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ORIGINAL RESEARCH / *ÖZGÜN ARAŞTIRMA*

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Factors Affecting Survival of Pregnant Women with COVID-19 and Our First Extracorporeal Membrane Oxygenation Results

COVID-19 ile Enfekte Gebelerin Sağkalımını Etkileyen Faktörler ve İlk Ekstrakorporeal Membran Oksijenasyonu Sonuçlarımız

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ABSTRACT *Objective:* The purposes of our study were to determine the relationship between coronavirus disease (COVID) pneumonia and mortality and immunization status of patients and to present our first extracorporeal membrane oxygenation (ECMO) experiences by retrospectively evaluating pregnant women.
Materials and Methods: The research was conducted by screening the files of 37 pregnant/postpartum COVID-2019 cases monitored and treated in the intensive care unit between March 1, 2020 and December 1, 2021. The patients' ages, systemic comorbidities, vaccination details, and clinical and laboratory features were recorded and analyzed. The patients were divided into two groups as survivors (group 1; n=17) and exitus ones (group 2; n=20); and the results were compared statistically.
Results: Of 37 patients, 17 (45.9%) survived (group 1) and 20 (54.1%) died (group 2) with a median of 31 gestational weeks and 9 days length of stay in the ICU. ICU admission time [which day of polymerase chain reaction (PCR)+] and cesarean time (which day of PCR+) were 8 days. Nine (24%) patients received ECMO and mechanical ventilation, with 6 (66.6%) exitus and 3 (33.3%) survivors who were discharged from the hospital without sequelae. Of 37 pregnant/postpartum patients, 36 were unvaccinated.
Conclusion: Vaccination should be given priority in pregnant women, and ECMO may be effective in the recovery of oxygenation in pregnant COVID-19 patients.
Keywords: COVID-19, ECMO, pregnancy, vaccines, ICU

ÖZ *Amaç:* Çalışmamızın amacı, gebeleri retrospektif olarak değerlendirerek koronavirüs hastalığı (COVID) pnömonisi ile mortalite, hastaların bağışıklama durumları arasındaki ilişkiyi ortaya koymak ve ilk ekstrakorporeal membran oksijenasyonu (ECMO) deneyimlerimizi sunmaktır.
Gereç ve Yöntem: Araştırma, 1 Mart 2020 ile 1 Aralık 2021 tarihleri arasında yoğun bakım ünitesinde takip ve tedavi edilen toplam 37 gebe/postpartum COVID-2019 olgusunun dosyaları taranarak gerçekleştirildi. Hastaların yaşları, sistemik komorbiditeleri, aşı detayları, klinik ve laboratuvar özellikleri kaydedildi ve analiz edildi. Hastalar sağkalanlar (grup 1; n=17) ve eksitus olanlar (grup 2; n=20) olarak 2 gruba ayrıldı ve sonuçlar istatistiksel olarak karşılaştırıldı.
Bulgular: Çalışmamızda 37 hastanın 17'si (%45,9) hayatta kaldı (grup 1) ve 20'si (%54,1) öldü (grup 2). Medyan gebelik haftası 31 hafta olup, yoğun bakım yatış süresi 9 gündü. Yoğun bakım ünitesine yatış günü [polimeraz zincir reaksiyonu (PZR) pozitifliğinin (+) kaçıncı günü] ve sezeryan süresi [polimeraz zincir reaksiyonu (PZR) pozitifliğinin (+) kaçıncı günü] ortalama 8. gündü. Dokuz (%24) hasta ECMO ve mekanik ventilasyon desteğinde takip edildi, bu hastaların 6'sı (%66,6) eksitus oldu. Üç (%33,3) sağ kalan hasta sekelsiz taburcu edildi. Otuz yedi gebe/postpartum hastanın 36'sı aşısızdı.
Sonuç: Gebelerde aşı ile bağışıklamaya öncelik verilmelidir, ECMO COVID-19(+) gebe hastalarda oksijenlenmenin düzenlenmesinde etkili olabilir.
Anahtar Kelimeler: COVID-19, ECMO, gebelik, aşı, YBÜ

Introduction

The respiratory tract infections observed in the pregnant women may be severer due to the physiological, anatomical, and immunological changes in this group (1). Several studies have shown that the mortality and morbidity of pregnant patients infected with viral agents such as influenza, Middle East respiratory syndrome and severe acute respiratory syndrome caused by H_1N_1 are higher than their peers (2,3).

Although the guide issued by the World Health Organization in March 2020 states that the incidence of novel coronavirus disease-2019 (COVID-19) is relatively low among pregnant women, recent studies have reported serious hypoxia requiring mechanical ventilation (MV), increased mortality and morbidity in the pneumonia cases (4-6). We planned this study considering that descriptive studies, (that include high numbers of patients), to be conducted in this field would decrease maternal and fetal losses, and ensure planning stronger strategies in monitoring and treatment.

In our hospital, which is one of the first pandemic hospitals, 1,302 polymerase chain reaction (PCR) positive COVID-19 cases were monitored from March 1, 2020 to December 1, 2021. Of these pregnant women, 37 were monitored in intensive care unit (ICU). In the present study, we aimed to investigate the relationship between COVID-19 pneumonia and mortality, immunization status of patients and to present our first extracorporeal membrane oxygenation (ECMO) experiences in pregnant women.

Materials and Methods

This single-center, retrospective study was conducted at the University of Health Sciences Turkey, Sancaktepe Şehit Prof. Dr. İlhan Varank Training and Research Hospital Anesthesiology and Reanimation ICU of a tertiary care center between March 1st, 2020 and December 1st, 2021. The files of pregnant/postpartum COVID-19 cases who were treated in the ICU due to COVID-19 pneumonia were reviewed. The patients, who had unproven positive status of PCR analysis, under 18 years of age, referred to an external center due to the lack of ICU beds in our institution, or still being treated in our hospital during the collection of data were excluded. The vaccination details of the included patients were acquired through the electronic data system of the Republic of Turkey, Ministry of Health. During the study period, a total of 1,302 PCR-positive COVID-19 cases were admitted to our hospital. Of these pregnant women, 37 who were monitored in the ICU setting were included. The study was approved by the University of Health Sciences Turkey, Sancaktepe Şehit Prof. Dr. İlhan Varank Training and Research Hospital Non-invasive Clinical Research Ethics Committee (no: 2022-260, date: 12.01.2022) and conducted in accordance with the principles of the Declaration of Helsinki.

Through the electronic data system of our hospital, data including age, systemic comorbidities, on which day of COVID-19 positive status they were admitted to ICU, and if they had ceserean section (C/S), on which day of PCR-positive status they had it, the reason for C/S, the anesthesia method used in C/S, the immunomodulatory drugs, antibiotics, antiviral drugs, anticoagulants used, the dose and length of corticosteroid administration, blood/trachea/urine culture results, laboratory analyses at the time of ICU admission such as white blood cell (WBC) count, C-reactive protein (CRP), procalcitonin, aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase (LDH), creatinine, ferritin, fibrinogen, D-dimer, hemoglobin, hematocrit, platelet count, international normalized ratio (INR), eosinophil count and triglyceride, radiological imaging results, need for oxygen (O_2) support, MV requirement, ECMO requirement, length of ICU stay were recorded and analyzed.

The patients were divided into two groups as survivors (group 1) and non-survivors (group 2); and the results were compared statistically.

In the ICU admission, the standard third-level ICU admission criteria [dyspnea and respiratory distress, respiratory rate over 30, partial pressure of oxygen (PaO_2)/fraction of inspired oxygen (FiO_2) <300, oxygen saturation (SpO_2<90%) or PaO_2<70 mmHg, despite the oxygen therapy of 5 L/min, hypotension, development of acute organ failure, high lactate levels, confusion] were employed. Depending on the patients' clinical status, the conventional oxygen therapies [mask, reservoir, high-flow nasal oxygen (HFNO) and continuous positive airway pressure (CPAP)] and MV were applied. For the patients in whom sufficient oxygenation could not be achieved through MV despite the maximum support, ECMO initiated.

If PaO_2<60 mmHg and/or PaO_2/FiO_2<100 with conventional therapies, HFNO and CPAP were applied. If PaO_2<60 mmHg and/or PaO_2/FiO_2<100 with HFNO and CPAP, invasive MV was applied. For the endotracheally intubated patients in whom sufficient oxygenation could not be achieved through MV less than 7 days, and if they

met one of the following criteria; 1) PaO_2/FiO_2<50 for >3 hours, 2) PaO_2/FiO_2<80 for >6 hours, 3) pH <7.25 with partial carbondioxide pressure (pCO_2)≥60 mmHg, respiratory rate increased to 35 breaths min^{-1}, and plateau pressure ≤32 mmHg despite the maximum ventilator support (FiO_2≥0.80, a tidal volume of 6 mL kg^{-1} of predicted body weight, and a positive end-expiratory pressure ≥10 cm H_2O), ECMO was initiated.

If PaO_2<60 mmHg and/or PaO_2/FiO_2<100 general anestesia was applied in the C/S as anesthesia method.

Statistical Analysis

Statistical analysis was performed using the SPSS version 22.0 software (IBM Corp., Armonk, NY, USA). Descriptive data were expressed in mean ± standard deviation, median (minimum-maximum) or number and frequency, where applicable. The normality distribution of the variables was checked using the Kolmogorov-Smirnov and Shapiro-Wilk. The Student t-test was used to compare normally distributed variables, while the Mann-Whitney U test was used to compare non-normally distributed variables. The Fisher Exact chi-square test, Fisher-Freeman-Halton exact chi-square test, and Continuity (Yates) correction were used to compare the qualitative data. A p-value of <0.05 was considered statistically significant.

Results

During the study, totally 37 COVID positive pregnant women, who were older than 18 years old, were evaluated.

The gestational weeks were ranging from 18 weeks to 38 weeks with an average of 30.08±5.03 and a median of 31 weeks. While the average length of stay (LOS) in the service before the transfer to ICU was 4.43±2.62 days with a median of 4 days, 2 patients were admitted directly to the ICU due to maternal hypoxia after emergency application to the hospital. The ICU LOS was ranging from 1 to 70 days with an average of 14.48±14.07 and a median of 9 days. The total LOS in hospital was ranging from 3 to 72 days with an average of 22.27±14.90 and a median of 18 days. Of the pregnant women in the study, 20 (54.1%) became ex.

Of 37 pregnant/postpartum patients, 36 were unvaccinated. One patient received a single dose of messenger ribonucleic acid vaccine 14 days before getting infected. Demographic and clinical characteristics of the patients are shown in Table 1.

Three of six patients in whom C/S was not applied died. The gestational week of the patients who died was below 21 weeks (18, 20, 20 weeks). In the surviving group, the pregnancy of three patients (20, 26, and 33 weeks) continued healthily, and they were discharged from the ICU uneventfully.

According to mortality, there was no statistically significant difference in terms of average ages, gestational weeks, LOS in hospital before the ICU transfer, the day of ICU admission after PCR + result, rates of observing asthma, hypothyroidism, and varicose, C/S etiology and anesthesia methods (spinal/general), and the rates of secondary infections as confirmed by blood culture and trachea culture (p>0.05).

The rate of use of azithromycin in group 1 was statistically significantly higher than group 2 (23.5% vs. 0%, respectively) (p=0.036). The rate of use of cefuroxime axetil in group 2 was statistically significantly higher than group 1 (35% vs. 5.9%, respectively) (p=0.048). There was no statistically significant difference in the rates of the use of other drugs between the two groups (p>0.05).

There was no statistically significant difference between 2 groups in terms of the doses of use of methyl prednisolone (p>0.05). The duration of methyl prednisolone administration in group 1 was ranging from 3 to 10 days with an average of 5.27±1.68 and a median of 5 days. The duration of methylprednisolone administration in group 2 was ranging from 3 to 10 days with an average of 6.39±2.87 and a median of 5 days. There was no statistically significant difference between the durations of methylprednisolone administration by mortality as well (p=0.470) (Table 2).

The rate of MV support in group 2 was statistically significantly higher than group 1 (100% vs. 35.3%, respectively) (p=0.001 and p<0.05) (Table 3). The mean duration of MV support was 7.65±13.8 days in group 1 and 11.05±9.28 in group 2, indicating a statistically significant difference between the groups (p=0.016 and p<0.05).

There was no statistically significant difference between the groups in terms of ECMO rates (p>0.05) (Table 3). The duration of ECMO in group 1 was ranging from 26 to 50 days with an average of 37.0±12.12 and a median of 35 days. The duration of ECMO in group 2 was ranging from 1 to 27 days with an average of 17.83±10.15 and a median of 23 days. When two groups were compared, the duration of ECMO in group 1 was statistically significantly longer than group 2 (p=0.038; p<0.05) (Table 3).

There was no statistically significant difference between the groups in terms of the rates of use of HFNO and CPAP in the ICU (p>0.05).

The computed tomography (CT) involvement was above 50% in 85% of the patients in group 2 while this ratio was 29.4% in group 1, indicating a significant difference between two groups (p<0.001) (Table 3).

According to the laboratory analysis results at the time of ICU admission, the ferritin levels (p=0.007), INR levels (p=0.034), and platelet counts (p=0.019) were statistically significantly higher in group 2. There was no statistically significant difference in the other biochemical parameters between the groups according to mortality (p>0.05) (Table 4).

There was no statistically significant difference between group 1 and group 2 in terms of ICU LOS and total LOS in hospital (p>0.05) (Table 5).

Discussion

In the present study, we investigated the relationship between COVID-19 pneumonia and mortality and reported our first ECMO experiences in pregnant women during the pandemic. Of the cases, 45.9% (n=17) survived, while 31.03% of the patients required MV support (MV, MV + ECMO). Despite conventional oxygen therapy, these patients needed to be transferred to ICU due to hypoxia and dyspnea. Totally 26 patients were monitored with MV. Thoracic CT of non-survivors showed bilateral widespread ground-glass opacities, and all of these patients were monitored under the MV support. The ECMO (24%) was needed in nine patients who could not reach the target SpO_2 despite maximum MV support. Of these patients, six (66.6%) died and three (33.3%) were discharged without any sequelae. Of 37 pregnant/postpartum patients monitored in the ICU, 36 were unvaccinated. One patient had taken a single dose of mRNA vaccine 14 days before becoming COVID PCR positivity;

Table 1. Demographic and clinical characteristics of patients

		Group 1 (n=17)	Group 2 (n=20)	Total (n=37)	[1]p-value
		Mean ± SD (median)	Mean ± SD (median)	Mean ± SD (median)	
Age		28.53±4.78 (28)	31.3±5.73 (32.5)	30.03±5.43 (30)	0.138
Gestational week		31.65±4.65 (32)	28.75±5.08 (28)	30.08±5.04 (31)	0.067
Length of stay in the service (before ICU)		3.82±2.9 (3)	4.95±2.31 (5)	4.43±2.62 (4)	0.097
ICU admission time (which day of PCR+)		8.94±2.08 (9)	8.35±2.11 (8)	8.62±2.09 (8)	0.476
C/S time (which day of PCR+)		8.57±1.99 (8.5)	8.71±3.14 (9)	8.65±2.64 (9)	0.984
		n (%)	n (%)	n (%)	
Comorbid diseases	Asthma	2 (11.8%)	1 (5%)	3 (8.1%)	[2]0.584
	Diabetes	0 (0%)	0 (0%)	0 (0%)	-
	Hypertension	0 (0%)	0 (0%)	0 (0%)	-
	Hypothyroidism	3 (17.6%)	1 (5%)	4 (10.8%)	[2]0.315
	Varicose	1 (5.9%)	0 (0%)	1 (2.7%)	[2]0.459
C/S etiology	Not done	3 (17.6%)	3 (15%)	6 (16.2%)	[3]1.000
	Maternal hypoxia	12 (70.6%)	14 (70%)	26 (70.3%)	
	Preeclampsia	2 (11.8%)	3 (15%)	5 (13.5%)	
C/S anesthesia type	Not done	3 (17.6%)	3 (15%)	6 (16.2%)	[3]0.090
	Spinal	13 (76.5%)	10 (50%)	23 (62.2%)	
	General	1 (5.9%)	7 (35%)	8 (21.6%)	
Culture result	Blood culture	6 (35.3%)	10 (50%)	16 (43.2%)	[4]0.571
	Urinary culture	0 (0%)	0 (0%)	0 (0%)	-
	Trachea culture	2 (11.8%)	3 (15%)	5 (13.5%)	[2]1.000

[1]Mann-Whitney U test, [2]Fisher's Exact test, [3]Fisher-Freeman-Halton Exact test, [4]Continuity (Yates) correction, ICU: intensive care unit, C/S: caesarean section, SD: standard deviation

Table 2. Evaluation of drugs used according to patient groups					
		Group 1 (Surviving; n=17)	Group 2 (Exitus; n=20)	Total	
		n (%)	n (%)	n (%)	p-value
Drugs	Azithromycin	4 (23.5%)	0 (0%)	4 (10.8%)	[1]0.036*
	Linezolid	1 (5.9%)	0 (0%)	1 (2.7%)	[1]0.459
	Meropenem	7 (41.2%)	10 (50%)	17 (45.9%)	[2]0.837
	Vancomycin	2 (11.8%)	8 (40%)	10 (27%)	[1]0.073
	Piperacillin/tazobactam	4 (23.5%)	10 (50%)	14 (37.8%)	[2]0.189
	Colistimethate sodium	2 (11.8%)	4 (20%)	6 (16.2%)	[1]0.667
	Cefuroxime axetil	1 (5.9%)	7 (35%)	8 (21.6%)	[1]0.048*
	Clarithromycin	1 (5.9%)	4 (20%)	5 (13.5%)	[1]0.348
	Hydroxychloroquine	2 (11.8%)	1 (5%)	3 (8.1%)	[1]0.584
	Lopinavir/ritonavir	8 (47.1%)	9 (45%)	17 (45.9%)	[2]1.000
	Favipiravir	10 (58.8%)	13 (65%)	23 (62.2%)	[2]0.963
	IVIG	0 (0%)	1 (5%)	1 (2.7%)	[1]1.000
	Plasmapheresis	1 (5.9%)	4 (20%)	5 (13.5%)	[1]0.348
	Tocilizumab	3 (17.6%)	3 (15%)	6 (16.2%)	[1]1.000
	Immune plasma	0 (0%)	1 (5%)	1 (2.7%)	[1]1.000
Anticoagulant	Service	17 (100%)	20 (100%)	37 (100%)	-
	ICU	17 (100%)	20 (100%)	37 (100%)	-
Methylprednisolone	Not administered	6 (35.3%)	2 (10%)	8 (21.6%)	[3]0.220
	40 mg	2 (11.8%)	1 (5%)	3 (8.1%)	
	250 mg	8 (47.1%)	15 (75%)	23 (62.2%)	
	1000 mg	1 (5.9%)	2 (10%)	3 (8.1%)	

[1]Fisher's Exact test, [2]Continuity (Yates) correction, [3]Fisher-Freeman-Halton Exact test, *p<0.05, ICU: intensive care unit, IVIG: intravenous immunoglobuline

Table 3. Evaluation of oxygen therapies and CT results according to patient groups					
		Group 1 (n=17)	Group 2 (n=20)	Total	p
		n (%)	n (%)	n (%)	
MV		6 (35.3%)	20 (100%)	26 (70.3%)	[1]0.001*
ECMO + MV		3 (17.6%)	6 (30%)	9 (24.3%)	[2]0.462
ICU COT	Nasal	9 (52.9%)	0 (0%)	9 (24.3%)	[2]0.000*
	Reservoir	10 (58.8%)	0 (0%)	10 (27%)	[2]0.000*
	HFNO	7 (41.2%)	9 (45%)	16 (43.2%)	[1]1.000
	CPAP	5 (29.4%)	9 (45%)	14 (37.8%)	[1]0.526
Pulmonary involvement on CT	Not taken	3 (17.6%)	3 (15%)	6 (16.2%)	
	Below 50%	9 (52.9%)	0 (0%)	9 (24.3%)	
	Above 50%	5 (29.4%)	17 (85%)	22 (59.5%)	[3]0.000*

[1]Continuity (Yates) correction, [2]Fisher's Exact test, [3]Fisher-Freeman-Halton Exact test, *p<0.05.
ECMO: Extracorporeal membrane oxygenation, MV: mechanical ventilation, ICU: intensive care unit, COT: conventional oxygen therapy, HFNO: high flow nasal oxygen, CPAP: continuous positive airway pressure, CT: computed tomography

Table 4. Biochemical parameters according to patient groups				
	Group 1 (n=17)	Group 2 (n=20)	Total	p-value
	Mean ± SD (median)	Mean ± SD (median)	Mean ± SD (median)	
WBC (4.00-10.00 10^3/uL)	11.76±4.59 (11.42)	15.52±8.58 (12.99)	13.79±7.2 (12)	0.315
CRP (0-5 mg/L)	60.72±61.88 (32.63)	89.83±57.34 (96.5)	76.46±60.44 (72.48)	0.053
Procalcitonin (<0.05 mcgr/L)	0.38±0.36 (0.2)	1.15±2.5 (0.26)	0.79±1.87 (0.23)	0.116
Ferritin (13-150 mcgr/L)	141.68±122.63 (104.7)	256.02±152.73 (238.3)	203.48±149.44 (166.4)	0.007*
D-dimer (0-0.55 mg/L)	5.59±8.28 (3.43)	6.9±9.13 (4.04)	6.3±8.66 (3.65)	0.583
Fibrinogen (200-400 mg/dL)	534.06±112.26 (543)	517.6±213.54 (479.5)	525.16±172.44 (499)	0.253
INR (0.75-1.27)	0.97±0.1 (0.95)	1.08±0.17 (1.07)	1.03±0.15 (0.98)	0.034*
LDH (135-214 U/L)	453±124.47 (460)	541.45±217.81 (462)	500.81±184.18 (460)	0.368
Creatinine (0.5-0.9 mg/dL)	0.49±0.19 (0.46)	0.51±0.28 (0.46)	0.5±0.24 (0.46)	0.915
AST (6-40 U/L)	72.82±97.78 (42)	65.86±81.04 (45)	69.06±87.91 (42)	0.964
ALT (6-33 U/L)	83.32±141.67 (24)	66.29±144.29 (22.5)	74.11±141.36 (23)	0.807
EOS (0.02-0.5 10^3/uL)	0.05±0.06 (0)	0.12±0.21 (0)	0.09±0.16 (0)	0.472
Hemoglobin (12-16 gr/dL)	10.46±1.24 (10.6)	10.16±1.1 (9.9)	10.3±1.16 (10.1)	+0.426
Hematocrit (40-54%)	32.03±2.99 (32)	31.39±3.27 (30.7)	31.68±3.12 (31.3)	+0.542
Platelet (100-400 10^3/uL)	231.65±99.26 (210)	315.55±106.67 (292.5)	277±110.37 (253)	+0.019*

Mann-Whitney U test, +Student t-test, *p<0.05
CRP: C-reactive protein, WBC: white blood cell, AST: aspartate aminotransferase, ALT: alanine aminotransferase, LDH: lactate dehydrogenase, INR: international normalized ratio, EOS: eosinophil, SD: standard deviation

Table 5. Length of ICU stay and total length of hospital stay according to patient groups				
	Group 1 (n=17)	Group 2 (n=20)	Total	p-value
	Mean ± SD (median)	Mean ± SD (median)	Mean ± SD (median)	
ICU length of stay	16±18.4 (9)	13.2±9.3 (10.5)	14.49±14.07 (9)	0.647
Total length of stay in hospital	27.65±18.54 (20)	17.7±9.14 (17.5)	22.27±14.9 (18)	0.099

Mann-Whitney U test, ICU: intensive care unit, SD: standard deviation

she was in the week 21 of her pregnancy, and she died due to multiple organ dysfunction.

Earlier studies conducted on pregnant COVID-19 patients in the United States showed that the pregnant women with COVID-19 and the patients who were not pregnant had similar disease characteristics, with a milder disease severity (7). In other words, COVID-19 was not a risk factor for pregnancy. Another study conducted in the United Kingdom including 91,412 female patients between the ages of 15 and 44 years and of whom 8,207 were pregnant reported that the pregnant women needed hospitalization, ICU, and MV support more (8). However, the aforementioned study excluded non-survivors. Another cohort study conducted by Tekbali et al. (9) in pregnant women within the first four weeks of the pandemic also found that although the hospitalization rate increased, this increase was relatively low compared to the overall population.

On the other hand, studies conducted in the ongoing process have shown that the COVID-19 is associated with increased maternal mortality and morbidity in pregnant women. Mortality in infected pregnant women has been shown to be correlated with ethnicity, gestational week, comorbidity, the need for oxygen at the time of hospital admission, and the need for ICU and MV support. The ICU admission time of the hospitalized pregnant COVID-19 patients varies from 7 to 10 days (10-12). Similarly, in our study, the average time to ICU admission was 8 days.

All pregnant women monitored in the study of Hessami et al. (13) were in the third trimester. Obesity, diabetes mellitus, hypertension, and asthma were the most frequently

observed comorbidities. The maternal age was higher in the deceased cases (13). Another study examining 20 maternal deaths between the ages of 20 and 43 years showed that 11 patients had comorbidities accompanying severe pneumonia. Asthma was the most frequently observed comorbidity (14). In our study, eight patients had comorbidities, although there was no difference between two groups. None of our patients had diabetes and/or hypertension. One patient with asthma history died, while two other patients survived. Three patients, who had hypothyroidism, survived while one other patient died. In the non-survivor group, the mean maternal age was 31.3±5.73 (32.5) years, and the gestational age was 28.75±5.08 (28) weeks. Although there was no statistically significant difference in our study, the maternal age was higher among the non-survivors.

The study conducted by Juan et al. (15), in which they examined the maternal deaths caused by the COVID-19, reported that severe pulmonary damage had been detected in all patients in consequence of CT evaluation, and that the ground glass opacity was the most specific finding. In our study, all of 31 patients who were examined with CT had pulmonary findings, and all of the non-survivors had widespread bilateral infiltration and ground glass opacity (above 50%). However, although they had over 50% CT involvement, five pregnant patients (22%) survived.

Although there is a limited number of data regarding the ECMO application in PCR-confirmed COVID-19 pregnant patients, there are case reports with satisfactory results (16-18). In our study, we applied venous-venous ECMO therapy to nine patients in whom sufficient oxygenation could not be achieved despite the maximum MV support. Eight cases were supported with ECMO after emergency C/S due to maternal hypoxia. The survival rate was 33.3%. In only one of these cases (gestational age: 26 weeks), pregnancy continued; this patient, whose pregnancy continued healthily, was discharged without any sequelae in the room air after discharging her from the ECMO unit. In her follow-up, a healthy and normal infant was born at the 36th week of pregnancy. The mean ECMO duration was longer among survivors, and this duration was shorter in six patients who died, and these patients were lost due to multiple organ dysfunction syndrome caused by prolonged hypoxia and insufficient tissue perfusion. Taken together, we believe that the ECMO support is beneficial in eligible cases to prevent pulmonary damage caused by the COVID-19 and prolonged hypoxia in the lung tissue recovery period.

In our study, the emergency C/S was applied to 70.3% of the patients in the ICU settings due to maternal hypoxia and to 13.5% due to preeclampsia. Three of the six patients to whom C/S was not died. The gestational week of non-surviving patients was below 21 weeks (18, 20, and 20 weeks). All of them had over 50% pulmonary involvement on CT and were under MV support due to maternal hypoxia. In the surviving group, the pregnancy of three patients (20, 26, and 33 weeks) continued healthily; lung involvement on CT was below 50%, and the patients receiving conventional oxygen therapy were discharged from the ICU. The results of the INTERCOVID study comparing 706 COVID-19 positive pregnant women with 1,424 non-infected pregnant patients also indicate that the premature C/S, maternal morbidity and mortality risks in the infected pregnant women have increased due to eclampsia/preeclampsia, fetal distress, or maternal hypoxia (10).

In our study, there were 23 patients, who gave birth to their children under the spinal anesthesia method. During the operation no changes were made about respiratuar support or anesthesia method. But after the surgery 16 of these patients needed MV support due to maternal hypoxia, and 11 of these patients were lost. Based on these findings, we consider that it is necessary to evaluate the clinical condition, arterial blood gas analysis, and oxygenation of the patient while selecting the most appropriate anesthesia method.

In the COVID-19 pneumonia characterized by tachypnea, hypoxaemia, widespread pulmonary infiltration, and diffuse lung damage, acute respiratory distress syndrome (ARDS) is the most frequently observed cause of death (19). The RECOVERY trial recommended the administration of the low-dose dexamethasone for the patients whose oxygen needs were high or for patients under MV support (20). There are also reports suggesting the use of methylprednisolone that has a higher implantation to the lung tissue in ARDS treatment (21,22). In our study, there was no relationship between the use of methylprednisolone and mortality. On the other hand, the corticosteroids may cause increase in the maternal infections due to immunosuppression (23). We consider that the use of corticosteroid may have played a role in the existence of the bacterial secondary infections confirmed with the blood and trachea cultures in the single intensive care rooms of our hospital that was transformed into a pandemic hospital in March 2020 despite the tight control of the Infection Control Committee and the maximum hand

hygiene and isolation measures. Therefore, we consider that a careful cost-benefit analysis in the patient selection and a close follow-up of the patients using corticosteroid against the bacterial secondary infections would be beneficial.

In the clinical follow-up of COVID-19 cases, the laboratory findings are also critical and, thus, INR, D-dimer, fibrinogen, procalcitonin, CRP, WBC, platelet count, and ferritin must be monitored. In our study, the elevated levels of ferritin, INR, and platelet counts were found to be correlated with mortality. However, although these values were higher among non-survivors, the INR and platelet counts were with in normal limits. Overall, we detected low levels of anemia and eosinophil count, as well as high D-dimer, fibrinogen, LDH, WBC, procalcitonin, and CRP levels. Our results are consistent with previous findings in the literature (24,25).

Several studies have reported that vaccination decreases ICU admission and mortality in the course of the COVID-19 infection. It was not different for the pregnant patients, either (26,27). None of the patients who were in the ICU and included in our study was immunized (one patient was vaccinated incompletely, while 36 patients were not vaccinated at all). As there is still no definitive treatment method and antiviral medication for the pregnant patients infected with COVID-19, we consider that immunization by vaccination must be given the top priority in this patient group that may have high mortality rates, as well.

Nonetheless, there are some limitations to this study. Since our study was designed retrospectively, it did not include information on the variant analysis of the infected patients. At the beginning of the pandemic, the clinical results of the pregnant patients were not different when compared to the non-pregnant patients in the same age group. Meanwhile, the dominant variant was the alpha variant. We consider that the later reports of mortality may have been caused by the change in the dominant viral variants. Conducting a variant analysis in the future studies may be a guide in predicting the course of the disease.

As the case number increases, new prognostic factors would be identified in relation to mortality.

Conclusion

In conclusion, advanced age, gestational week, vaccination status, ICU LOS, pulmonary involvement on CT (over 50%), and MV requirement can affect the mortality status of pregnant women infected with COVID-19. In addition, MV combined with ECMO is an effective rescue therapy for pregnant women with COVID-19 pneumonia in the ICU setting. However, anesthesia method for delivery should be selected individually. Further large-scale, prospective studies are warranted to confirm these findings and to gain a better understanding of COVID-19 pneumonia in pregnant women.

Ethics

Ethics Committee Approval: The study was approved by the University of Health Sciences Turkey, Sancaktepe Şehit Prof. Dr. İlhan Varank Training and Research Hospital Non-invasive Clinical Research Ethics Committee (no: 2022-260, date: 12.01.2022) and conducted in accordance with the principles of the Declaration of Helsinki.

Informed Consent: Retrospective study.

Authorship Contributions

Surgical and Medical Practices: S.T., Concept: S.T., Design: S.T., E.A., N.B., Data Collection and Process: S.T., E.E.Ö., Analysis or Interpretation: S.T., E.A., N.B., Literature Search: S.T., Writing: S.T.

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