.001). Neonates born to mothers with severe disease had significantly lower Apgar scores (p<0.001).

Obstetric and neonatal outcomes also differed by disease severity. Women with severe COVID-19 were significantly more likely to undergo caesarean delivery and delivered at a significantly earlier gestational age. Neonates born to mothers with severe disease had significantly lower Apgar scores (p<0.001). Birthweight tended to be lower among severe cases, although this difference did not reach statistical significance.

Table IV : Risk factors for severe COVID-19 in pregnant women (n=159)

Variable	Adjusted OR (95% CI)	SE	z	P value
BMI	1.12 (1.02, 1.22)	0.05	2.33	0.020
CRP ≥50 mg/L at admission	16.96 (3.20, 89.8)	14.42	3.33	0.001
Day of Illness at admission	1.30 (1.05, 1.61)	0.14	2.45	0.014
ALC on admission	0.04 (0.01, 0.22)	0.04	-3.75	<0.001
Vaccination status (yes)	0.24 (0.04, 1.51)	0.22	-1.53	0.127

Note: Adjusted odds ratios were obtained from multivariable logistic regression analysis

Risk factors for severe COVID-19 in pregnant women

Complete case analysis approach was used for multivariable logistic regression in determining the risk factors for severe COVID-19. Five variables were chosen by stepwise method to include in final model. After excluding participants with missing data in any of the variables included in the regression model, 159 participants were retained for the multivariable analysis.

The proportions of data for key variables not included in the regression model were as follows: BMI (21%), vaccination status (17%), day of illness (44%), CRP (31%), and ALC (36%). Characteristics of participants included in and excluded from the multivariable analysis due to missing data were compared. No statistically significant differences were observed for the key factors included in the final model, suggesting that exclusion due to missing data was unlikely to introduce substantial bias. In addition, a non-significant result (p>0.05) of Little's test for Missing Completely at Random (MCAR) indicating that the missing data were consistent with the MCAR assumption.

As shown in Table IV, individuals with a higher BMI were more likely to experience severe COVID-19. Those with a C-reactive protein (CRP) level above 50 were 17 times more likely to develop severe outcomes. Each additional day of illness increased the likelihood of severe outcomes by 30%. Conversely, those with a higher ALC at admission were less likely to develop severe outcomes. Vaccinated pregnant women had reduced odds of developing severe COVID-19, although this association did not reach statistically significant. The area under ROC curve of the regression model was 0.897.

DISCUSSION

One of the significant findings of our study was that the patients with severe disease had a higher BMI compared to the non-severe group. Higher BMI was significantly associated with severe COVID-19 in pregnancy,[9,10] likely reflecting the combined effects of obesity-related chronic inflammation, impaired respiratory mechanics, increased thrombotic risk, and clustering of metabolic comorbidities. Our finding regarding obesity is consistent with the study by Knight et al.[11]

More than 80% of pregnant patients were unvaccinated, particularly among those with severe disease. As pregnant women were excluded from initial COVID-19 vaccine clinical trials, there were no clear early guidelines regarding the safety of COVID-19 vaccination during pregnancy. Consequently, a high proportion of pregnant women remained unvaccinated. In Malaysia, pregnant women at that time were generally advised to defer vaccination until the second trimester or, if already in the third trimester, to postpone vaccination until after delivery, which likely contributed to the low vaccination uptake observed.

Subsequently, multiple studies demonstrated that maternal COVID-19 vaccination has no adverse effects on pregnancy outcomes, and that the benefits of vaccination outweigh potential risks. Vaccination during pregnancy was later recommended by the WHO, the Centres for Disease Control and Prevention (CDC), and major international guidelines, including those from the Royal College of Obstetricians and Gynaecologists

(RCOG), regardless of gestational age.[12,13] In our study, although vaccination appeared to be protective against severe COVID-19, this association did not statistically significance, possibly due to the limited number of vaccinated patients during the study period.

The median day of clinical deterioration occurred on day 8 of illness. This finding is consistent with previous studies describing deterioration patterns in COVID-19, in which the highest risk period occurs between days 5 and 10, with severe disease commonly developing after day 8.[14,15] This highlights the importance of close monitoring for clinical deterioration from day 5 onwards in symptomatic patients with risk factors.

Viral infections are generally associated with a reduction in total lymphocyte count, resulting in lymphopenia, which is a well-recognised feature of COVID-19 infection. Conversely, the NLR increases in states of infection, inflammation, and sepsis. Previous data during the COVID-19 pandemic have identified laboratory markers associated with increased disease severity and mortality, including lymphopenia, neutrophilia, and elevated serum ALT, AST, LDH, CRP, and ferritin levels.[16,17,18] In our study, severe COVID-19 patients had lower ALC, higher NLR, and higher CRP levels (>50 mg/L) on admission. Throughout their illness, severe patients demonstrated lower ALC, higher NLR, and elevated CRP levels compared to those with non-severe disease. However, ferritin levels were found to be normal despite severe disease. This is likely because ferritin is an unreliable biomarker of hyperinflammation in pregnancy due to physiological iron depletion, hepcidin suppression, immune modulation, and plasma volume expansion, resulting in lower ferritin levels even in clinically severe disease. These findings are supported by other international studies.[19,20]

Severe COVID-19 is known to be associated with respiratory failure and acute respiratory distress syndrome (ARDS).[21] In our study, 42% of patients with severe disease required mechanical ventilation, pulmonary embolism (PE) occurred in 50% of patients with severe COVID-19, while 61% developed organising pneumonia and 6% developed pneumothorax or pneumomediastinum. Given the synergistic prothrombotic effects of pregnancy and COVID-19, all severe disease patients underwent CTPA, which may partly explain the exceptionally high rate of PE detection. In addition to heightened diagnostic surveillance, the high prevalence of PE likely reflects combined hypercoagulability from pregnancy and SARS-CoV-2–induced endothelial injury, compounded by critical illness and suboptimal thromboprophylaxis early in the pandemic.

Patients admitted to the ICU were more likely to develop complications compared to non-ICU patients. Liver impairment was also common, with 26% of patients demonstrating elevated liver enzymes. Elevated ALT is recognised as a biochemical marker associated with severe COVID-19. Notably, four patients in the non-severe group (category 3) had organising pneumonia detected incidentally on CT imaging. This aligns with previous study, which reported that 74.5% of patients with organising pneumonia were in the non-severe group, while 25.5% were in the severe group.[22] Patients with severe disease demonstrated more extensive consolidations and involvement of multiple lobes, resulting in greater residual lung lesions on follow-up CT scans. This may explain the incidental detection of organising pneumonia in the non-severe group in our study.

Only eight patients with severe COVID-19 had positive blood cultures, three of which grew coagulase-negative staphylococci, likely representing skin contamination. Four patients had *Acinetobacter baumannii* bacteraemia, consistent with opportunistic infection in critically ill patients. Among 28 intubated patients with severe disease, 11 had positive tracheal aspirate cultures. These findings suggest that significant bacterial co-infection is relatively uncommon in COVID-19.

Our study also demonstrated that severe COVID-19 was associated with longer hospitalisation and more than half of patients with severe disease required ICU care. This highlights that severe disease not only causes significant morbidity but also results in increased healthcare utilisation and cost.

Majority of pregnant patients with severe COVID-19

received intravenous dexamethasone, followed by intravenous methylprednisolone, oral prednisolone, or intravenous hydrocortisone. A small number of patients received tocilizumab, while none received baricitinib, as it was not included in the Malaysian COVID-19 treatment guidelines at the time. The guidelines recommended oral prednisolone or intravenous hydrocortisone for pregnant patients who did not require corticosteroids for foetal lung maturation, explaining the high use of dexamethasone in our cohort. Despite limited safety data at the time, clinicians utilised tocilizumab as a rescue therapy in pregnant patients with severe disease refractory to steroids. Importantly, none of the infants born to mothers with severe COVID-19 had congenital anomalies.

Seven pregnant women with severe COVID-19 died; one of these cases was associated with stillbirth, while the remaining foetuses survived following emergency lower segment caesarean section (LSCS). Severe disease was associated with delivery at a lower gestational age, lower birthweight, and lower Apgar scores. The majority of patients underwent LSCS, largely due to the lack of negative-pressure ventilation in labour rooms. Although vaginal delivery is not contraindicated, the perceived increased risk of aerosol generation during the second stage of labour contributed to the preference for LSCS. Prematurity among neonates born to mothers with severe COVID-19 was largely iatrogenic for maternal indications. Lower birthweight and Apgar scores were likely multifactorial, predominantly driven by maternal hypoxia, placental vascular pathology (COVID-19 placentitis), thrombo-inflammation, endothelial dysfunction, placental microthrombosis, and reduced placental perfusion. Of the 209 live-born infants, only one tested positive for COVID-19, indicating that vertical transmission is possible but rare.

Several limitations should be considered when interpreting our findings. First, this was a single-centre study, which may limit generalisability. Secondly, missing data may have affected result accuracy. A complete-case analysis approach was used; although only 159 patients with complete data on BMI, day of illness, vaccination status, CRP, and ALC were included in multivariable logistic regression, Little's MCAR test suggested that missingness was random and unlikely to introduce systematic bias.[23] Comparisons between included and excluded patients showed no significant differences, supporting the MCAR assumption and the appropriateness of complete-case analysis. Finally, the relatively small sample size limits statistical power. Larger, multi-centre studies are needed to validate these findings and improve generalisability.

CONCLUSIONS

Severe COVID-19 in pregnancy is associated with identifiable and potentially modifiable risk factors, including higher BMI, lack of vaccination, and early laboratory markers of inflammation and immune dysregulation. Elevated CRP, lymphopenia, and increased NLR ratio, on admission were associated with disease severity and clinical deterioration. Patients with severe disease experienced higher rates of thrombotic and respiratory complications, prolonged hospitalisation, and adverse maternal and neonatal outcomes, including iatrogenic prematurity, lower birthweight, and reduced Apgar scores.

These findings have direct clinical implications. Early risk stratification using readily available clinical and laboratory parameters may enable timely escalation of care, targeted thromboprophylaxis, and closer foetal surveillance in high-risk pregnant patients.

At a policy level, our results support prioritisation of pregnant women particularly those with obesity or other risk factors for vaccination, early referral, and specialised care pathways during COVID-19 surges. Collectively, severe COVID-19 in pregnancy represents a distinct high -risk clinical entity, where early identification and preventive strategies can mitigate maternal morbidity, reduce healthcare burden, and improve perinatal outcomes.

Competing interests

The authors declare there is no competing interests.

INSTITUTIONAL REVIEW BOARD (ETHIC COMMITTEE)

We obtained approval from the Medical Research and Ethics Committee (MREC) and the Ministry of Health Malaysia (MOH), registered under NMRR ID-22-00994-OKI (IIR).

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