Pregnant and Peripartum Women with COVID-19 Have High Survival with Extracorporeal Membrane Oxygenation: An Extracorporeal Life Support Organization Registry Analysis

To the Editor:

In the United States, 131,512 pregnant and peripartum women have been affected by coronavirus disease (COVID-19), with 200 associated deaths (0.15%) (1). The hormonal, physiological, and immunomodulatory changes during pregnancy increase susceptibility to respiratory infections and may predispose women to more severe presentations of COVID-19 (2). COVID-19 in pregnant or peripartum women is associated with higher risk for preterm birth, preeclampsia, cesarean delivery, and perinatal death and higher rates of ICU admission, mechanical ventilation, and extracorporeal membrane oxygenation (ECMO) when compared with pregnant or peripartum women without COVID-19 or when compared with nonpregnant women with COVID-19 (2–4). Venovenous (VV) ECMO is an invasive strategy to support oxygenation and ventilation for respiratory failure when conventional therapies have failed. We investigated the survival and complications of pregnant and/or peripartum women with COVID-19 supported with VV ECMO reported to the Extracorporeal Life Support Organization (ELSO) Registry.

This retrospective cohort study included all adult women (≥18 yr) supported on VV ECMO with COVID-19 between January 2020 and April 2021 reported to the ELSO Registry, representing 213 international centers in 36 countries. The primary outcome was survival to hospital discharge, and secondary outcomes were ECMO-related complications in the pregnant and/or peripartum cohort. Pregnant state was collected in the ELSO COVID-19 addendum as a comorbidity. Comorbidities and ECMO-related complications were defined according to ELSO data definitions. This study was granted an exemption by the Baylor College of Medicine Institutional Review Board. We compared pregnant and peripartum patients with the nonpregnant female cohort with categorical variables as exact numbers with percentages and continuous variables as median values with interquartile ranges. Categorical data were analyzed with Fisher's exact or Pearson's chi-square and continuous variables with the Wilcoxon-Mann-Whitney test. Overlap propensity score weighting was performed to investigate the effects of pregnancy on outcomes while adjusting for bias due to potential confounders. Propensity scores for patients being pregnant were estimated using a multivariable logistic regression model with *a priori* identified factors (race, age, pre-ECMO cardiac arrest, admission time to ECMO initiation, driving pressure, mean airway pressure, pH, Pa_{O_2}/FI_{O_2} ratio, asthma, chronic heart disease, diabetes, hypertension, overweight/obesity, disseminated intravascular coagulation, neurological disease, chronic kidney disease, acute kidney injury, acute respiratory distress syndrome, heart failure, myocarditis, pneumonia, pneumothorax, septic shock, nonpulmonary infections, pulmonary vasodilators, buffering agents, and renal replacement therapy). Then, overlap propensity score–weighted logistic regression models were used to compare outcomes between pregnant and nonpregnant patients, in which each patient is weighted by the probability of belonging to the opposite status of her pregnancy (5). Bonferroni correction was used to correct for 10 outcomes in the propensity score analysis, leading to statistical significance if a P value $< 0.05/10 = 0.005$.

There were 1,180 adult female patients supported with VV ECMO for COVID-19, of whom 100 were pregnant or peripartum patients. Univariate analysis showed that pregnant or peripartum patients were younger (32.4 vs. 49.3 yr; $P < 0.01$) and more commonly Hispanic (27.0% vs. 20.7%; odds ratio [OR], 2.33; 95% confidence interval [CI], 1.30–4.2), Black (19.0% vs. 16.7%; OR, 2.04; 95% CI, 1.08–3.87), or Asian (13.0% vs. 8.4%; OR, 2.77; 95% CI, 1.34–5.69) (Table 1). Nonpregnant patients were more likely to have comorbidities. The majority of patients in both groups were proned before ECMO. There were no differences in pre-ECMO status or ECMO duration (Table 1). Comparing the pregnant and/or peripartum cohort with the propensity score–adjusted comparator cohort, the pregnant or peripartum group were more likely to survive to hospital discharge (84% vs. 51.5%; overlap propensity score–weighted OR, 1.18; 95% CI, 1.10–1.27) and suffered fewer ECMO-related renal complications (overlap propensity score–weighted OR, 0.90; 95% CI, 0.84–0.97) (Figure 1). There were no other ECMO-related complication differences between cohorts.

Pregnant and peripartum women with COVID-19 have increased morbidity, ICU admission, mechanical ventilation, need for ECMO support, and mortality when compared with nonpregnant women with COVID-19 (2–4). The Society for Maternal-Fetal Medicine guidelines for the management of severe COVID-19 acute respiratory distress syndrome endorses the use of ECMO for postpartum patients and pregnant women <32 weeks' gestation with refractory hypoxemia, to facilitate *in utero* fetal development (6). The Society for Maternal-Fetal Medicine recommends that ECMO should not be withheld from pregnant patients who may potentially benefit (6). Indeed, our study supports the use of VV ECMO in this population, with increased survival for pregnant and peripartum women with severe COVID-19 who received VV ECMO support compared with a propensity-matched cohort of VV ECMO–supported nonpregnant women with COVID-19.

We report that pregnant and peripartum women supported on ECMO for COVID-19 were more likely to be Hispanic, Black, or Asian when compared with the nonpregnant cohort. Severe maternal morbidity, or unexpected outcomes of pregnancy that result in short- or long-term health consequences, are more prevalent in non-Hispanic Black women and Hispanic women than in White women in the United States (7). During the pandemic, Black and Hispanic pregnant women were

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Table 1. Demographics, Comorbidities, Pre-ECMO Support, and ECMO Run Variables of Pregnant or Peripartum and Nonpregnant Women Supported on VV ECMO for COVID-19

	All Pregnant or Peripartum Patients (*N* = *100*)	All Nonpregnant Female Patients (*N* = *1,080*)	*P* Value
Age, yr	32.4 (28.4–36.8)	49.3 (40.6–57.6)	<0.001
Weight, kg	85.0 (71.4–104.5)	92.0 (77.7–111.0)	0.02
Overweight or obesity	53 (53.0)	735 (68.1)	<0.01
Race/ethnicity			
White	22 (22.0)	426 (39.4)	Reference
Hispanic	27 (27.0)	224 (20.7)	0.005
Black	19 (19.0)	180 (16.7)	0.03
Asian	13 (13.0)	91 (8.4)	0.01
Comorbidities			
Asthma	15 (15.0)	219 (20.3)	0.24
Malignancy	0	27 (2.5)	0.11
Immunocompromised	0	79 (7.3)	<0.01
Chronic heart disease	1 (1.0)	26 (2.4)	0.37
Hypertension	20 (20.0)	392 (36.3)	<0.01
Heart failure	5 (5.0)	35 (3.2)	0.35
Chronic lung disease	0	48 (4.4)	0.03
Diabetes	20 (20.0)	362 (33.5)	<0.01
Neurological disease	11 (11.0)	121 (11.2)	0.95
DIC	3 (3.0)	15 (1.4)	0.21
ARDS	80 (80.0)	910 (84.3)	0.27
Pneumonia	61 (61.0)	665 (61.6)	0.91
Pneumothorax	14 (14.0)	128 (11.9)	0.53
Septic shock	24 (24.0)	282 (26.1)	0.64
Chronic kidney failure	1 (1.0)	31 (2.9)	0.27
Acute kidney failure	13 (13.0)	271 (25.1)	<0.01
Pre-ECMO support			
Invasive ventilation: PEEP, cm H_2O	14 (12–16) (*n* = 89)	14 (11–16) (*n* = 927)	0.97
Invasive ventilation: PIP, cm H_2O	35 (31–38) (*n* = 70)	34 (31–39) (*n* = 730)	0.92
Invasive ventilation: MAP, cm H_2O	23 (19–26) (*n* = 55)	22 (19–25) (*n* = 577)	0.76
Invasive ventilation: driving pressure, cm H_2O	21 (28–26) (*n* = 70)	21 (17–25) (*n* = 709)	0.55
PF ratio	68 (57–87) (*n* = 87)	70 (57–91) (*n* = 876)	0.55
Any pulmonary vasodilators	33 (33.0)	376 (34.8)	0.72
Neuromuscular blockers	71 (71.0)	823 (76.2)	0.25
Prone positioning	58 (58.0)	627 (58.1)	0.99
Intubation to ECMO initiation, h	97 (25–187) (*n* = 87)	77 (25–149) (*n* = 933)	0.30
Pre-ECMO cardiac arrest	3 (3.0)	29 (2.7)	0.90
ECMO run			
Hours ECMO	396 (219–735)	401 (211–688) (*n* = 1,080)	0.65

Definition of abbreviations: ARDS = acute respiratory distress syndrome; COVID-19 = coronavirus disease; DIC = disseminated intravascular coagulation; ECMO = extracorporeal membrane oxygenation; MAP = mean airway pressure; PEEP = positive end-expiratory pressure; PF = $Pa_{O_2}/F_{I_{O_2}}$; PIP = peak inspiratory pressure; VV ECMO = venovenous extracorporeal membrane oxygenation.
Data are shown as median (interquartile range) or *n* (%).

disproportionately affected by COVID-19 (4, 8). These racial and ethnic disparities in severe maternal morbidity and mortality are evident in our study.

Pregnant and peripartum women were less likely to sustain renal complications than the women of reproductive age supported on ECMO in our study. Angiotensin II, progesterone, and increased nitric oxide, produced during pregnancy, increase renal plasma flow by decreasing vascular resistance, which may explain the lower rates of renal injury (9). Although previously considered higher-risk ECMO candidates, pregnant and peripartum women did not sustain more ECMO-related complications, consistent with other reports (10). Importantly, no pregnant or peripartum women sustained limb complications, despite the majority experiencing femoral vein cannulations. Lastly, these pregnant and peripartum women with COVID-19 sustained few bleeding complications and no more than their matched nonpregnant cohort, despite anticoagulation and pregnancy-related coagulation changes.

Our study has limitations. Retrospective, registry-based studies are at risk of selective reporting by centers. Unidentified confounders may be present, despite incorporating a propensity score analysis with overlap weighting by accounting for 28 variables. The pregnancy indicator in the ELSO COVID-19 addendum does not distinguish if actively pregnant or how many weeks postpartum. In addition, the outcomes of the pregnancy and outcomes beyond hospital discharge are not known.

The use of VV ECMO to support pregnant and peripartum women with respiratory failure from COVID-19 was associated with

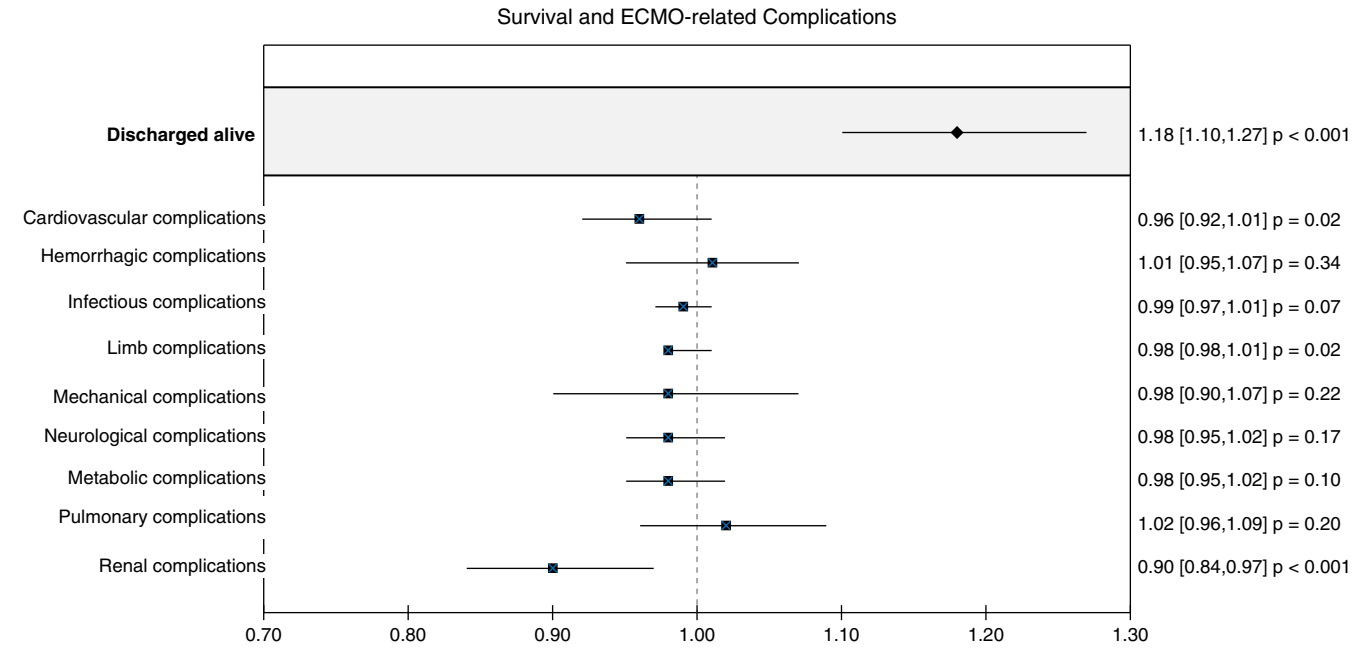

Figure 1. Survival and extracorporeal membrane oxygenation (ECMO)-related complications of the propensity score–matched cohorts, comparing the pregnant and peripartum patients with the nonpregnant female patients. Pregnant and peripartum patients had higher survival (overlap propensity score–weighted odds ratio, 1.18; 95% confidence interval, 1.10–1.27) and suffered fewer ECMO-related renal complications (overlap propensity score–weighted odds ratio, 0.90; 95% confidence interval, 0.84–0.97) than the nonpregnant group.

lower in-hospital mortality and ECMO-related renal complications than those in nonpregnant females. This vulnerable population should be considered for VV ECMO support for COVID-19. ■

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Patients with Obstructive Sleep Apnea on Oronasal Continuous Positive Airway Pressure Breathe Predominantly through the Nose during Natural Sleep

To the Editor:

Obstructive sleep apnea (OSA) is characterized by complete or partial pharyngeal obstruction during sleep, causing recurrent desaturations and arousals (1). Continuous positive airway pressure (CPAP) applied through the nose splints the airway open and abolishes OSA (2). Oronasal CPAP violates this principle, because oral pressure neutralizes positive airway splinting pressure transmitted inside the collapsible portion of the airway (pharynx) delivered by nasal pressure (3, 4). One recent study confirms this hypothesis by showing that the acute change from nasal CPAP to oronasal and oral CPAP during induced sleep resulted in progressive obstruction of the upper airway in patients with OSA (5). In another study, a high percentage of oral breathing was associated with failure of CPAP titration during midazolam-induced sleep (6). A recent meta-analysis showed that oronasal CPAP is associated with higher residual apnea–hypopnea index (AHI), higher pressure, and lower adherence than nasal CPAP (7). Despite all this evidence, oronasal masks are widely used, and several patients with OSA are well adapted to oronasal CPAP in clinical practice (6). We therefore hypothesized that patients with OSA who are well adapted to oronasal CPAP will breathe predominantly through the nose during natural sleep.

Methods

Patients with OSA from the sleep outpatient clinic of the Heart Institute regularly using CPAP with an oronasal mask were invited to this two-step study. The protocol was approved by the ethics committee (SDC 4149/14/129). All patients who evaluated the acute effects of CPAP route change during midazolam-induced sleep (6) were invited. In the present study, the patients underwent a full-night polysomnography (PSG; Embla) for CPAP titration using an oronasal mask with sealed oral and nasal compartment. The flow and pressure of the compartments were determined by two heated pneumotachograph and a calibrated pressure transducer, captured in a data acquisition system (Spike2), that was synchronized to the PSG system. Breaths obtained during the sleep study were individually analyzed using the nasal and oral pneumotachograph signals (5). Based on the absence or presence of flow (>10% of the total flow on the nasal or oral compartment), each breath was classified as nasal, oronasal, or oral. When flow in the oral compartment occurred only during inspiration or expiration, that particular breath was classified as oral inspiration or oral expiration, respectively. Each patient was classified as nasal, oronasal, and oral breather based on the breathing pattern of the majority of breaths (>70%) throughout the sleep study. The breathing pattern was also analyzed according to the state (awake vs. sleep), sleep stage, and position. Paired Student's *t* test and Wilcoxon signed-rank test was used to compare the breathing pattern according to tested covariates.

Results

All 13 patients analyzed previously during induced sleep (6) agreed to participate. One patient was excluded owing to technical problems. The patients ($n = 12$) were on oronasal CPAP for 5 ± 4 years and were predominantly males (62%), age 61 ± 9 years, with body mass index 29.7 ± 3.6 kg/m^2, and had a baseline apnea–hypopnea index of 44 ± 18 events/h. Total sleep duration was 5.7 ± 0.7 hours, and sleep efficiency was $76.4\% \pm 7\%$. CPAP was successfully titrated in all 12 patients at a median of 10 (range, 8–17) cm H_2O. The residual AHI at the best CPAP level was 6 ± 4 events/h. A total of 76,996 breaths were analyzed during sleep (ranging from 4,452 to 7,925 per patient). Eleven patients were classified as nasal breathers (mean nasal breaths, $93.5\% \pm 7.3\%$; range, 75.9–99.9%) (Figure 1). Optimal CPAP of the nasal breathers was

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