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Characteristics and Outcomes of COVID-19 Patients Supported by Venoarterial or Veno-Arterial-Venous Extracorporeal Membrane Oxygenation

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Objectives: Cardiac injury has been reported in up to 20%-to-30% of patients with COVID-19, and severe disease can lead to cardiopulmonary failure. The role of mechanical circulatory support in these patients remains undetermined. The authors here aimed to determine the characteristics and outcomes of patients with COVID-19 requiring venoarterial extracorporeal membrane oxygenation (VA ECMO) or veno-arterial-venous (VAV) ECMO support.

Design and Setting: A multicenter, retrospective case series.

Participants: The cohort consisted of adult patients (18 years of age and older) with confirmed COVID-19 requiring VA ECMO or VAV ECMO support in the period from March 1, 2020, to April 30, 2021. Outcomes were recorded until July 31, 2021.

Measurements and Main Results: To show factors related to death during hospitalization, patients were grouped as survivors and nonsurvivors. Kaplan-Meier analysis was used to estimate 90-day in-hospital mortality. Overall, 37 patients from 12 centers comprised the study cohort. The median patient age was 44 years old (interquartile range [IQR], 35-52), and 12 (32%) were female patients. The duration of ECMO support ranged from 2-to-132 days. At the end of the follow-up period, 13 patients (35%) were discharged or transferred alive, and 24 patients (65%) died during the hospitalization. The cumulative in-hospital mortality at 90 days was 64% (95% confidence interval: 47-81). During the time from intubation to VA ECMO or VAV ECMO initiation (1 day [IQR 0-7.5] *v* 6 days [IQR 2.5-14], p = 0.0383), body mass index (32 [IQR 26-36] *v* 37 [IQR 33-40], p = 0.009), and baseline C-reactive protein (7.15 *v* 38.9 mg/dL, p = 0.009) were higher in those who expired.

Conclusion: Only one-third of the patients with COVID-19 requiring VA ECMO or VAV ECMO survived to discharge. Close monitoring of at-risk patients with early initiation of ECMO with circulatory support may further improve outcomes.

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Key Words: circulatory support devices; venoarterial extracorporeal membrane oxygenation; VA ECMO; VAV ECMO; coronavirus disease 2019; COVID-19

CORONAVIRUS DISEASE 2019 (COVID-19) continues to pose an overwhelming global healthcare challenge, with more than 4.5 million deaths attributed to the pandemic worldwide to date.[1]

Cardiac injury has been reported in up to 20%-to-30% of patients with COVID-19, and severe disease can lead to cardiopulmonary failure.[2] The role of mechanical circulatory support in these patients remains undetermined.

Abbreviations: ECMO, Extracorporeal membrane oxygenation; IQR, interquartile range; VA, venoarterial; VAV, venoarterial venous; VV, venovenous

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The use of extracorporeal membrane oxygenation (ECMO) has been reported predominantly for refractory pulmonary failure from COVID-19, with estimates of 90-day mortality ranging from 37%-to-46%.[3-5] While these studies showed that ECMO use during COVID-19 is promising, its role in cardiopulmonary failure largely remains unknown. In such reports, the proportion of patients receiving venoarterial or veno-arterial-venous extracorporeal membrane oxygenation (VA ECMO or VAV ECMO) for combined heart and lung failure was only about 4%-to-6%, and reports focusing only on VA ECMO use during COVID-19 are scarce.[6-8]

Proponents of VA ECMO use propose that the early initiation for refractory cardiogenic shock in appropriately selected patients can lead to favorable outcomes.[9,10] Appropriate patients tend to be younger and have fewer comorbidities.[10] On the other hand, VA ECMO support is extremely resource-intensive, and many patients with COVID-19 can have multiorgan dysfunction, arguing against VA ECMO use.[11] Accordingly, the study authors performed a multicenter study to determine the characteristics, outcomes, and clinical factors associated with death during hospitalization in patients with COVID-19 supported with VA ECMO or VAV ECMO.

Methods

This study was a multicenter, retrospective case series of patients aged 18 years and older, with COVID-19 confirmed via positive real-time reverse transcriptase-polymerase chain reaction assay, who received either VA EMCO or VAV ECMO support anytime between March 1, 2020, and April 30, 2021. Patients were divided into those who survived to transfer and/or discharge and those who did not survive the hospitalization.

Investigators at the data coordination site at the Montefiore Medical Center invited other centers for participation by directly contacting the surgical directors of mechanical circulatory programs. A data use agreement was mutually agreed upon between every participating center and the data-coordinating institution at the Montefiore Medical Center, Albert Einstein College of Medicine. The study was approved by the institutional review board at all of the participating centers, and informed consent was waived. The institutional review board approval was granted on April 5, 2020, under protocol number 2020-11375. A data capture tool was created using Research Electronic Data Capture (REDCap) for record entry by the participating centers. Data fields included demographic characteristics, laboratory parameters, ECMO characteristics, and patient outcomes. All data were anonymized. Before data entry, sites individually were familiarized with the data capture tool, and consistency was ensured by continuous technical support provided by the corresponding author at the data coordination center throughout the data collection period. To maintain accuracy, the data capture fields contained checks for validity, such as input masks and range rules for date fields and branching logic. Data consistency was maintained through built-in drop boxes with standardized responses. Records were inspected manually for data entry errors, such as those in date temporality, by the data-coordination center and rectified by sites before analysis.

Follow-up began at the time of ECMO placement and was completed until the time of discharge and/or transfer or in-hospital mortality. In-hospital follow-up was until July 30, 2021. The study authors used Kaplan-Meier curves to estimate the probability of in-hospital mortality at 90 days after ECMO placement. Patients were not censored at the time of any changes in ECMO configuration and retained their initial group classification to adhere to principles of original treatment intention. Additional outcomes that were reported included the development of secondary infections, deep venous thrombosis, stroke, limb ischemia, and renal failure requiring dialysis after ECMO placement. Causes of death during hospitalization also were reported.

Continuous data are reported as medians and interquartile ranges (IQR), and categorical data are shown as counts and percentages. The Mann-Whitney *U* test and the chi-square test were used to assess significant differences in quantitative and categorical variables, respectively. No data were imputed. Stata version 16 (Stata Corp, LLC, College Station, TX) was used for all statistical analyses.

Results

Patient Characteristics

The study cohort included 37 patients from 12 centers who were supported by either VA ECMO or VAV ECMO during the study period. The median age was 44 years old (IQR, 35-52), and 32% were female patients. Within the cohort, the median body mass index (BMI) was 36 (IQR, 31-38). Twenty-five (68%) patients had preexisting conditions, with 12 (32%) patients having hypertension and 11 (30%) with diabetes mellitus. Twenty-five (68%) patients were transferred from another center for ECMO placement, and 11 (30%) patients were supported by ECMO after having received cardiopulmonary resuscitation previously during admission. Eighteen (49%) patients had an echocardiogram performed prior to ECMO placement; 9 (50%) of whom had a left ventricular ejection fraction less than 40%. Fourteen (38%) patients were not proned prior to ECMO in the authors' cohort. Of those, 11 patients were also on vasopressors and presumptively were not proned due to hemodynamic instability. In the authors' cohort, the median time from intubation to initiation of any ECMO modality was 1 day (IQR, 0-5 days), whereas the median time from intubation to either VA ECMO or VAV ECMO was 6 days (IQR, 1-11 days). The duration of ECMO support ranged from 2-to-132 days. Inflammatory markers, including ferritin (1,024; IQR, 685-2,270 ng/mL), C-reactive protein (CRP) (14.7; IQR, 4.9-88.8 mg/dL), d-dimer (6.1; IQR, 3.5-1,112 mg/mL), and lactate dehydrogenase (744; IQR, 316-1,317 U/L), were highly elevated before ECMO placement.

Outcomes

By the end of the follow-up period, 24 (65%) patients had died during the hospitalization, and 13 (35%) patients were discharged or transferred alive. The probability of death during

hospitalization at 90 days was 64% (95% confidence interval: 47%-81%) (Fig 1) Table 1 shows a comparison of the differences in the baseline demographic characteristics and laboratory parameters of patients who died and those who were discharged or transferred. Patients who expired had a higher BMI (37 [IQR: 33-40] *v* 32 [IQR 26-36], p = 0.009), higher baseline CRP (38.9 *v* 7.15 mg/dL, p = 0.009), and a longer time from intubation to either VA ECMO or VAV ECMO initiation (6 days [IQR: 2.5-14] *v* 1 day [IQR: 0-7.5], p = 0.038).

The most common causes of death were multiorgan failure (8 patients; 33%), cardiac failure (4; 17%), and respiratory failure (2; 8%). For patients who were discharged or transferred alive, 6 (46%) were discharged to a rehabilitation facility, 5 (38%) were transported to another healthcare facility, such as long-term acute care or lower-acuity hospital, and only 2 (15%) were discharged to home (Table 2).

ECMO Characteristics and Course

Seventeen (46%) patients initially were cannulated as veno-venous (VV ECMO), 15 (41%) as VA ECMO, and 5 (14%) as VAV ECMO. Fourteen (38%) patients eventually were switched to VAV ECMO (Fig 2). Patients receiving VA ECMO support had a mortality rate of 61%, while those placed on VAV ECMO had a mortality rate of 68%. Patients who were switched from VV ECMO to either VA ECMO or VAV-ECMO had a mortality of 82%, whereas patients supported by either VA ECMO or VAV ECMO only or switched from either VA ECMO or VAV ECMO to VV ECMO had mortality rates of 46% and 57%, respectively.

The most common location in the hospital for cannulation was at the bedside or in the intensive care unit procedure room (19 patients; 51%), followed by the operating room (14; 38%). Heparin was used for anticoagulation in 27 (73%) patients, argatroban in 5 (14%), and bivalirudin in 5 (14%) cases.

Secondary infections were common and occurred in almost half of the patients (46%). Of these infections, bacteremia (11 patients; 30%) and bacterial pneumonia (10; 27%) occurred most often, followed by urinary tract infections (3; 8%). Deep venous thrombosis was noted in 5 (14%) patients. Hemorrhagic stroke occurred in 3 (8%) patients, and ischemic stroke was noted in 2 (5%) patients. Renal replacement therapy was required in 19 (51%) patients. A lower proportion of survivors required renal replacement therapy (23% *v* 67%, p = 0.017). Bleeding requiring transfusion was noted in 24 (65%) patients.

Discussion

The major findings of this multicenter case series of patients with COVID-19 requiring either VA ECMO or VAV ECMO support were as follows: (1) in-hospital mortality was elevated at nearly 65%; (2) switching from VV ECMO to either VA ECMO or VAV ECMO was associated with the highest mortality; and (3) patients who expired were placed on either VA ECMO or VAV ECMO at a later time from intubation in comparison to those who survived. Those who survived incurred significant morbidity, as only a minority were able to be discharged directly to their home.

This report found that patients with COVID-19 requiring ECMO for circulatory support had a significantly higher 90-day in-hospital mortality of 64% in comparison to 37%-to-46% reported in studies with nearly all patients requiring VV ECMO for respiratory support.[3-5,12-14] Although this study lacked a contemporary non-COVID-19 group, prior observational studies in non-COVID-19 patients with myocarditis requiring VA ECMO have reported lower mortality. In a meta-analysis of 170 patients, Cheng et al reported a pooled

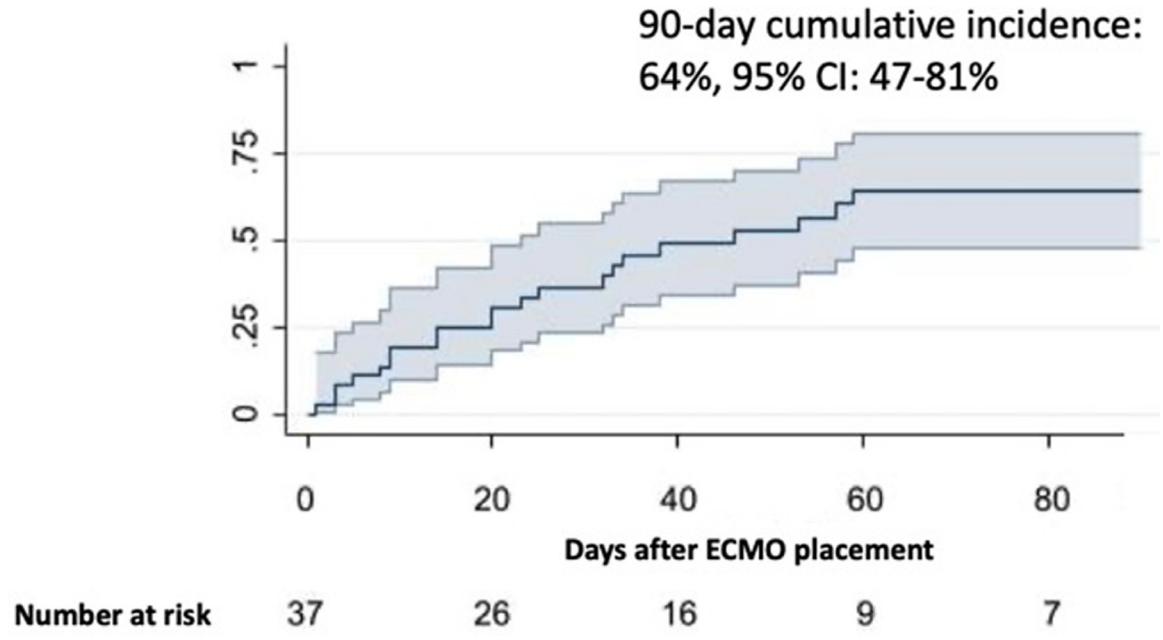

Fig. 1. Estimated cumulative incidence of in-hospital mortality after initiation of extracorporeal membrane oxygenation (ECMO) for COVID-19 at 90-days was 64% (95%CI: 47-81). The solid line shows the estimated cumulative incidence of in-hospital mortality and the shaded region represents the 95% CI.

Table 1
Baseline Characteristics of Patients With COVID-19 Supported by Venoarterial or Veno-Arterial-Venous Extracorporeal Membrane Oxygenation Support

	All Patients (n = 37)	Discharged or Transferred Alive (n = 13)	Deceased (n = 24)	p Value
Age, y	44 (35-52)	44 (34-51)	45 (36-53)	0.513
Sex, n (%)				
Female	12 (32)	3 (23)	9 (38)	0.476
Male	25 (68)	10 (77)	15 (63)	0.476
BMI, kg/m^2	36 (31-38)	32 (26-36)	37 (33-40)	0.009
Race/ethnicity, n (%)				
Asian	3 (8)	2 (17)	1 (4)	0.278
Hispanic	11 (30)	4 (33)	7 (28)	0.465
Non-Hispanic Black	9 (24)	1 (8)	8 (32)	0.119
Non-Hispanic White	12 (32)	4 (33)	8 (32)	1.000
Other/unknown	2 (5)	1 (8)	1 (4)	1.000
Preexisting comorbidities, n (%)				
Hypertension	12 (32)	3 (23)	9 (38)	0.400
Diabetes mellitus	11 (30)	5 (39)	6 (25)	0.400
Chronic respiratory disease	0 (0)	0 (0)	0 (0)	1.000
Malignant neoplasm	0 (0)	0 (0)	0 (0)	1.000
Coronary artery disease	2 (5)	1 (8)	1 (4)	1.000
Time from intubation to ECMO (any configuration), d	1 (0-5)	0 (0-4)	2 (1-6)	0.127
Time from intubation to VA- or VAV-ECMO, d	6 (1-11)	1 (0-7.5)	6 (2.5-14)	0.038
Time on ECMO support, d	20 (9-41)	13 (11-41)	24 (8.5-40)	0.784
Transferred to ECMO hospital, n (%)	25 (68)	8 (67)	16 (67)	0.155
CPR before ECMO, n (%)	11 (30)	3 (23)	8 (33)	0.652
eCPR n(%)	7 (19)	1 (8)	6 (25)	0.383
Prone positioning, n (%)	23 (62)	6 (46)	17 (71)	0.171
Hemodynamics				
Systolic blood pressure, mmHg	109 (97-128)	110 (96-119)	109 (99-132)	0.487
Diastolic blood pressure, mmHg	64 (54-72)	58 (44-69.5)	66 (58-72)	0.138
Mean arterial pressure, mmHg	79 (68-89)	76 (58-86)	80 (72-93)	0.223
Vasopressors, %	26 (72)	8 (62)	18 (75)	1.000
Inotropes, %*	12 (38)	5 (42)	7 (58)	0.65
Blood gas parameters				
pH	7.31 (7.17-7.35)	7.30 (7.19-7.36)	7.32 (7.14-7.35)	0.964
PaO_2/F_IO_2	75 (57-95)	91 (50-158)	69 (58-89)	0.449
$PaCO_2$, mmHg	54 (43-65)	48 (36-60)	56 (47-69)	0.103
Laboratory parameters				
White blood counts, $x10^3/uL$	15.1 (12.5-24.8)	15.1 (12.5-26.8)	14.5 (12.5-22.5)	0.460
Platelet count, $x10^3/uL$	220 (162-305)	196 (162-305)	221 (140-364)	0.827
Lactic acid, mmol/L	1.9 (1.5-3)	2.5 (1.2-3.8)	1.7 (1.5-2.5)	0.718
Creatinine, mg/dL	1 (0.7-2.2)	0.9 (0.6-1.6)	1.2 (0.7-2.4)	0.274
INR	1.2 (1.1-1.3)	1.2 (1.1-1.4)	1.2 (1.1-1.2)	0.582
Total bilirubin, mg/dL	0.7 (0.4-0.9)	0.6 (0.6-0.7)	0.7 (0.4-0.9)	0.876
Ferritin, ng/mL	1,024 (685-2,270)	1018 (602-1,728)	1030 (807-3,019)	0.555
C-reactive protein, mg/dL	14.7 (4.9 - 88.8)	7.15 (3.95-11.4)	38.9 (10.5-113.6)	0.009
D-Dimer, ug/mL	6.1 (3.5-1,112)	5.24 (1.4-4,000)	6.9 (4.1-677)	0.641
Fibrinogen, mg/dL	546 (304-700)	5.24 (1.4-4,000)	517 (285-876)	1.000
Lactate dehydrogenase, U/L	744 (316-1,317)	348 (275-1,262)	856 (627-1,510)	0.172
Procalcitonin, ng/mL	0.5 (0.2-1)	0.6 (0.2-0.9)	0.5 (0.2-1.1)	0.899

Percentages represent the proportion of reported observations. Continuous variables are displayed as median (IQR). Blood gas parameters were measured before ECMO placement.

Abbreviations: BMI, body mass index; eCPR, extracorporeal cardiopulmonary resuscitation; ECMO, extracorporeal membrane oxygenation; PaO_2/F_IO_2, partial pressure of oxygen/fraction of inspired oxygen; $PaCO_2$, partial pressure of carbon dioxide; VA, venoarterial, VAV, veno-arterial-venous.
*Reported in 32 cases.

mortality of 33%, with similar age and sex distributions to those patients within the authors' case series here.[15] The indication for VA ECMO in those studies, however, primarily was to provide circulatory support, whereas patients with COVID-19 usually require both respiratory and circulatory support given the primary pulmonary pathophysiology of the disease. Due to the lack of invasive hemodynamic monitoring and the absence of echocardiograms in most patients, the exact etiology of hemodynamic decompensation in the authors' cohort here could not be determined precisely and could have been cardiogenic, sepsis, vasoplegia, or mixed shock. Notwithstanding additional clinical confounders and patient selection, it is essential to identify methods to reduce mortality in patients with COVID-19 requiring VA ECMO.

Table 2
ECMO Characteristics and Outcomes

	All Patients (n = 37)	Discharged or Transferred Alive (n = 13)	Deceased (n = 24)	p Value
Type of initial ECMO support, n(%)				
Venovenous	17 (46)	3 (23)	14 (58)	0.082
Venoarterial	15 (41)	8 (62)	7 (29)	0.083
Veno-arterial-venous	5 (14)	2 (15)	3 (13)	1.000
Hospital location for ECMO initiation, n (%)				
Bedside or ICU procedure room	19 (51)	7 (54)	12 (50)	1.000
Operating room	14 (38)	3 (23)	11 (46)	0.288
Other	4 (11)	3 (23)	1 (4)	0.115
Intravenous anticoagulation, n (%)				
Heparin	27 (73)	9 (69)	18 (75)	0.716
Bivalirudin	5 (14)	1 (8)	4 (17)	0.638
Argatroban	5 (14)	3 (23)	2 (8)	0.321
Complications, n (%)				
Secondary infection	17 (46)	6 (46)	11 (46)	1.000
Bacterial pneumonia	10 (27)	4 (31)	6 (25)	0.716
Bacteremia	11 (30)	5 (38)	6 (25)	0.465
Central line infection	2 (5)	0 (0)	2 (8)	0.532
Urinary tract infection	3 (8)	0 (0)	3 (13)	0.538
Deep vein thrombosis	5 (14)	2 (15)	3 (13)	1.000
Hemorrhagic stroke	3 (8)	1 (8)	2 (8)	1.000
Ischemic stroke	2 (5)	0 (0)	2 (8)	0.532
Limb ischemia	4 (11)	1 (8)	3 (13)	1.000
Bleeding requiring transfusion	24 (65)	7 (54)	17 (71)	0.472
Circuit exchange	6 (16)	2 (15)	4 (17)	1.000
Renal replacement therapy	19 (51)	3 (23)	16 (67)	0.017
Expired during ECMO	18 (49)			
Cause of death, n (%)				
Cardiac failure	4 (17)			
Multiorgan failure	8 (32)			
Respiratory failure	2 (8)			
Septic shock	1 (4)			
Other	10 (40)			
Discharge location, n (%)				
Home	2 (15)			
Rehabilitation facility	6 (46)			
Other health care facility	5 (38)			

Percentages represent the proportion of reported observation.
Abbreviations: ECMO, Extracorporeal membrane oxygenation; ICU, intensive care unit.

A subgroup of patients who were switched to either VA ECMO or VAV ECMO incurred higher mortality than those placed on circulatory support at the onset. Due to the limits of data collection, the study authors cannot determine if such patients developed cardiac failure after placement on VV ECMO or whether there was unrecognized cardiac dysfunction that eventually declared itself and necessitated mechanical circulatory support. Regardless, the higher mortality of this subgroup indicated that baseline risk stratification of impending cardiac failure with echocardiography and, if needed, invasive hemodynamics, is critical and may identify appropriate candidates for early arterial cannulation. This further was underscored with survivors showing a lower time to either VA ECMO or VAV ECMO in comparison to non-survivors.

Patients who expired were noted to have higher CRP and a higher BMI than patients who survived. While obesity has not been shown to be a negative prognostic factor in cardiogenic shock requiring VA ECMO, this finding was consistent with literature showing obesity to be associated with increased risk of death from COVID-19 in adults younger than 65 years.[16,17] Higher CRP also has been associated with mortality in patients with COVID-19.[18,19]

Hematologic and neurologic disturbances occur with both COVID-19 and VA ECMO.[20-22] The authors noted a numerically higher burden of these adverse events during device support in comparison to prior studies of non-COVID-19 patients. The observed prevalence of bleeding (65%) and stroke (13%) were numerically higher in this series of patients in comparison to the reported rates of 40% and 6% during VA ECMO in non-COVID-19 patients, respectively.[22] This elevated burden of adverse events also may have contributed to greater mortality during ECMO support.

There were several limitations in this study. First, the authors' sample size was small. Second, the retrospective study design and the lack of a control group of non-COVID-19

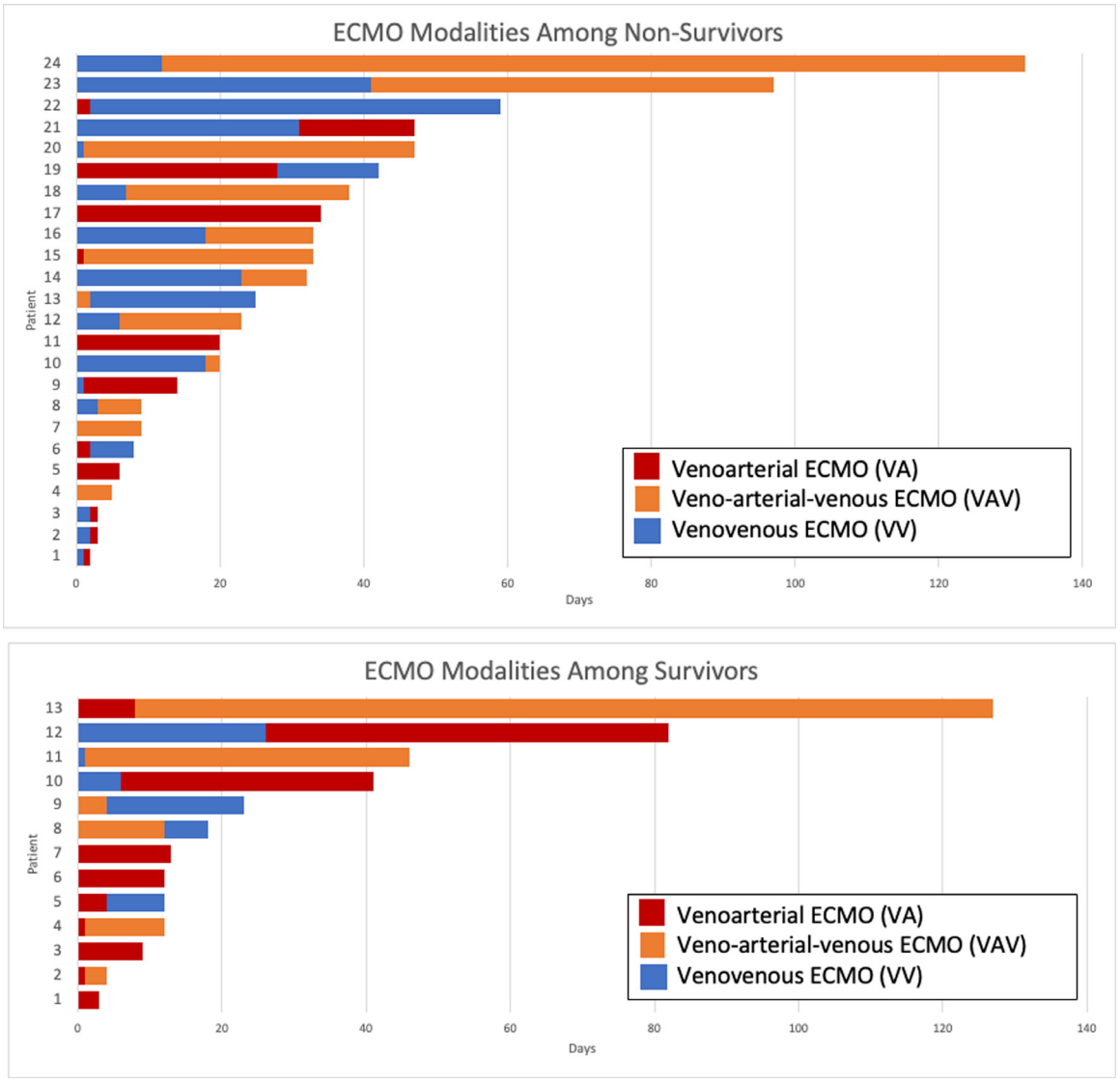

Fig. 2. Changes in the configuration of extracorporeal membrane oxygenation among survivors and non-survivors.

patients limited the interpretation of the findings. Third, outcomes from centers that participated in this study might not be reflective of those from institutions with different resource availability. There were no prespecified criteria for ECMO placement, and the decision to initiate mechanical circulatory support was institution-specific. Despite these limitations, the study shed light on a relatively understudied and extremely resource-intensive treatment modality in this pandemic.

In conclusion, this report showed that only one-third of patients with COVID-19 who received either VA ECMO or VAV ECMO survived. Methods to improve outcomes may involve close monitoring of at-risk patients with tenuous cardiac function, with the early initiation of ECMO with circulatory support in appropriate patients.

Conflict of Interest

None.

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