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Mortality Risk Assessment in COVID-19 Venovenous Extracorporeal Membrane Oxygenation

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ABSTRACT

BACKGROUND A life-threatening complication of coronavirus disease 2019 (COVID-19) is acute respiratory distress syndrome (ARDS) refractory to conventional management. Venovenous (VV) extracorporeal membrane oxygenation (ECMO) (VV-ECMO) is used to support patients with ARDS in whom conventional management fails. Scoring systems to predict mortality in VV-ECMO remain unvalidated in COVID-19 ARDS. This report describes a large single-center experience with VV-ECMO in COVID-19 and assesses the utility of standard risk calculators.

METHODS A retrospective review of a prospective database of all patients with COVID-19 who underwent VV-ECMO cannulation between March 15 and June 27, 2020 at a single academic center was performed. Demographic, clinical, and ECMO characteristics were collected. The primary outcome was in-hospital mortality; survivor and nonsurvivor cohorts were compared by using univariate and bivariate analyses.

RESULTS Forty patients who had COVID-19 and underwent ECMO were identified. Of the 33 patients (82.5%) in whom ECMO had been discontinued at the time of analysis, 18 patients (54.5%) survived to hospital discharge, and 15 (45.5%) died during ECMO. Nonsurvivors presented with a statistically significant higher Prediction of Survival on ECMO Therapy (PRESET)-Score (mean ± SD, 8.33 ± 0.8 vs 6.17 ± 1.8; $P = .001$). The PRESET score demonstrated accurate mortality prediction. All patients with a PRESET-Score of 6 or lowers survived, and a score of 7 or higher was associated with a dramatic increase in mortality.

CONCLUSIONS These results suggest that favorable outcomes are possible in patients with COVID-19 who undergo ECMO at high-volume centers. This study demonstrated an association between the PRESET-Score and survival in patients with COVID-19 who underwent VV-ECMO. Standard risk calculators may aid in appropriate selection of patients with COVID-19 ARDS for ECMO.

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Coronavirus disease 2019 (COVID-19) was first detected in the United States on January 20, 2020 and was declared a global pandemic by

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Abbreviations and Acronyms

ARDS = acute respiratory distress syndrome
CARDS = coronavirus disease 2019 acute respiratory distress syndrome
COVID-19 = coronavirus disease 2019 (COVID-19)
ECMO = extracorporeal membrane oxygenation
ELSO = Extracorporeal Life Support Organization
Fio_2 = fractional inspired oxygen
$Paco_2$ = arterial partial pressure of carbon dioxide
Pao_2 = arterial partial pressure of oxygen
Pao_2/Fio_2 = ratio of arterial oxygen partial pressure to fractional inspired oxygen
PRESET-Score = Prediction of Survival on ECMO Therapy Score
RESP = Respiratory ECMO Survival Prediction
SAPS = Simplified Acute Physiology
SOFA = Sequential Organ Failure Assessment
VV-ECMO = venovenous extracorporeal membrane oxygenation

the World Health Organization shortly thereafter, on March 11, 2020. Although many patients with COVID-19 are asymptomatic or have only mild symptoms, in a small percentage (5% to 12%), acute respiratory distress syndrome (ARDS) requiring intubation and mechanical ventilation will develop, with a correspondingly high mortality rate (81% to 88%).[1,2]

Since the Conventional Ventilatory Support vs Extracorporeal Membrane Oxygenation for Severe Adult Respiratory Failure (CESAR) trial, venovenous (VV) extracorporeal membrane oxygenation (ECMO) (VV-ECMO) has been widely accepted as support therapy for severe ARDS.[3,4] VV-ECMO use greatly increased after the favorable results reported during the influenza H1N1 pandemic in 2009.[5,6] However, evidence on the utility of ECMO and appropriate patient selection in refractory ARDS resulting from COVID-19 is lacking.

The World Health Organization and the National Institutes of Health designate ECMO as a possible therapy for patients with COVID-19 ARDS (CARDS) without suggesting routine use or providing COVID-19-specific supporting evidence.[7-9] Initial reports from Wuhan, China described poor outcomes using ECMO for COVID-19.[10,11] A pooled analysis of 17 ECMO-treated patients from China reported a mortality of 94.1%.[12] Small studies from Italy and the United States have shown more promising results.[13-15] The mortality reported in larger pooled analyses and registry databases was approximately 45%, similar to that reported with ECMO use for ARDS before the COVID-19 pandemic.[16,17]

Initial reports from China described risk factors for mortality in critically ill patients with COVID-19, including age older than 65 years and a high Sequential Organ Failure Assessment (SOFA) score (Supplemental Tables 1 and 2). No CARDS ECMO studies to date specifically address the previously validated Respiratory ECMO Survival Prediction (RESP), Simplified Acute Physiology (SAPS) II, or Prediction of Survival on ECMO Therapy (PRESET) scores (Supplemental Tables 3 to 5).[14,15,18-23] When resources are scarce, the ability to predict which patients have a reasonable chance of benefiting from ECMO is important, both to individual patient clinical decisions and to health care system and ECMO program management.

This study describes our single-center experience during the initial surge of patients in the COVID-19 pandemic. We hypothesized that application of ECMO support criteria similar to both our institutional guidelines and the Extracorporeal Life Support Organization (ELSO) guidelines would be associated with prediction of survival of patients with CARDS.

PATIENTS AND METHODS

DATA SOURCE. After obtaining approval from our Institutional Review Board (University of Maryland-Baltimore, Baltimore, MD), a retrospective chart review of a prospectively maintained ECMO database was conducted. Adult (age >18 years) patients with CARDS who were supported with ECMO in a dedicated biocontainment unit at a large urban academic medical center between March 15, 2020 and June 27, 2020 were included.

PARTICIPANTS. Criteria for consideration for VV-ECMO included the following: hypercapnia (partial pressure of carbon dioxide [$Paco_2$] >60 mm Hg with a pH <7.25); inability to ventilate adequately with plateau pressure of 30 cm H_2O or less; and severe hypoxemia (ratio of arterial oxygen partial pressure to fractional inspired oxygen [Pao_2/Fio_2] <50 mm Hg with Fio_2 >80% for >3 hours, or Pao_2/Fio_2 ratio <80 mm Hg with Fio_2 >80% for >6 hours) despite maximal ventilatory support and use of adjunctive therapies such as prone positioning, neuromuscular blockade, and inhaled pulmonary vasodilators. The decision to initiate VV-ECMO support was made after a multidisciplinary discussion and bedside evaluation by a cardiothoracic surgeon and 1 or more intensivists.

Relative contraindications to VV-ECMO support included age older than 60 years, body mass index greater than 50 kg/m^2, more than 10 days of mechanical ventilation, multiple organ failure, hemodialysis-dependent chronic renal failure, baseline severe lung disease requiring home oxygen therapy, severe neurologic insult (eg, cerebrovascular accident within 24 to 48 hours, or rapidly expanding hematoma or intracranial bleeding), severe chronic liver disease, acute fulminant hepatic failure, and terminal illness with a low predicted 1-year survival rate.

VV-ECMO cannulation was ultrasound guided and percutaneous. The typical configuration consisted of drainage from the right common femoral vein with return to the right internal jugular vein or rarely the contralateral femoral vein. The circuit consisted of a

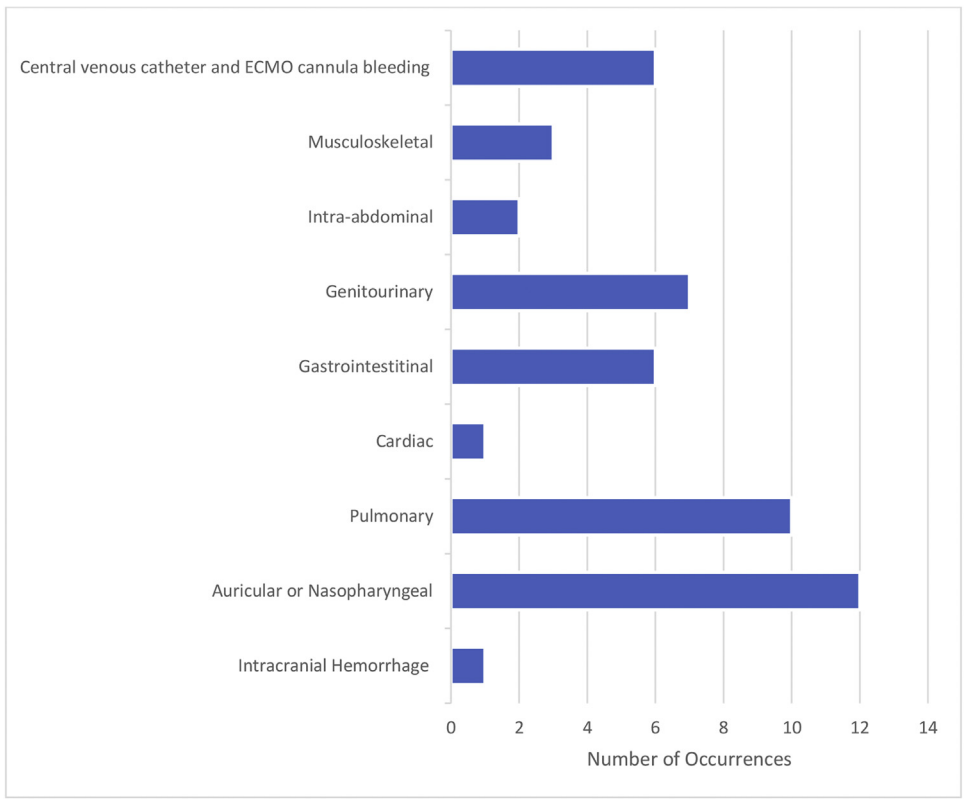

FIGURE 1 Number of bleeding complications in patients with COVID-19 treated with extracorporeal membrane oxygenation (ECMO). Total n = 40. Musculoskeletal bleeding included upper or lower extremity hematoma. Intraabdominal bleeding was retroperitoneal hematoma. Genitourinary bleeding was hematuria. Gastrointestinal included upper or lower gastrointestinal bleeding. Cardiac bleeding was a mediastinal hematoma. Pulmonary complications included hemothorax and tube thoracostomy site or tracheostomy site bleeding. Some patients had more than 1 episode or type of bleeding complication, and all occurrences were included in all relevant categories.

Rotaflow extracorporeal pump (Getinge, Gothenburg, Sweden) and a Quadrox-i adult membrane oxygenator (Getinge), and heat exchanger, and it was managed by an ECMO specialist. Given the increased risk of thrombotic events in patients with COVID-19, anticoagulation with an unfractionated heparin infusion was titrated to achieve a partial thromboplastin time of 60 to 80 seconds for all patients.[24]

A guiding principle for the management strategy of patients with CARDS who were undergoing ECMO was to have the ability to scale ECMO support for the equivalent of a cardiac index of approximately 2.4 L/min/m^2. After ECMO initiation, patients were transitioned to lung-protective ventilator settings to minimize plateau pressure and driving pressure.[25] Positive end-expiratory pressure was titrated to optimize compliance while maintaining plateau pressure of 20 to 25 cm H_2O whenever possible.[26] Driving pressure was maintained at 10 cm H_2O.[27] Refractory hypoxemia despite ECMO support, high positive end-expiratory pressure, and high Fio_2 was managed with rescue modes of ventilation such as airway pressure release ventilation. In these cases, plateau pressure was minimized to 25 cm H_2O or less whenever possible. Prone positioning was used where appropriate to recruit dependent atelectasis and aid with postural drainage of respiratory secretions.[26]

VARIABLES. Data collected included patient demographics, comorbidities, disease symptoms, hospital course, treatments received, ECMO characteristics, and short-term outcomes through hospital discharge and discharge disposition. SOFA, RESP, PRESET-Score, and SAPS II scores were calculated using the described criteria at time of ECMO initiation.[18-20,23] *Bleeding complications* were defined as more than 2 units of packed red blood cells in 6 hours, more than 4 in 24 hours, or documentation of intracranial, auricular, nasopharyngeal, cardiac, pulmonary, gastrointestinal, genitourinary, intraabdominal, musculoskeletal, or

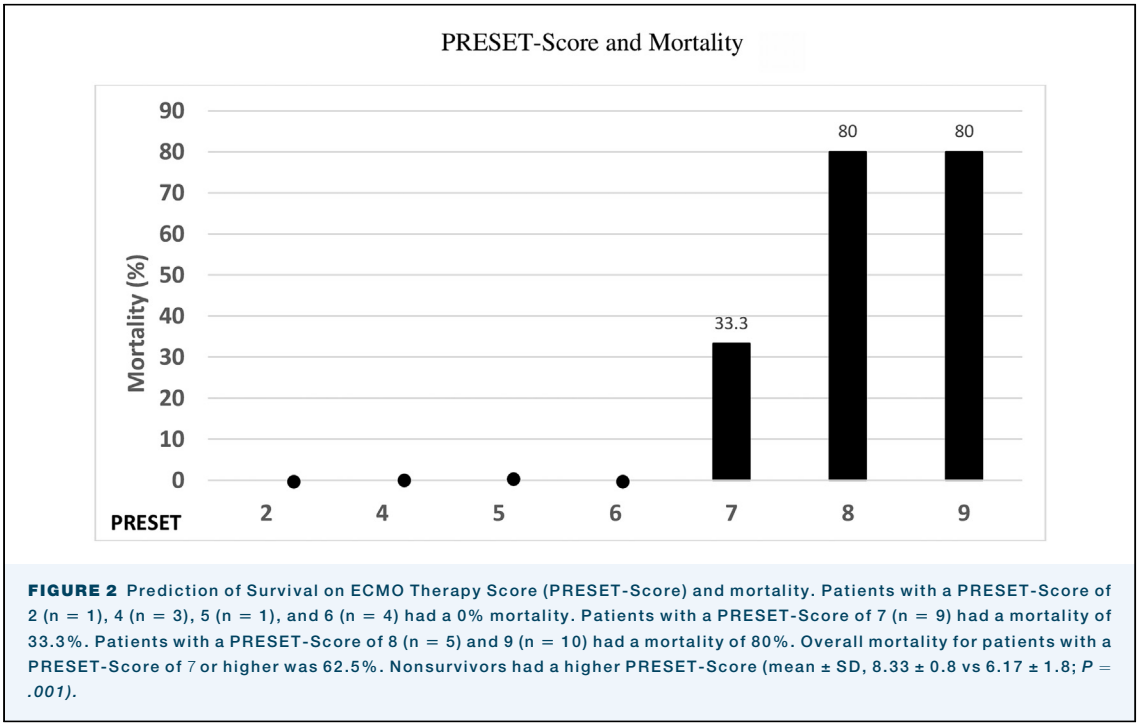

FIGURE 2 Prediction of Survival on ECMO Therapy Score (PRESET-Score) and mortality. Patients with a PRESET-Score of 2 (n = 1), 4 (n = 3), 5 (n = 1), and 6 (n = 4) had a 0% mortality. Patients with a PRESET-Score of 7 (n = 9) had a mortality of 33.3%. Patients with a PRESET-Score of 8 (n = 5) and 9 (n = 10) had a mortality of 80%. Overall mortality for patients with a PRESET-Score of 7 or higher was 62.5%. Nonsurvivors had a higher PRESET-Score (mean ± SD, 8.33 ± 0.8 vs 6.17 ± 1.8; *P = .001).*

cannula site hemorrhage requiring anticoagulation cessation or intervention. *Thrombotic complications* were defined as oxygenator change, circuit change, plasma free hemoglobin level greater than 20 g/dL, clotting within the VV hemofiltration circuit, deep venous thrombus not related to central venous catheter or ECMO cannula, cerebrovascular accidents, or other organ infarcts on imaging. *Days of mechanical ventilation* was defined as time from endotracheal intubation to liberation from mechanical ventilation (extubation or tracheostomy collar >24 hours). *Dynamic compliance* was calculated at cannulation and on the morning of decannulation or death by using the following formula: $\frac{Tidal\ volume\ (mL)}{peak\ pressure\ (cm\ H2O) - PEEP\ (cm\ H2O)}$. All tracheostomies were performed using percutaneous techniques at the bedside.

PRIMARY OUTCOME. The primary outcome was in-hospital mortality.

STATISTICAL ANALYSIS. A descriptive analysis of the entire cohort was performed using mean and SD for continuous variables and proportion (%) for categoric variables. The relationship between categoric variables and in-hospital mortality was assessed using the χ^2 and Fisher exact test. Differences in continuous variables were assessed using analysis of variance. We confirmed the analysis of variance test results with nonparametric tests (Mann-Whitney *U* test and Kruskal Wallis test). A *P* value lower than .05 was considered statistically significant.

RESULTS

Forty patients with CARDS were cannulated for VV-ECMO between March 15 and June 27, 2020. No patients with COVID-19 were supported with VA-ECMO primarily. One patient was initially cannulated for VV-ECMO, which was then reconfigured a few hours later to VV-arterial ECMO and converted back to VV-ECMO within 1 week. Demographics, clinical characteristics, hospital course, ECMO characteristics, and short-term outcomes are detailed in Supplemental Tables 6 and 7. Of note, 32 (80%) of the patients were of Hispanic ethnicity. At the time of analysis on July 17, 2020, of 33 patients (82.5%) who completed ECMO therapy, 18 (54.5%) were decannulated from ECMO and all 18survived to hospital discharge, whereas 15 (45.5%) of the 33 patients died on ECMO. Seven patients (17.5%) remained on ECMO at the time of analysis. Of the 18 patients who survived to hospital discharge, 14 (77.8%) were discharged directly home, and 4 (22.2%) were discharged to a rehabilitation facility.

Heparin-induced thrombocytopenia developed in 5 patients (12.5%), and they were transitioned to a direct thrombin inhibitor titrated to a partial thromboplastin time of 46 to 76 seconds. Bleeding complications were seen in 27 patients (67.5%) and are detailed in Figure 1. Thrombotic complications were seen in 17 patients (43%). There was no difference in any complications in patients with heparin-induced thrombocytopenia compared with the cohort.

Supplemental Tables 8 and 9 display demographics, clinical characteristics, hospital course, ECMO characteristics, and short-term outcomes for survivors and nonsurvivors. Nonsurvivors had a higher PRESET-Score (mean ± SD, 8.33 ± 0.8 vs 6.17 ± 1.8; $P = .001$), were more likely to have received antiretroviral treatment with remdesivir (40% vs 5.6%; $P = .016$), and had a lower RESP score although not statistically significant (2.9 ± 2.1 vs 4.3 ± 1.9; $P = .055$). Nonsurvivors had a higher precannulation $Paco_2$ (69.7 ± 16.7 mm Hg vs 57.9 ± 14.8 mm Hg; $P = .043$), and lactate level (3.4 ± 1.8 mg/dL vs 2 ± 0.5 mg/dL; $P = .003$). Furthermore, nonsurvivors developed more pneumothoraces after cannulation (73.3% vs 27.8%; $P = .009$). Dynamic compliance was similar between groups at time of cannulation (20.5 ± 6.9 vs 21.7 ± 9.7; $P = .684$); however, nonsurvivors never experienced an improvement in compliance as evident by a negative change in dynamic compliance at time of death (−13.3 ± 10.7 vs 21 ± 11.7; $P < .001$).

The most statistically significant predictor of mortality was the PRESET-Score. It demonstrated 100% accuracy, superseding all other risk factors. All patients with a PRESET-Score of 6 or lower survived, and all patients with a score of 7 or higher experienced a dramatic increase in mortality of 62.5%, and up to 80% for those with a PRESET-Score of 8 and 9 (Figure 2).

COMMENT

The COVID-19 pandemic poses an unprecedented challenge for health care systems. Although research into therapeutic options continues, patients with CARDS have high risk of mortality; ECMO remains a support modality for those patients in whom conventional management fails, and it may improve survival.[1,2,16] Given the resource-intensive nature of ECMO, identifying patients most likely to benefit is of great importance. For the COVID-19 pandemic, preliminary guidelines endorse the use of ECMO for patients with severe disease and high predicted mortality.[25] It has been suggested that young patients with minimal comorbidities are the highest priority for ECMO.[28] It seems reasonable that VV-ECMO be offered to patients with CARDS when benefits outweigh risks and a meaningful outcome may be expected.[29,30]

The largest published pooled multicenter analysis of patients with CARDS who underwent ECMO included 331 patients with a reported survival of 54%.[16] A recently published ELSO registry cohort analysis demonstrated a mortality slightly less than 40% in patients with CARDS who underwent ECMO.[17] This finding is similar to the overall 60% survival to discharge or transfer for patients undergoing VV-ECMO in 2019 according to the ELSO registry.

We describe a large US single-center experience of patients with CARDS who were treated with VV-ECMO. Of significance, only 7 patients remain on VV-ECMO at the time of analysis, thus reducing the risk of interim analysis bias. Of the 33 patients who completed their course of ECMO, all 18 (54.5%) decannulated patients survived to discharge. Fifteen patients died on ECMO for a 45.4% mortality rate, in concordance with the current ELSO rate for CARDS. Despite results similar to ELSO rates, our survival is lower than historic performance.[28] This outcome is likely multifactorial and may be related to COVID-19 disease-specific parameters and altered care delivery during a pandemic. As the surge abates, mortality may improve as we approach normal care delivery. Survival may also improve as therapeutic options become better available and understood. Another avenue for improvement is refining ECMO selection criteria for patients with CARDS.

Survival prediction models such as the SAPS II score, although not specific to ECMO, nevertheless have been useful in predicting outcomes in patients who do not have COVID-19 and who undergo ECMO.[31] Predictive models for VV-ECMO survival, such as RESP and PRESET-Score, are validated tools that help clinicians' decision making regarding ECMO candidacy and likelihood of survival.[19,20] However, these tools have not been evaluated in patients with CARDS, and therefore during the pandemic we were not using these scores to aid decision making.

The PRESET-Score was associated with high accuracy for mortality prediction in our cohort of patients with CARDS who underwent ECMO. When initially published, a low PRESET-Score (≤5) was associated with a 74% survival within its initial derivation cohort and was then internally validated with an 86% survival in a subsequent cohort.[20] In our study, we observed a 100% survival with a PRESET-Score of 6 or lower, a dramatic increase in mortality of 62.5% with a PRESET-Score of 7 or higher, and up to 80% mortality with an increasing score of 8 or higher (Figure 2). Although it is not clear why the PRESET-Score was predictive and other scores were not, it is interesting that the PRESET-Score does not use the Glasgow Coma Scale (SOFA and SAPS II), age (RESP and SAPS II), and type of admission or diagnosis (RESP and SAPS II). These factors may be subject to confounding for patients with CARDS who are undergoing ECMO. Further confirmatory studies are needed to assess the validity of this threshold because there appears to be a strong association between the PRESET-Score and survival. If our results are corroborated, the PRESET-Score, in conjunction with sophisticated clinical judgment, may aid in selection of patients with CARDS for VV-ECMO.

The RESP score, although not statistically significant in our study ($P = .055$), warrants further study in larger

cohorts.[32] Interestingly, despite suggestions that the SOFA score may be of utility, neither the SOFA score nor the SAPS II score demonstrated any utility in predicting mortality in our study.[33] This is an important finding insofar as some hospital systems have advocated the use of these scores to allocate critical care resources in Covid-19.[34]

Recent publication of the preliminary results of the Adaptive COVID-19 Treatment Trial indicates that remdesivir improved time to recovery compared with placebo.[35] In that trial, only 25.6% of patients were undergoing mechanical ventilation or ECMO, so direct comparisons with our study are difficult. Our analysis revealed an association between remdesivir and mortality, but it is unclear whether this association is clinically relevant. Most patients received remdesivir under emergency use authorization and not under any trial protocol, during a time in the pandemic when the drug was scarce, thus introducing potential sample or selection bias. No other COVID-19-specific therapy had any statistically significant association with mortality. Larger studies are needed to examine these agents further.

The predominance of Hispanic ethnicity within our cohort may relate to socioeconomic status. Disparities in health care among racial minority groups during this pandemic must be contextualized with data on socioeconomic status, which unfortunately were not available for this study.[36] Further studies are needed to address these issues.

One of the strengths of this study, in relation to previous reports, is that it describes the entire experience during the first surge of COVID-19 in a large tertiary care medical center. It also describes a large single-center CARDS ECMO experience in the United States. Furthermore, less than 18% of our patients are undergoing ECMO at the time of analysis, thus greatly reducing interim analysis bias. These factors may explain why the wide variability in mortality in previous reports was not observed in our study.[10-16] The similarity between the mortality observed in this study and the international ELSO registry statistics suggests that this study can be generalized to most existent high-volume ECMO centers. These results may not be generalizable to small-volume ECMO centers.

The limitations of this study are that it is a retrospective single-center case series, and the sample size is relatively small, at 40 patients. In the factors analyzed that lacked significance, and failed to reject the null hypothesis, it is possible that this reflected a lack of power rather than a lack of effect.

In conclusion, the unprecedented COVID-19 pandemic is a crisis that places an enormous strain on health care systems with finite resources. Management of patients with COVID-19 is supportive because currently there is no known cure. Patients with CARDS in whom conventional ventilator management fails may be candidates for VV-ECMO. Our results suggest that reasonable outcomes are possible at high-volume ECMO centers. We also demonstrate a strong association of the PRESET-Score with mortality in patients with CARDS who undergo VV-ECMO. This scoring system may help identify patients with CARDS who are appropriate candidates for VV-ECMO support. Refinement of scoring systems to aid in decision making regarding VV-ECMO use in CARDS remains an important focus for study and may result in more favorable outcomes.

The following individuals have made substantial contributions to the work reported in this article but do not fulfill authorship criteria. The authors have obtained permission from all individuals named in this section.

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