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COVID-19-associated morbidity and mortality outcomes in pregnant patients admitted to intensive care unit

Yoğun bakım ünitesine kabul edilen hamile hastalarda COVID-19 ilişkili morbidite ve mortalite sonuçları

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ABSTRACT

Background: Our study aimed to evaluate the clinical characteristics and maternal-fetal outcomes of pregnant women admitted to the ICU due to COVID-19 pneumonia.
Materials and Methods: Demographic data, presenting complaints, laboratory values, pregnancy outcomes, delivery method, and ICU mortality were recorded.
Results: A total of 10 pregnant patients were admitted to the intensive care unit of our hospital due to SARS-COV-2 infection during the 2-year period. Arterial blood oxygen saturation values measured at admission to the ICU were higher in the surviving patients. Six of the 10 patients died. Only one of the 7 patients requiring invasive mechanical ventilation survived.
Conclusions: We found that COVID-19-infected pregnant women with severe symptoms have several maternal morbidities and poor obstetric outcomes, such as prolonged intensive care unit stay, increased mortality, neonatal deaths, and caserean section.
Keywords: Acute respiratory distress syndrome, COVID-19, Maternal outcomes, Obstetric outcomes

ÖZET

Amaç: Çalışmamız, yoğun bakım ünitesine COVID-19 pnömonisi nedeniyle yatırılan gebe kadınların klinik özelliklerini ve anne-fetal sonuçlarını değerlendirmeyi amaçladı.
Materyal ve Metot: Demografik veriler, başvuru şikayetleri, laboratuvar değerleri, gebelik sonuçları, doğum şekli ve yoğun bakım mortalitesi kaydedildi.
Bulgular: 2 yıllık süreçte SARS-COV-2 enfeksiyonu nedeniyle hastanemizin yoğun bakım ünitesine toplam 10 hamile hasta yatırıldı. Yaşayan hastalarda yoğun bakım ünitesine girişte ölçülen arteriyel kan oksijen satürasyonu değerleri daha yüksekti. 10 hastadan 6'sı hayatını kaybetti. İnvazif mekanik ventilasyon gerektiren 7 hastadan sadece biri hayatta kaldı.
Sonuç: Şiddetli semptomları olan COVID-19 ile enfekte hamile kadınlarda, uzamış yoğun bakım ünitesinde kalış süresi, artmış mortalite, yenidoğan ölümleri ve sezaryen gibi kötü obstetrik sonuçlar ve maternal morbiditelerin olduğunu tespit ettik.
Anahtar Kelimeler: Akut respiratuar distres sendromu, COVID-19, Anne sonuçları, Obstetrik sonuçlar

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INTRODUCTION

The SARS-CoV-2 pandemic, which first emerged in 2019 and has become a serious public health problem, is still ongoing worldwide. The clinical picture of patients infected by the virus may be mild or may progress to a clinical condition that may lead to acute respiratory distress syndrome (ARDS) and death (Zhonghua Liu Xing Bing Xue Za Zhi, 2020; Huang C, et al.,2020). Previous studies reported that pregnant women with COVID-19 are at high risk of severe disease and maternal mortality (Ellington S et al.,2020; Allotey J et al., 2020).

Alterations in the respiratory system result in a predisposition for the progression of infections to severe disease in pregnant women. During pregnancy, the diaphragm rises by about 4 cm due to the uterus, and the functional residual capacity (FRC) decreases by up to 30%. Alterations in the respiratory system that occur are more pronounced in the third trimester. The decrease in the residual capacity causes dyspnea, which becomes more severe, particularly in the third trimester. COVID-19-associated pneumonia in pregnant women is considered a risk factor for adverse outcomes such as perinatal death, preterm delivery, and cesarean delivery in all pregnant women, particularly in the third trimester (Di Mascio D et al., 2020; Chen H et al., 2020; Hui DSC, Zumla A, 2019; Wastnedge EAN et al., 2021; LoMauro A, Aliverti A, 2015).
In the SARS-CoV-1 and MERS-CoV pandemics, it was shown that 50% of pregnant women developing severe acute respiratory syndrome (SARS) were admitted to intensive care units with a mortality rate of up to 25%. In the COVID-19 pandemic, it was found that 9.6% of the infected pregnant women were admitted to intensive care units, with a maternal mortality rate of 1.6% (Wong SF, et al.,2004; Turan O, et al.,2020).
Our study aimed to evaluate the clinical characteristics and maternal-fetal outcomes of pregnant women admitted to the intensive care unit (ICU) due to COVID-19 pneumonia. Our study also aimed to provide related data to clinicians and for future studies.

MATERIALS AND METHODS

Our study was a retrospective, single-center study, and all procedures of the study were performed in compliance with the Helsinki Declaration. Our study included pregnant or postpartum patients aged 18 years or older who required intensive care due to COVID-19 pneumonia between March 1, 2020 and March 31, 2022. The study excluded pregnant women with immunological deficiencies and individuals with negative COVID-19 PCR results. Our ICU was a tertiary care intensive care unit with 42 beds. Patient data were collected from the hospital's medical record system and patient charts. The demographic data, time from PCR positivity to hospital admission, presenting complaints, comorbidities, high-flow nasal cannula (HFNC) requirement, time from ICU admission to intubation, peripheral oxygen saturation (SpO_2), laboratory values, pregnancy outcomes, delivery method (cesarean section, normal vaginal delivery), invasive mechanical ventilation (IMV) requirement, ICU mortality, and length of stay (LOS) in ICU were recorded. SARS COV-2 variant identification was unknown.

Disease severity was assessed according to oxygenation: mild ARDS, $200\ mmHg < PaO_2/FiO_2 \leq 300\ mmHg$ with $PEEP/CPAP \geq 5\ cmH_2O$; moderate ARDS, $100\ mmHg < PaO_2/FiO2 \leq 200\ mmHg$ with $PEEP \geq 5\ cmH_2O$; and severe ARDS, $PaO_2/FiO_2 \leq 100\ mmHg$ with $PEEP \geq 5\ cmH_2O$ (ARDS Definition Task Force; Ranieri VM, et al.,2012).
The use of prone positioning, vasopressors, and inotropes was evaluated. All ICU-admitted pregnant patients were consulted by an obstetrician and a perinatologist.

Patients with ongoing pregnancy were administered lopinavir/ritonavir as an antiviral treatment based on the COVID-19 Treatment Guidelines of the Turkish Ministry of Health. The patients whose pregnancies ended received favipiravir. All patients were unvaccinated.

The clinical courses of the patients after ICU admission are presented separately for each patient. The reasons for the pregnancy outcomes (obstetric reasons/Covid-19-related maternal problems) are presented. The pregnancy outcomes of patients with ongoing pregnancy were followed up. Our study was granted ethics approval by the Ethics Committee for Non-interventional Studies of X University with Approval No. 2021/118.
Data were analyzed using the Statistical Package for the Social Sciences (SPSS) Version 21.0 (IBM Corp, Armonk, NY, USA.). Continuous variables were presented as median, as appropriate. Categorical data are presented as frequencies (n) and percentages (%). The Mann-Whitney U test was used for continuous variables, as appropriate. $p<0.05$ was considered statistically significant.

RESULTS

A total of 10 pregnant patients were admitted to the intensive care unit of our hospital because of SARS-COV-2 infection during the 2-year period. The median age of the patients was 29.5 years. The demographics and clinical characteristics of the patients are presented in Table 1, 2. The flowchart of all patients is presented in Figures 1 and 2.

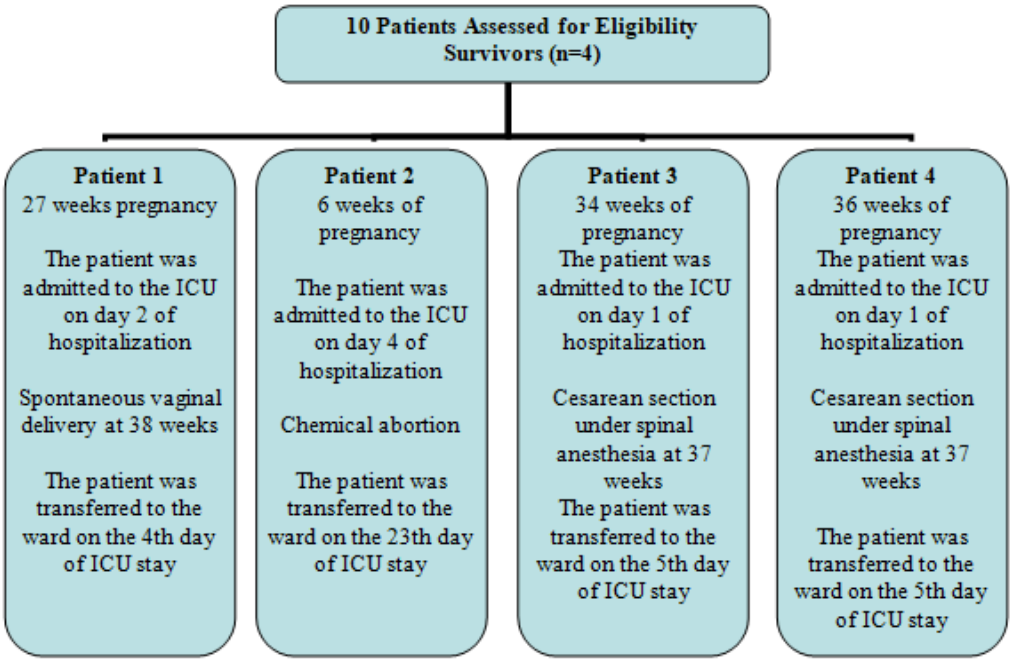

Figure 1. Flow chart of survivors

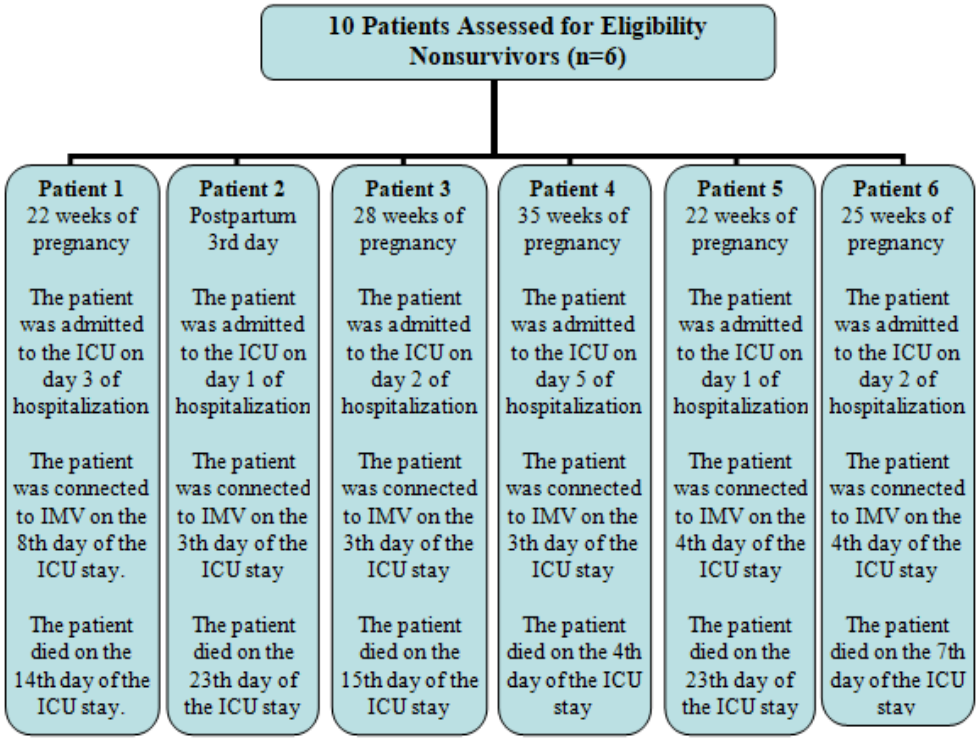

Figure 2. Flowchart of nonsurvivors

The main presenting complaints were cough, malaise/fatigue, and respiratory failure. Six of the 10 patients died (Table 1). The median age of non-surviving pregnant women was 31.5 years. The presenting complaint of most non-surviving patients was respiratory failure. High-flow nasal oxygen treatment was required in 6 patients at admission. Only one of these 6 patients survived. Three patients received only supplemental oxygen with a reservoir mask (6-15 L/min).

Table 1. Demographic and clinical characteristics of pregnant women with COVID-19

	All Patients (n=10)	**Survivors (n=4)**	**Non-Survivors (n=6)**	***p* values**
Median Age (IQR), (min/max)	29.5 (18/40)	28.5 (27/36)	31.5 (18/40)	0.670
LOS (median, min/max)	10.5 (4/23)	5 (4/23)	14.5(4/23)	0.328
Time to apply to hospital (days) (median, min/max)	5 (3/7)	4.5 (3/7)	5 (4/6)	0.507
Gestational Age (week) (Median) (min/max)	27.5 (6/38)	30.5 (6/36)	26.5(22/38)	1.000

p<0,05; Mann-Whitney U test; IQR: Interquartile Range; LOS: Length Of Stay

Table 2. Clinical characteristics of pregnant women with COVID-19

Signs and Symptoms	**All Patients (n=10)**	**Survivors (n=4)**	**Non-Survivors (n=6)**
Fever (n, %)	1(10)	1 (25)	-
Cough (n, %)	8 (80)	4 (100)	4 (66.6)
Fatigue (n, %)	7 (70)	4 (100)	3 (50)
Headache (n, %)	2 (20)	2 (50)	-
Respiratory Failure (n, %)	7 (70)	1 (25)	6 (100)
Pregnancy outcome	**All Patients (n=10)**	**Survivors (n=4)**	**Non-Survivors (n=6)**
Spontaneous abortion (n, %)	1 (10)	1 (25)	
Cesarean section (CS) (n, %)	6 (60)	2 (50)	4 (66.6)
Due to obstetrical indications (CS) (n, %)	3 (30)	1 (25)	2 (33.3)
Due to concern about Covid-19 (CS) (n, %)	3 (30)	1 (25)	2 (33.3)
Neonatal Death (n, %)	2 (20)		2 (33.3)
Perinatal Death (n, %)	1 (10)		1 (16.6)
Pregnancy ongoing (n, %)	2 (20)	2 (50)	
Vaginal delivery (n, %)		1 (25)	
Cesarean section (CS) (n, %)		1 (25)	

Only one of the 7 patients requiring invasive mechanical ventilation survived. This patient was at 6-weeks of gestation and her pregnancy ended in spontaneous abortion. The patient was considered to have cytokine storm and tocilizumab was administered. Upon deterioration in consciousness and development of desaturation on the third day of intensive care stay, the patient was electively intubated and MV was set to achieve a PEEP of 10 cmH2O and a FiO2 of 100 percent. Intermittent prone positioning was performed. The patient' was weaned from MV on day 17 of the intensive care unit stay and was discharged on day 23 of the intensive care unit. The patient was discharged with full recovery afterward follow-up.

Because the other surviving patients did not exhibit respiratory distress or an increase in oxygen demand during the intensive care follow-ups, two patients were taken to the service on the fifth day of intensive care hospitalization and one patient on the fourth day.

The clinical status of 6 patients who did not survive was consistent with severe ARDS ($PaO_2/FiO_2 \leq 100$ mmHg). These patients intermittent prone positioning was performed. HFNC was initiated or intermittent non-invasive ventilation (NIV) was administered to all patients according to their clinical status. Three patients required invasive mechanical ventilation on day 3 of the intensive care unit stay. Invasive mechanical ventilation was performed in two patients on the fourth day and in one patient on the eighth day. Norepinephrine infusion was initiated in all hypotensive patients to keep the mean arterial pressure above 60 mmHg. Despite all efforts, two patients died on the 23rd day, one on the 14th day, one on the 15th day, one on the 7th day, and one on the 4th day.

The pregnancy outcomes are presented in Table 2. The pregnancies of two out of 4 surviving patients were ongoing after discharge. The post-discharge follow-ups of these patients were reviewed. One patient had normal a vaginal delivery at 38 weeks of gestation (10 weeks later). The other patient underwent a cesarean section due to obstetric indications during the ward stay at 36 weeks of gestation. No problems were observed in these infants. Of the other surviving patients, one had a stillbirth, and the other was admitted to the ICU following cesarean section.

The pregnancy outcomes of the patients who were nonsurvivors were as follows. In three patients, three live babies were delivered via cesarean section. A dead baby weighing 920 g was delivered by cesarean section in one patient. Obstetric examination revealed no fetal heartbeat in one patient. One patient had a spontaneous vaginal delivery.

Table 3. Laboratory findings of pregnant women with COVID-19

	All Patients (n=10)	**Survivors (n=4)**	**Non-Survivors (n=6)**	***p* values**
Glucose (mg/dL)	110 (84/169)	108.5 (101/114)	121.5 (84/169)	0.336
Urea (mg/dL)	21.5 (7.2/83)	25 (7.2/83)	20 (8.5/34)	0.670
Creatinine (mg/dL)	0.58 (0.4/1.86)	0.63 (0.5/1.86)	0.56 (0.4/0.7)	0.240
AST (U/L)	32 (18/79)	33 (25/50)	28.5 (18/79)	0.520
ALT (U/L)	24 (16/47)	29 (24/47)	22 (16/39)	0.281
LDH (U/L)	330 (237/996)	488 (272/996)	323 (237/859)	0.522
Sodium (mmol/L)	137 (125/141)	136 (125/138)	138 (133/141)	0.185
Potassium (mmol/L)	3.7 (3.06/5.4)	3.5 (3.06/4.3)	3.9 (3.3/5.4)	0.286
CRP (mg/dL)	5.8 (4.1/9.7)	6.8 (5.3/9.7)	5.14 (4.1/8.1)	0.201
WBC (10^3/uL)	11 (5/21.6)	10 (8.4/21.6)	12.7 (5/19)	0.831
Hemoglobin (g/dL)	11.3 (9.7/13.5)	11.7 (11.3/12.8)	10.7 (9.7/13.5)	0.199
Hematocrit (%)	33.8 (30.5/39)	34.8 (33.7/37.7)	32.9 (30.5/39)	0.201
Neutrophil (10^3/uL)	10 (4.1/18)	8.87 (6.8/18)	11.2 (4.1/17.2)	0.831
Lymphocyte (10^3/uL)	1.05 (0.36/2.37)	1.24 (0.3/2.3)	0.98 (0.5/2)	0.522
Ferritin	212.5 (33/2000)	345 (85/714)	144 (33/2000)	0.394
Procalcitonin	0.18 (0.05/7.9)	0.13 (0.08/7.9)	0.2 (0.05/2.6)	0.669
D-dimer	2.6 (0.21/12.6)	7.74 (1.4/12.6)	0.67 (0.2/7.9)	0.088
Saturation % (in blood gas)	90.5 (80/98)	98 (90/98)	89.5 (75/96)	**0.040**
Lactate (mmol/L) (in blood gas)	2.25 (0.8/3)	1.95 (1.1/3)	2.4 (0.8/3)	0.830

Median (min/max), $p<0,05$; Mann-Whitney U test; AST: Aspartate aminotransferaz; ALT: Alanine aminotransferase; LDH: Lactate dehydrogenase; WBC: White blood cell

The laboratory values are given in Table 3. Arterial blood oxygen saturation values measured at admission to the ICU were higher in the surviving patients (p=0.04). Six patients received antiviral treatment. Only two of the patients receiving antiviral treatment survived.

One patient underwent left tube thoracostomy due to pleural effusion, one patient received thrombolytic treatment due to pulmonary embolism, and one patient required renal replacement therapy.

DISCUSSION

The data presented here represent pregnant women admitted to the intensive care unit in a single center. It was reported that in pregnant women infected with Covid-19, the clinical course and severity of the disease were worse than in nonpregnant women. A surveillance study showed that negative maternal outcomes were more commonly seen at the end of the second trimester and in the third trimester of pregnancy (DeBolt CA, et al. 2021; Knight M, et al. 2020). Our study also observed that pregnant women admitted to the intensive care unit were mostly at the end of the second trimester or in the third trimester of pregnancy. It was observed that COVID-19-associated mortality was high in pregnant women infected with Covid-19 (60%). Moreover, low SpO_2 at admission to the intensive care unit was associated with increased mortality. The most common symptoms observed in pregnant women in our study were consistent with previous studies (Allotey J, et al.,2020; Faraz S, et al.,2022; Hantoushzadeh S, et al., 2020; Sitter M, et al., 2022; Zaigham M, Andersson O. 2020). The main presenting symptom of the non-surviving patients was respiratory failure, while the surviving patients mostly presented with fatigue and headache. The fact that respiratory failure is the major presenting symptom in non-surviving patients shows that it is a serious risk factor for mortality. Perinatal and neonatal deaths were also observed in our study's pregnancy outcomes.

Pregnant women with COVID-19 disease may require intensive care depending on the severity of the disease. During the pandemic period, there has been an increase in the proportion of pregnant women admitted to intensive care units (Allotey J, et al.,2020). A study on pregnant women with COVID-19 reported that 9.6% of the patients were admitted to intensive care units and that most of these patients were in the third trimester of pregnancy. The intensive care unit mortality rate in these patients was 16.4% (10 of 61 patients) (Turan O, et al. 2020). In another study, it was stated that among 385 pregnant women, 17 were admitted to the intensive care unit with one maternal death (Elshafeey F, et al.,2020). Moreover, in a study on 123 COVID-19-positive pregnant women, 30 patients (24.4%) had severe COVID-19 symptoms requiring intensive care unit admission, and 6 of these patients (20%) died (Faraz S, et al.,2022). In two studies reporting higher mortality rates compared to these studies, it was stated that 10 out of 14 and 7 out of 9 patients admitted to ICUs died, respectively (Hantoushzadeh S, et al.,2020; Ríos-Silva M, et al.,2020).

The symptoms caused by COVID-19 disease may vary among pregnant women. They may also lead to the need for intensive care depending on the disease severity. In three studies, 35.2%, 40%, and, 83.6% of the pregnant women admitted to the intensive care units required IMV, respectively (Turan O, et al. 2020; Faraz S, et al.,2022; Elshafeey F, et al. 2020). Our study also found a high mortality rate (60%) and an increased need for IMV (70%), similar to the reported rates in the mentioned studies. Only one of the patients requiring IMV survived. This group of patients admitted to intensive care units due to severe clinical symptoms are observed to have high mortality rates associated with COVID-19-related severe ARDS. Therefore, preventive measures and immunization play a very important role in decreasing the elevated morbidity and mortality risk in the susceptible population of pregnant women. Furthermore, it has been reported in the literature that COVID-19 patients with high levels of IL-6-induced inflammation may benefit from treatment with myo-inositol, and that tocilizumab, an IL-6 receptor inhibitor, can improve oxygenation and clinical outcomes in COVID-19 patients (Bizzarri M, et al.,2020; Bezerra Espinola MS, et al.,2021).
In a study conducted in the UK, three postpartum patients admitted to the intensive care unit had intensive care unit stays of 15, 17, and 35 days. Two of these patients required prone positioning. It was stated that none of these patients experienced cytokine storm and all 3 patients were discharged (Morton S, et al.,2021). Two postpartum patients were included in our study. The patient with mild to moderate symptoms was discharged, while the patient presenting with severe symptoms died. Only one patient in the study population received treatment for cytokine storm.

It was shown that in-hospital death, preterm delivery, cesarean section, preeclampsia, placental separation, and disseminated intravascular coagulation (DIC) were statistically significantly more common in pregnant women with COVID-19 infection compared to normal pregnant women. The neonatal mortality rate was reported to range from 0% to 11.7% (Vergara-Merino L, et al.,2021; Litman EA, et al.,2022; Epelboin S, et al.,2021; Antoun L, et al.,2020; Jafari M, et al.,2021). In addition, severe cases are associated with longer hospital stays and intensive care unit admissions (Faraz S, et al.,2022). The rate of cesarean section was higher in patients in our study, and severe COVID-19 infection was associated with an increased risk of cesarean section.

COVID-19 does not only affect the respiratory system. It was shown that COVID-19 may also cause endothelial inflammation, cardiomyopathy, multiorgan dysfunction, neurological syndromes, and hypercoagulation (Behzad S, et al.,2020). It was observed that thrombotic events were more common in these patients and the potential importance of COVID-19-associated venous thromboembolism (VTE) was emphasized (Turan O, et al.,2020; Zaigham M, Andersson O. 2020; Jering KS, et al.,2020; Sebuhyan M, et al.,2020; Thondapu V, et al.,2021). COVID-19 affects many systems, resulting in increased complications in patients. Our cases are consistent with the literature. Maternal death, neonatal death, perinatal death, pulmonary embolism, stillbirth, and preterm delivery were observed in our cases.

Elevation in some laboratory parameters may be associated with poor prognosis in COVID-19 patients. Elevated CRP and ferritin levels were associated with worse COVID-19 in the third trimester of pregnancy (Kim HM, et al.,2022). In the literature, it has been reported that pregnant women infected with COVID-19 have lower or normal lymphocyte percentage and higher CRP, procalcitonin, and D-dimer levels compared to non-pregnant women. CRP, WBC, ferritin, procalcitonin, and D-dimer levels were high in our patients due to severe COVID-19 (Wang Z, et al.,2020; Chen L, et al.,2020). However, these values were not significant between survivors and non-survivors, because all our patients were pregnant and their clinical conditions were severe.
Some factors limited the research. Our study had no control group and only included a limited number of patients admitted to the intensive care unit due to COVID-19 pneumonia. The study was a single-center, retrospective study.

CONCLUSION

In conclusion, we found that COVID-19-infected pregnant women with severe symptoms have several maternal morbidities and poor obstetric outcomes,

such as prolonged intensive care unit stay, increased mortality, neonatal deaths, and cesarean section. It is important to carefully follow pregnant women in their second and third trimesters of pregnancy and inform them about preventive measures because they are at a high risk of having serious outcomes.

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Ethics Committee Approval: It was conducted with the approval of Malatya Turgut Ozal University

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Conflict of Interest: The authors have no conflicts of interest to declare.

Author Contributions:

Idea/Concept: Ahmet AYDIN, Sevgi KUTLUSOY, Erdinç KOCA **Design:** Ahmet AYDIN **Supervision/Consulting:** Sevgi KUTLUSOY, Erdinç KOCA **Data Collection and/or Processing:** Ahmet AYDIN, Sevgi KUTLUSOY, Erdinç KOCA **Analysis and/or Interpretation:** Ahmet AYDIN **Literature Review:** Ahmet AYDIN **Writing of the Article:** Ahmet AYDIN **Critical Review:** Sevgi KUTLUSOY, Erdinç KOCA **Resources and Funding:** Ahmet AYDIN

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