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Original Article

Prediction of Adverse Outcomes among Women in the Third Trimester of Pregnancy with Coronavirus Disease 2019

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ABSTRACT

Background: This study aimed to compare the clinical and laboratory characteristics of two groups of women (favorable and adverse outcome groups) in the third trimester of pregnancy with coronavirus disease 2019 (COVID-19) and to investigate the predictors of specific adverse outcomes.
Materials and Methods: We retrospectively reviewed the medical records of patients hospitalized with COVID-19 between November 2020 and October 2021 at Kyungpook National University Chilgok Hospital. Adverse outcomes were clinically defined using the Novel Coronavirus Pneumonia Emergency Response Epidemiology Team criteria. The group without adverse outcomes was defined as the "favorable outcome" group and the rest as the "adverse outcome" group. We compared the clinical characteristics between the two groups and examined the correlation between their laboratory results and adverse outcomes.
Results: Of the 70 pregnant women included, 37 were in their third trimester. No significant differences in clinical characteristics, except the length of hospitalization, were noted between the groups. In laboratory tests conducted immediately after hospitalization, C-reactive protein (CRP) (1.0 [0.3 - 1.4] *vs.* 2.3 [1.3 - 3.6], $P = 0.001$) and ferritin (25.0 [14.5 - 34.5] *vs.* 53.1 [36.0 - 98.0], $P < 0.03$) levels were significantly different between the groups. Logistic regression analysis revealed that CRP (odds ratio [OR]: 2.26; 95% confidence interval [CI]: 1.09 - 5.51, $P = 0.040$) and ferritin (OR: 1.06; 95% CI: 1.01 - 1.15, $P = 0.047$) levels were predictors of adverse outcomes.
Conclusion: CRP and ferritin levels are associated with poor prognosis and can predict adverse outcomes in women with COVID-19 in the third trimester of pregnancy.

Keywords: Coronavirus disease 2019; Pregnancy trimester, Third; Adverse outcomes; C-reactive protein; Ferritin

INTRODUCTION

After the World Health Organization's declaration of coronavirus disease 2019 (COVID-19) as a pandemic, a global COVID-19 outbreak is ongoing despite vaccination. In a previous

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study, several patients with COVID-19 showed self-limiting manifestations of mild respiratory illness, but some were hospitalized due to life-threatening organ dysfunction, such as acute respiratory distress syndrome that resulted in high mortality [1]. Researchers consider pregnant women to be a high-risk group for COVID-19 based on accumulated evidence that they are more likely to experience COVID-19 complications than non-pregnant women [2]. According to recent data from the Centers for Disease Control and Prevention, pregnant women are at a greater risk of requiring intensive care unit (ICU) admission and mechanical ventilation than non-pregnant women of reproductive age [3-5]. Another study by the Public Health Agency of Sweden reported a four-fold increase in the risk of intubation in pregnant women with COVID-19 than in age-matched controls [6]. Some studies on the severity of COVID-19 in pregnant women have shown conflicting results. Some studies have shown severe COVID-19 outcomes in pregnant women, although these adverse outcomes appeared to be associated with underlying conditions, such as advanced age, high body mass index, pre-existing diabetes, and chronic hypertension, rather than the pregnancy itself [7-10].

A recent study revealed that pregnancy significantly increased the risk of severe COVID-19, as defined by standardized criteria, such as the World Health Organization Ordinal Scale for Clinical Improvement (WHOOSCI) and the Novel Coronavirus Pneumonia Emergency Response Epidemiology Team (NCPERET) [11] criteria. However, there are rare data on prognosis determination and prediction of disease progression among pregnant women with COVID-19, especially during the third trimester of pregnancy. Physical changes occur more in the third trimester of pregnancy than in the first and second trimesters, which cause respiratory symptoms in pregnant women. In addition, the condition of the mother, who is at imminent delivery, can have a close effect on the fetus.

Therefore, we aimed to compare the maternal clinical symptoms, pregnancy-related complications, and prognosis of newborn infants by dividing the Korean mothers with COVID-19 in the third trimester of pregnancy into two groups according to the severity of outcomes at a single tertiary center. Additionally, among the maternal characteristics and various factors assessed at the time of hospitalization, we investigated the factors that predicted disease progression of COVID-19 in the third trimester of pregnancy.

MATERIALS AND METHODS

1. Data collection

The medical records of 70 pregnant women, hospitalized for COVID-19 and delivered between November 2020 and October 2021 at Kyungpook National University Chilgok Hospital, were retrospectively reviewed. Of these, 33 were excluded from the study because they were in the first or second trimester of pregnancy at the time of the COVID-19 diagnosis. Therefore, 37 pregnant women were included in this study. The COVID-19 diagnosis was confirmed with a positive result in the reverse transcription polymerase chain reaction (RT-PCR) test, regardless of symptoms. The adverse outcome group was determined according to the NCPERET criteria. These constitute standardized clinical criteria that define severe COVID-19, and adverse outcome is defined if any of the following are present: dyspnea, respiratory rate of ≥30 breaths per minute, blood oxygen saturation of ≤93%, a ratio of arterial oxygen partial pressure to fractional inspired oxygen (PaO_2/FiO_2) of <300, or lung infiltrates involving >50% on imaging. The group without any adverse outcomes was defined as the "favorable outcome" group and the rest as the "adverse outcome" group.

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The following characteristics were noted in pregnant women with COVID-19: age, gestational age (GA) at admission, comorbidities (obesity, hypertension, diabetes mellitus, and asthma), presence of clinical symptoms of COVID-19, laboratory and imaging test results on admission, length of hospitalization, oxygen therapy, and ICU admission. Furthermore, we evaluated obstetrical complications, such as non-reassuring fetal heart rate indicating fetal distress, premature rupture of membranes, preterm labor, and postpartum hemorrhage. Moreover, the following neonatal outcomes were assessed: 1- and 5-min APGAR scores, admission to the neonatal ICU, and nasopharyngeal swab results for COVID-19.

2. Ethics statement

This study was approved by the institutional ethics board of Kyungpook National University Chilgok Hospital (2021-04-012). The requirement of informed consent from the study participants was waived because of the retrospective nature of the study.

3. Statistical analysis

All the data were analyzed using R version 4.0.0 (R Foundation for Statistical Computing, Vienna, Austria. URL http://www.R-project.org/) and SPSS version 26.0 (SPSS Inc., Chicago, IL, USA). The clinical characteristics of the two groups were compared using the Chi square test for binary categorical data and Mann–Whitney *U* test for continuous numerical data. The data are presented as percentage of the number of binary categorical variables, mean ± standard deviation (mean ± SD) for continuous variables with a normal distribution, and median and interquartile ranges (median [IQR]) for non-normally distributed data. Statistical *P*-value was set at $P < 0.05$. Logistic regression analyses were conducted to investigate the correlation between laboratory variables and the adverse outcomes of COVID-19. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated. The area under the curve (AUC) was analyzed to test the diagnostic performance of the variables and the strength of the association considered in predicting adverse outcomes.

RESULTS

During this period, 70 pregnant women who tested positive for COVID-19 using RT-PCR were admitted to the COVID-19 isolation ward. Of the 70 women, 37 (52.9%) were in the third trimester of pregnancy. According to the NCPERET criteria, if the patient developed dyspnea that required O_2 supplementation or if more than 50.0% of the lung infiltration is shown in the image, the patient was assigned to the adverse outcomes group. In this study, of the 37 women, 23 (62.2%) were included in favorable outcome group and 14 (37.8%) in the adverse outcome group.

The general characteristics, clinical symptoms of the pregnant women with COVID-19 are presented in **Table 1**. The median GA at admission was approximately 33.6 weeks of gestation (IQR: 29.5 - 36.3). None of the enrolled pregnant women had been vaccinated. Seventeen (45.9%) women were nulliparous. At the time of admission, 24 (64.9%) women were symptomatic with cough (66.5%) being the most common symptom followed by fever (41.7%). Patients in the adverse outcome group had significantly longer hospital stays than those in the favorable outcome group (10.0, IQR: 10.0 - 10.0 *vs.* 11.5, IQR: 10.0 - 14.0, $P = 0.001$). The patients were hospitalized within 1 or 2 days of onset of symptoms because the study was conducted early in the pandemic period. At that time, regardless of whether they were symptomatic or asymptomatic, if they had had contact with an infected person, they would be

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Table 1. General characteristics and clinical symptoms of women with COVID-19 in the third trimester of pregnancy

Characteristics	Total (N = 37)	Favorable outcome (N = 23)	Adverse outcome (N = 14)	*P*-value
Maternal general characteristics				
Maternal age, years	31.8 ± 5.0	31.2 ± 5.6	32.6 ± 3.9	0.411
Nulliparity, n (%)	17 (45.9)	10 (43.5)	7 (50.0)	0.963
GA at admission, weeks	33.6 (29.5 - 36.3)	34.4 (30.4 - 36.2)	32.8 (29.0 - 36.4)	0.521
Vaccination	0	0	0	
Period from the onset of symptoms to admission (day)	1 (0 - 1)	1 (1 - 1)	1 (0 - 1)	0.345
Method of diagnosis				0.862
Contact tracing, n (%)	22 (61.1)	14 (63.6)	8 (57.1)	
Symptomatic, n (%)	11 (30.6)	6 (27.3)	5 (35.7)	
Screening, n (%)	3 (8.2)	2 (9.1)	1 (7.1)	
Clinical symptoms				
Presence of symptoms, n (%)	24 (64.9)	12 (52.2)	12 (85.7)	0.086
Fever, n (%)	10 (41.7)	6 (50.0)	4 (33.3)	0.679
Cough, n (%)	16 (66.7)	9 (75.0)	7 (58.3)	0.665
Myalgia, n (%)	5 (20.8)	1 (8.3)	4 (33.3)	0.315
Headache, n (%)	2 (8.3)	1 (8.3)	1 (8.3)	1.000
Sore throat, n (%)	11 (45.8)	6 (50.0)	5 (41.7)	1.000
Rhinorrhea, n (%)	5 (20.8)	2 (16.7)	3 (25.0)	1.000
Medical comorbidities (%)	6 (16.2)	3 (13.0)	3 (21.4)	0.833
HTN (%)	0 (0.0)	0 (0.0)	0 (0.0)	
DM (%)	0 (0.0)	0 (0.0)	0 (0.0)	
Asthma (%)	1 (2.7)	0 (0.0)	1 (7.1)	0.799
Thyroid disease (%)	3 (8.1)	0 (0.0)	3 (21.4)	0.090
GDM (%)	3 (8.1)	2 (8.7)	1 (7.1)	1.000
Gestational HTN (%)	0 (0.0)	0 (0.0)	0 (0.0)	
Preeclampsia (%)	1 (2.7)	1 (4.3)	0 (0.0)	1.000
Height, cm	160.9 ± 4.9	160.8 ± 5.7	161.1 ± 3.6	0.872
Prepregnant weight, kg	54.0 (50.0 - 62.0)	55.0 (53.0 - 62.0)	51.0 (49.0 - 60.5)	0.168
Current weight, kg	64.0 (61.0 - 73.0)	65.0 (63.5 - 72.0)	62.0 (60.0 - 75.0)	0.301
Prepregnant BMI, kg/m^2	20.1 (18.4 - 22.5)	21.6 (18.6 - 22.8)	19.5 (18.4 - 20.1)	0.423
Current BMI, kg/m^2	25.6 (23.4 - 29.3)	26.5 (25.1 - 28.9)	24.0 (22.5 - 28.8)	0.529
Vital signs at the time of admission				
SBP, mmHg	117.5 ± 13.2	119.7 ± 13.1	113.9 ± 12.9	0.200
DBP, mmHg	75.2 ± 8.9	76.7 ± 5.7	72.8 ± 12.4	0.282
HR, beats/min	94.4 ± 14.7	90.5 ± 13.4	100.8 ± 14.8	0.037[a]
RR, breaths/min	20 (19 - 20)	20 (20 - 20)	20 (18 - 20)	0.316
BT, °C	37 (36.4 - 36.8)	36.5 (36.3 - 36.8)	36.5 (36.4 - 36.8)	0.625
SpO_2, %	98 (97 - 99)	98 (97 - 99)	97 (97 - 98)	0.655
Case to meet NCPERT criteria at the time of admission (%)	5 (13.5)	2 (8.7)	3 (21.4)	0.547

[a]*P*-values of <0.05 are marked with the superscript "a" ([a]).
Adverse outcomes are recorded according to NCPERT criteria, defined by the presence of any of the following: dyspnea, respiratory rate of ≥30 breaths per minute, blood oxygen saturation of ≤93%, a ratio of arterial oxygen partial pressure to fractional inspired oxygen (PaO_2/FiO_2) of <300, or lung infiltrates involving >50% on imaging.
GA, gestational age; HTN, hypertension; DM, diabetes mellitus; GDM, gestational diabetes; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; RR respiratory rate; BT, body temperature; SpO_2, saturation of percutaneous oxygen; NCPERT, Novel Coronavirus Pneumonia Emergency Response Epidemiology Team.

tested immediately. However, no significant differences in basal characteristics, such as maternal age, parity, GA at the time of diagnosis of COVID-19, and infection route were observed between the two groups. The adverse outcome group had a higher rate of symptomatic complaints at the time of admission; however, this difference was statistically insignificant.

The initial chest imaging and laboratory findings of the two groups are compared in **Table 2**. The adverse outcome group showed some images of possible pneumonia or pneumonia at the time of hospitalization compared with the favorable outcome group, although this had a low statistical significance (8.7% *vs.* 21.4%, $P = 0.547$). In the adverse outcome group, white blood cell, absolute neutrophil, and lymphocyte counts were low, although this was statistically

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Table 2. Comparison of initial chest imaging and laboratory findings between the study groups

Initial findings	Favorable outcome (N = 23)	Adverse outcome (N = 14)	*P*-value
Initial chest image			
Pneumonia or suspected pneumonia, n (%)	2 (8.7)	3 (21.4)	0.547
Laboratory findings			
HbA1c (%)	5.3 (5.1 - 5.4)	5.1 (5.0 - 5.3)	0.232
WBC, × 10^3/mm^3	7,027.4 ± 2,244.6	6,142.9 ± 1,539.8	0.203
ANC, × 10^3/mm^3	5,288.7 ± 1,793.2	4,868.6 ± 1,353.3	0.456
Lymphocytes, × 10^3/mm^3	1,044.8 ± 472.1	815.0 ± 313.8	0.116
NLR	5.8 ± 3.0	6.3 ± 3.5	0.620
Ferritin, ng/mL	25.0 (14.5 - 34.5)	53.1 (36.0 - 98.0)	0.003[a]
CRP, mg/dL	1.0 (0.3 - 1.4)	2.3 (1.3 - 3.6)	0.001[a]
OT, U/L	25.0 (19.0 - 28.0)	21.0 (20.0 - 29.0)	0.730
PT, U/L	18.0 (11.5 - 26.5)	14.5 (12.0 - 24.0)	0.433
LDH, U/L	209.0 (183.5 - 239.5)	196.0 (181.0 - 244.0)	1.000
NT-proBNP, pg/mL	39.0 (24.3 - 62.5)	47.4 (32.0 - 74.0)	0.567
Procalcitonin positive (≥0.10), ng/mL	2 (9.5%)	2 (14.3%)	1.000
Lactic acid, mmol/L	1.5 ± 0.5	1.7 ± 0.6	0.434
Fibrinogen, mg/dL	440.5 ± 57.5	445.6 ± 77.9	0.823
D–dimer, μg/mL	1.0 (0.8 - 1.3)	1.0 (0.8 - 1.4)	0.749

[a]*P*-values of <0.05 are marked with the superscript "a" ([a]).
HbA1c, hemoglobin A1c; WBC, whole blood cell; ANC, absolute neutrophil count; NLR, neutrophil-lymphocyte ratio; CRP, complement-reactive protein; OT, oxaloacetic transaminase; PT, pyruvic transaminase; LDH, lactate dehydrogenase; NT-proBNP, N-terminal-pro B-type natriuretic peptide.

insignificant. However, ferritin (25.0 [14.5 - 34.5] *vs.* 53.1 [36.0 - 98.0], *P* <0.003) and C-reactive protein (CRP) (1.0 [0.3 - 1.4] *vs.* 2.3 [1.3 - 3.6], *P* = 0.001) levels were significantly different between the groups.

Logistic regression analysis revealed that CRP (OR: 2.26; 95% CI: 1.09 - 5.51; *P* = 0.040) and ferritin (OR: 1.06; 95% CI: 1.01 - 1.15; *P* = 0.047) levels were predictors of adverse outcomes. **Figure 1** shows the receiver operating characteristic (ROC) curve analysis for adverse outcome predictors in women with COVID-19 in the third trimester of pregnancy. The optimal cut-off point of CRP that predicted adverse outcomes was 2.14 (AUC, 0.82; *P* <0.001), with a sensitivity and specificity of 64.3% and 91.3%, respectively. The optimal cut-off point of

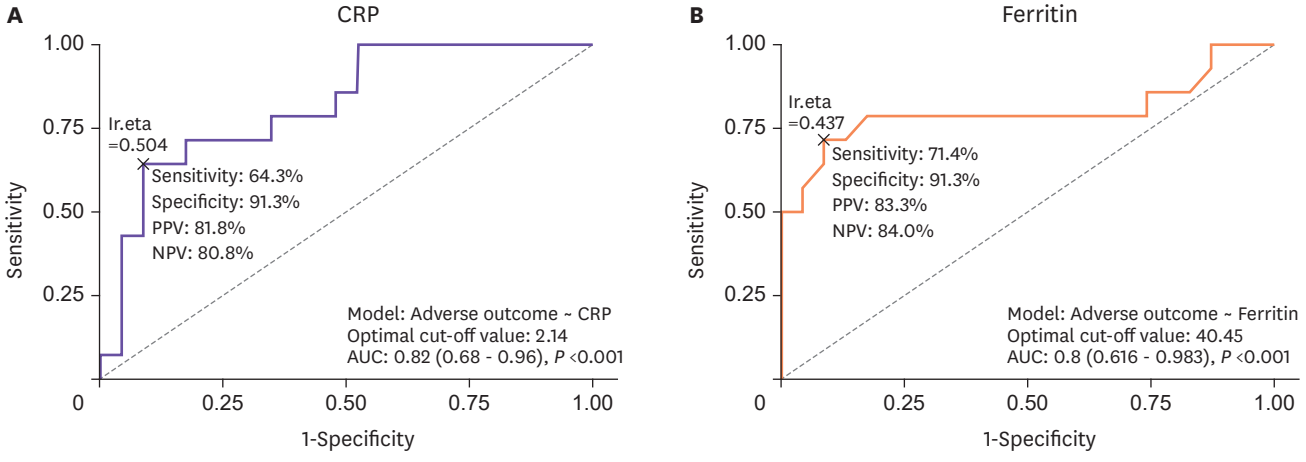

Figure 1. An ROC curve analysis for the predictors of adverse outcomes in women with COVID-19 in the third trimester of pregnancy.
(A) The optimal cut-off point of CRP that predicts adverse outcomes is 2.14 (area under curve [AUC], 0.82; *P* <0.001) with a sensitivity and specificity of 64.3% and 91.3%, respectively. (B) The optimal cut-off point of ferritin that predicts adverse outcomes is 40.45 (AUC, 0.8; *P* <0.001), with a sensitivity and specificity of 71.4% and 91.3%, respectively.
ROC, receiver operating characteristic; COVID-19, coronavirus disease 2019; CRP, complement-reactive protein.

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ferritin that predicted adverse outcomes was 40.45 (AUC, 0.8; P <0.001), with a sensitivity and specificity of 71.4% and 91.3%, respectively.

A comparison of maternal outcomes between the two groups is presented in **Table 3**. Of the 37 patients, 14 (37.8%) experienced adverse outcomes. In addition to steroids used for fetal lung maturation, steroid therapy for 10 days to treat patients with deterioration was also more common in the adverse outcome group.

A comparison of obstetrical and neonatal outcomes between the two groups is presented in **Table 4**. Of the 37 patients, 13 (65.0%) delivered at the time of hospitalization due to COVID-19. The median GA at the time of delivery was 38.1 weeks (IQR: 37.2 – 38.5). There were four (20.0%) cases of preterm births. The GA at delivery did not differ significantly between the groups (38.0, IQR: 37.1 - 39.1) *vs.* 38.1, IQR: 37.3 - 38.3, P = 0.585), and no difference in the rate of preterm birth and delivery during isolation was noted (P = 1.000, P = 0.348). The mode of delivery was mainly cesarean delivery, which was divided into three main sections: women with a previously scarred uterus or requesting to undergo cesarean delivery were defined

Table 3. Comparison of maternal outcomes between the study group

Maternal outcomes	Total (N = 37)	Favorable outcome (N = 23)	Adverse outcome (N = 14)	*P*-value
Length of hospital stay, days	10.0 (10.0 - 11.0)	10.0 (10.0 - 10.0)	11.5 (10.0 - 14.0)	0.001[a]
ICU admission (%)	1 (2.70)	0 (0.0)	1 (7.1)	0.787
Oxygen supplement (%)	10 (27.0)	0 (0.0)	10 (71.4)	<0.001[a]
Nasal prongs	9	0	9	
HFNC	1	0	1	
Intubation and mechanical ventilation	0	0	0	
Lung infiltrates involving >50% on imaging, n (%)	7 (18.9)	0 (0.0)	7 (53.8)	0.001[a]
ACS for lung maturation (%)	16 (43.2)	8 (34.8)	8 (57.1)	0.322
Steroid for 10 days (%)	5 (13.5)	0 (0.0)	5 (35.7)	0.010[a]
Remdesivir (%)	3 (8.1)	0 (0.0)	3 (21.4)	0.090
Regdanvimab (%)	1 (2.7)	0 (0.0)	1 (7.1)	0.799

[a]*P*-values of <0.05 are marked with the superscript "a" ([a]).
ICU, intensive care unit; HFNC, high-flow nasal cannula; ACS, antenatal corticosteroid.

Table 4. Comparison of obstetrical and neonatal outcomes between the study groups

Outcomes	Total (N = 37)	Favorable outcome (N = 23)	Adverse outcome (N = 14)	*P*-value
Obstetrical outcomes	20	10	10	
GA at delivery, weeks	38.1 (37.2 - 38.5)	38.0 (37.1 - 39.1)	38.1 (37.3 - 38.3)	0.585
Delivery during quarantine (%)	13 (65.0)	5 (50.0)	8 (80.0)	0.348
Preterm birth (%)	4 (20.0)	2 (20.0)	2 (20.0)	1.000
Cesarean delivery (%)	18 (90.0)	8 (80.0)	10 (100.0)	0.456
Maternal indication (%)	10 (55.6)	5 (62.5)	5 (50.0)	0.958
Fetal indication	0			
COVID-19 (%)	8 (44.4)	3 (37.5)	5 (50.0)	0.958
Period from diagnosis to delivery	18.3 ± 26.2	37.9 ± 32.6	6.6 ± 6.7	0.030[a]
Neonatal outcomes				
Neonatal weight, g	2,910.8 ± 429.4	2,985.0 ± 429.9	2,836.5 ± 438.4	0.454
Male sex (%)	9 (45.0)	6 (60.0)	3 (30.0)	0.369
A/S at 1 min	7 (7 - 8)	7 (7 - 8)	7 (6 - 8)	0.656
A/S at 5 min	9 (8 - 9)	9 (8 - 9)	9 (8 - 9)	0.574
Oxygen supplement (%)	4 (20.0)	3 (37.5)	1 (10.0)	0.410
COVID-19 (+) (%)	0 (0.0)	0 (0.0)	0 (0.0)	

[a]*P*-values of <0.05 are marked with the superscript "a" ([a]).
GA, gestational age; preterm birth, delivery before GA 37.0 weeks; COVID-19 (+), positive results of nasopharyngeal swab for SARS-CoV-2 in newborns, A/S, APGAR score.

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as cases of maternal indications; those with reasons of fetal distress were defined as cases of fetal indications; and those with COVID-19 infection were defined as cases of COVID-19. Moreover, there was no significant difference in the prognosis of newborns between the two groups, including birth weight, 1- and 5-min APGAR scores, and O_2 administration. In the present study, COVID-19 was not confirmed in newborns.

DISCUSSION

Pregnant women are generally vulnerable to certain viral infections, especially cell-mediated viral infections, such as COVID-19, owing to immunological and physiological changes that occur in pregnancy. As cardiac and pulmonary reserves are reduced, pregnant women are less likely to experience a rapid loss of cardiopulmonary compensation [12, 13]. In the third trimester of pregnancy, the enlarged uterus compresses the lungs, reducing functional residual capacity and expiratory reserve volume. This potentially increases the risk of severe hypoxia, particularly in critically ill patients. Moreover, in the setting of an underlying severe systemic infection, physiological adaptations during labor, delivery, and the immediate postpartum period can aggravate an uncontrolled inflammatory cascade [14-16]. Changes in the immune system of pregnant women are not well understood; however, pregnancy is considered to be an immunocompromised state. Maternal immunity is modified to tolerate fetal antigens by inhibiting cell-mediated immunity. However, certain immune cells, such as natural killer cells, regulatory T cells, and macrophages can also increase during normal pregnancy, creating an inherent immune state that can increase sensitivity to intracellular pathogens, including viruses and bacteria [17,18]. More physiological changes occur in the third trimester of pregnancy than in the first and second trimesters; therefore, the respiratory symptoms are more affected in this period. In addition, the condition of the mother, who is at imminent birth, can have a close effect on the fetus. Therefore, it is important to study the effects of COVID-19 on the third trimester of pregnancy.

Based on previous experiences with severe acute respiratory syndrome, Middle East respiratory syndrome, and influenza, pregnant women are more likely to develop severe pneumonia when infected with respiratory pathogens than non-pregnant women [12, 13, 19]. When COVID-19 severity was determined according to ICU admission and intubation, pregnant women were found to be more susceptible to COVID-19 infection because of the higher incidence of ICU admission and intubation than non-pregnant women [2,3]. However, some studies on the severity of COVID-19 in pregnant women have shown conflicting results. Some studies have shown severe adverse outcomes in pregnant women, although these adverse outcomes seemed to be related to the underlying condition rather than the pregnancy itself. Maternal risk factors associated with severe COVID-19 during pregnancy were advanced age, high body mass index, chronic hypertension, and pre-existing diabetes. Considerable data have shown that the impact of severe COVID-19 is not much different in pregnant women with underlying conditions than in those without underlying conditions and the general population. Immunological and physiological adaptations during pregnancy were thought to make the pregnant women vulnerable to viral infections, but these changes may provide more protection for them [7-10]. A recent study showed that pregnancy significantly increased the risk of severe COVID-19, as defined by clinical criteria such as the WHOOSCI and NCPERET [11] criteria. However, studies comparing cases of severe and non-severe disease progression among pregnant women with COVID-19 are rare; therefore, we attempted to reveal the differences between the groups and predictors of disease progression.

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This study was conducted at a relatively early stage of the pandemic when pregnant women were considered to be at high risk for COVID-19. At that time, even in the absence of symptoms, the investigations were performed using the contact history of the infected person. If symptoms appeared, a PCR test was immediately performed. Once the COVID-19 was confirmed by PCR, hospital admission was mandatory. The quarantine period in the hospital was 10 days for asymptomatic cases, and the quarantine was lifted for symptomatic patients only after assessing for improvement in symptoms. Therefore, the length of hospital stay might have varied depending on the severity of the symptoms. Vaccination for pregnant women has been delayed compared to the general population because it was excluded from the preauthorization clinical trials. At the time of this study, none of the enrolled pregnant women had been vaccinated.

Previous studies have shown that pregnant women infected with COVID-19 are a higher risk of preterm birth [20, 21]. However, in our study, no significant differences were noted in the baseline characteristics of the two groups, and the maternal age and GA did not affect the progression of COVID-19. Additionally, no significant differences in obstetric complications, such as GA at delivery and preterm birth, or in the prognosis of newborns, such as APGAR scores, were observed between the groups. This indicated that COVID-19 in the third trimester of pregnancy did not significantly affect the prognosis of mothers and newborns. Even when the maternal condition worsened with COVID-19, there was no difference noted in the fetal condition or obstetric complications between the groups because of the acute stage of infection. However, the sample size was too small to judge, and a larger study is needed to determine the long-term prognosis throughout pregnancy.

In pregnant women who are vulnerable to infection, it is important to identify the factors that can worsen after COVID-19. Especially for women in the third trimester of pregnancy who are about to give birth, the infection may have a direct or indirect effect on the fetus; therefore, prediction of the patient's condition will help in the management of mother and fetus. Several studies have identified markers in the serum of patients with COVID-19 that play an important role in inflammation during the disease progression. Lymphopenia, defined as a lymphocyte count <1,000/mm^3, can affect the host adaptive immune responses and the clinical process in acute viral infections. Researchers believe that a low lymphocyte count might be a predictive factor for disease deterioration since the first descriptive study in China regarding COVID-19 [22]. Unlike the previous studies, there tended to be no correlation between lymphopenia and adverse outcomes in our study. However, lymphopenia was more frequent in the adverse outcome group than in the favorable outcome group.

Among the tests performed immediately after hospitalization, the maternal serum ferritin and CRP levels showed a statistically significant difference between the two groups, with higher levels in the group with adverse outcomes. Therefore, CRP and ferritin levels may serve as prognostic factor of disease progression. Several studies have reported a direct correlation between the prognosis of COVID-19, hyperferritinemia, and elevated CRP levels in non-pregnant patients [22, 23]. CRP is an acute-phase serum reactant, and its concentration rapidly increases in response to tissue trauma or inflammation [24]. In a study of non-pregnant patients, patients with severe COVID-19 had a significantly higher CRP level than those with non-severe disease [24]. The median CRP levels during pregnancy and labor were higher in pregnant women than in nonpregnant women. Of the non-laboring pregnant women, 95% had CRP levels of ≤1.5 mg/dL, and the GA did not affect the serum CRP levels. Several tests performed to diagnose inflammation cannot be reliably used during pregnancy; however, CRP level could be useful as a predictor of poor prognosis in COVID-19.

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Several studies have reported a direct correlation between COVID-19 prognosis and hyperferritinemia. This suggests that the virus has the potential to interfere with the antiviral function of natural killer cells by utilizing iron metabolism [25, 26]. Ferritin is an iron storage and serum marker that decreases with iron-deficiency anemia. Moreover, ferritin levels increase during viral infection and are used as markers of viral replication [27]. When severe infection occurs, several inflammatory cytokines, such as IL-6, TNF-α, IL-1β, IL-12, and IFN-γ are rapidly produced, stimulating macrophages, Kupffer cells, and hepatocytes to secrete ferritin [28, 29]. In previous studies, high ferritin levels were defined as 500 ng/L or higher [30], and a ferritin concentration of >500 ng/mL was considered to be associated with a mortality rate of 58.0% [31, 32]. However, in this study, no specific value was defined as high ferritin level. However, the difference between the two groups was clear and significant results were obtained in the prediction model.

This study was conducted relatively early in the pandemic period; therefore, it includes the results of tests that were performed in asymptomatic patients or in those who were hospitalized early at the onset of symptoms. Although there were no significant differences in symptoms between the adverse outcomes and favorable outcomes groups, the hematological investigation showed a difference, which could be a predictor of the course of further disease deterioration. However, this study had some limitations. First, it had a small sample size, which limits the generalizability of our findings. A large-scale study is needed to predict prognosis, identify preliminary findings, and evaluate potential specific treatments. Second, only mothers with COVID-19 in their third trimester of pregnancy were included. In the future, the effects of COVID-19 on mothers and newborns should be investigated by analyzing COVID-19 cases throughout pregnancy or during each trimester of pregnancy. This study did not compare pregnant and non-pregnant women, which is consistent with other studies, but a comparison was made between pregnant patients with and without adverse outcomes of COVID-19. Moreover, all hospitalized pregnant women underwent the same laboratory tests and had detailed medical histories, enabling the prediction of their condition at the time of hospitalization and disease progression.

To conclude, CRP and ferritin levels were associated with poor prognosis of COVID-19 in the third trimester of pregnancy. The results imply that even if the symptoms are mild or patients are asymptomatic, an increase in CRP or ferritin levels indicates a high possibility of adverse outcomes; therefore, an active treatment plan should be established.

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