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Worse survival in patients with right ventricular dysfunction and COVID-19–associated acute respiratory distress requiring extracorporeal membrane oxygenation: A multicenter study from the ORACLE Group

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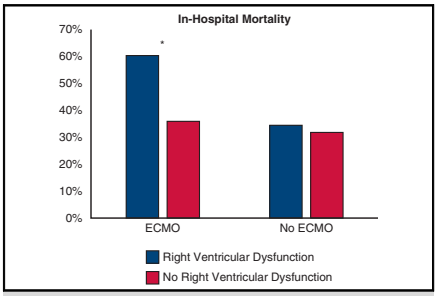
ABSTRACT

Objective: We sought to determine the impact of right ventricular dysfunction on the outcomes of mechanically ventilated patients with COVID-19 requiring veno-venous extracorporeal membrane oxygenation.

Methods: Six academic centers conducted a retrospective analysis of mechanically ventilated patients with COVID-19 stratified by support with veno-venous extracorporeal membrane oxygenation during the first wave of the pandemic (March to August 2020). Echocardiograms performed for clinical indications were reviewed for right and left ventricular function. Baseline characteristics, hospitalization characteristics, and survival were compared.

Results: The cohort included 424 mechanically ventilated patients with COVID-19, 126 of whom were cannulated for veno-venous extracorporeal membrane oxygenation. Right ventricular dysfunction was observed in 38.1% of patients who received extracorporeal membrane oxygenation and 27.4% of patients who did not receive extracorporeal membrane oxygenation with an echocardiogram. Biventricular dysfunction was observed in 5.5% of patients who received extracorporeal membrane oxygenation. Baseline patient characteristics were similar in both the extracorporeal membrane oxygenation and non–extracorporeal membrane oxygenation cohorts stratified by the presence of right ventricular dysfunction. In the extracorporeal membrane oxygenation cohort, right ventricular dysfunction was associated with increased inotrope use (66.7% vs 24.4%, $P < .001$), bleeding complications (77.1% vs 53.8%, $P = .015$), and worse survival independent of left ventricular dysfunction (39.6% vs 64.1%, $P = .012$). There was no significant difference in days ventilated before extracorporeal membrane oxygenation, length of hospital stay, hours on extracorporeal membrane oxygenation, duration of mechanical ventilation, vasopressor use, inhaled pulmonary vasodilator use, infectious complications, clotting complications, or stroke. The cohort without extracorporeal membrane oxygenation cohort demonstrated no statistically significant differences in in-hospital outcomes.

Conclusions: The presence of right ventricular dysfunction in patients with COVID-19–related acute respiratory distress syndrome supported with veno-venous extracorporeal membrane oxygenation was associated with increased in-hospital mortality. Additional studies are required to determine if mitigating right ventricular dysfunction in patients requiring veno-venous extracorporeal membrane oxygenation improves mortality. (J Thorac Cardiovasc Surg 2023;■:1-10)



Percent mortality for patients stratified by the presence of RVD.

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CENTRAL MESSAGE

The presence of RVD in patients with COVID-19 requiring veno-venous ECMO support was associated with increased mortality.

PERSPECTIVE

This multi-institutional study demonstrates a significant increase in mortality associated with the presence of RVD in patients with COVID-19 requiring veno-venous ECMO support.

See Commentary on page XXX.

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Abbreviations and Acronyms

ARDS = acute respiratory distress syndrome
ECMO = extracorporeal membrane oxygenation
ICU = intensive care unit
LV = left ventricle
ORACLE = Outcomes and Recovery After COVID-19/Critical illness Leading to ECMO
RV = right ventricle
RVAD = right ventricular assist device
RVD = right ventricular dysfunction
VV-ECMO = veno-venous extracorporeal membrane oxygenation

Scanning this QR code will take you to the table of contents to access supplementary information.

Despite the changing virulence of COVID-19, acute respiratory distress syndrome (ARDS) remains a persistent disease phenotype. ARDS develops in approximately 31% to 67% of patients hospitalized with COVID-19[1-3] and is associated with significant mortality, more than 52%.[1,2,4] Management of COVID-19–associated ARDS in the initial waves of the pandemic focused on early intubation,[5] lung protective ventilation,[5,6] and prone positioning.[7-10] Despite these strategies, a subset of these patients progressed to develop refractory hypoxemia or hypercarbia, necessitating advanced therapies such as veno-venous extracorporeal membrane oxygenation (VV-ECMO).[1-3,5,11-17]

The role of ECMO in management of COVID-19–associated ARDS has largely consisted of using VV-ECMO to address severe refractory hypoxemia and hypercarbia. Interestingly, right ventricular dysfunction (RVD) has been demonstrated to be relatively common in this cohort, with RVD shown to occur in approximately 25% to 40% of patients with COVID-19–associated ARDS.[18-21] Some centers have advocated for early, aggressive right ventricle (RV) support with a right ventricular assist device (RVAD) in conjunction with ECMO in response to early studies that suggest increased mortality for patients with RVD in the setting of COVID-19.[22,23] Despite this trend, RVD in patients who require ECMO support for COVID-19–associated ARDS has not yet been shown to impact survival. Given the relative infrequency of ECMO for COVID-19 at any one center and the complexity of appropriate management of these patients, multicenter collaborative analysis has become essential to better understand the role advanced therapies play in treating this novel disease.[24,25]

The Outcomes and Recovery After COVID-19/Critical illness Leading to ECMO (ORACLE) group is an interdisciplinary collaboration across 6 academic medical centers that aims to define the recovery and ongoing needs of survivors of COVID-19–associated ARDS. Established in 2020, the overarching goal of the ORACLE research collaborative is to better understand how ECMO impacts long-term outcomes of survivors. We present an analysis of the ORACLE registry with a specific focus on evaluating the impact of RVD on clinical outcomes. We hypothesized that the presence of RVD in patients with COVID-19 supported with VV-ECMO is associated with worse clinical outcomes and higher mortality.

MATERIALS AND METHODS

We conducted a retrospective analysis using data collected at 6 academic medical centers across the United States (University of Colorado, University of Kentucky, University of Virginia, Johns Hopkins University, Vanderbilt University, University of Pittsburgh Medical Center) representing the ORACLE interdisciplinary collaborative.[26] Participating sites were experienced ECMO centers and strictly adhered to Extracorporeal Life Support Organization guidelines when considering ECMO candidacy. Each center used specialized teams to manage ECMO-supported patients and manage ECMO-supported patients per Extracorporeal Life Support Organization guidelines both before and after ECMO cannulation.[27] Guidelines for cannulation included presence of single organ failure, intubation less than 10 days, age less than 70 years, P:F less than 80 mm Hg for greater than 6 hours or P:F less than 50 mm Hg for greater than 3 hours, and pH less than 7.25 with PaCO2 greater than 60 mm Hg for more than 6 hours. Patients with known cardiac dysfunction were not cannulated for VV-ECMO, and VA-ECMO was not offered to this cohort. Each institution maximized matching resources to patient need independently based on local dynamics, and efforts to provide all necessary resources were maintained at each participating center during the pandemic. All patients considered for ECMO had been intubated before evaluation. The study was approved by the Institutional Review Board at each site, and a waiver of informed consent was granted (University of Colorado and all other sites: COMIRB#20-0731, approved April 4, 2020).

Study investigators at each site performed a retrospective chart review of all adult patients with COVID-19 admitted to the intensive care unit (ICU) during the first wave of the pandemic from March to August 2020.

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The study was approved by the Institutional Review Board at each site, and a waiver of informed consent was granted (University of Colorado and all other sites: COMIRB#20-0731, approved April 4, 2020).

Received for publication Sept 6, 2022; revisions received Dec 8, 2022; accepted for publication Dec 16, 2022.

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0022-5223/$0.00

Published by Elsevier Inc. on behalf of The American Association for Thoracic Surgery

https://doi.org/10.1016/j.jtcvs.2022.12.013

Eligible patients were age 18 years or older with documented COVID-19 infection. Patients who did not require mechanical ventilation were excluded. Data were available for all mechanically ventilated patients from 3 sites (University of Colorado, University of Kentucky, University of Virginia), and data for patients cannulated for VV-ECMO were collected at all 6 sites. Investigators gathered patient demographic characteristics and clinical parameters from the index ICU stay including ventilator days, presence of RVD by echocardiography, receipt of vasoactive medications and investigational COVID-19 therapies, in-hospital complications, laboratory values collected at the time of intubation, length of stay, and discharge disposition. Additional data collected for patients who received ECMO included mechanically ventilated days before cannulation and total hours on ECMO.[28] All transesophageal and transthoracic echocardiograms obtained during the index hospitalization for COVID-19 were reviewed. The presence of any RVD was determined and categorized dichotomously at the discretion of providers certified in adult echocardiography at each participating institution; however, RVD was broadly defined as a composite of size ratio and elevated RV pressure or presence of septal dyskinesia on transthoracic or transesophageal imaging.[29] Left ventricular (LV) dysfunction was defined as LV ejection fraction less than 50% as documented in the echocardiography report. Patients who did not receive a clinically indicated echocardiogram were not included in the full analysis (Figure 1).

Data from all sites were combined for analysis. Patient demographics and in-hospital characteristics, including survival at discharge, were compared based on ECMO status using chi-square tests for categorical variables and *t* tests or Kruskal–Wallis tests for continuous variables. We used Kaplan–Meier survival curves and log-rank *P* values to test the association between survival to discharge and RVD separately for ECMO-supported patients and patients supported only with mechanical ventilation. Analyses were performed using R software (R Foundation for Statistical Computing).

RESULTS

The study included 424 mechanically ventilated patients with COVID-19 across 6 institutions. Of these patients, 159 were cannulated for VV-ECMO and 242 received a clinically indicated echocardiogram during their index hospitalization for COVID. A total of 79.2% (126/159) of the ECMO cohort had echocardiograms. RVD was observed in 38.4% (48/126) of ECMO-supported patients. A total of 44.2% (117/265) of the non-ECMO cohort received echocardiograms. Comparison of the demographics and outcomes of patients supported with ECMO and the non-ECMO cohort demonstrated ECMO-supported patients were younger, traveled further to receive care, and had less chronic renal disease. ECMO-supported patients had greater vasopressor, steroid, and inhaled pulmonary vasodilator use (Table E1). ECMO-supported patients had increased use of tracheostomy, longer duration of ventilation, and a longer hospitalization without a significant reduction in mortality (Table E2). Further analysis focused on those patients who received a clinically indicated echocardiogram and was stratified by both ECMO use and RVD. RVD was observed in 27.4% (32/117) of this group (Figure 1). The majority of RVD was isolated, with biventricular dysfunction observed in 5.6% (7/126) of ECMO-supported patients, whereas isolated LV ejection fraction less than 50% was observed in 2.4% (3/126) of ECMO-supported patients. Non–ECMO-supported patients had an observed rate of biventricular dysfunction of 9.0% (10/117) and isolated LV dysfunction of 4.0% (5/117). Given the potential for LV dysfunction to confound the relationship between RV dysfunction and mortality, we used logistic regression to estimate the adjusted odds of death for RV dysfunction, LV dysfunction, and an interaction between them. The interaction term was not significant; therefore, we fit a model with 2 binary factors for each of these variables. RV dysfunction was significantly associated with increased odds of death in the VV-ECMO cohort (odds ratio [OR], 2.50; 95% confidence interval [CI], 1.17-5.47; $P = .02$). LV dysfunction was not significantly associated with mortality (OR, 1.62; 95% CI, 0.49-5.84). Additional modeling removing patients with identified LV dysfunction from the analysis demonstrated a preserved increased odds

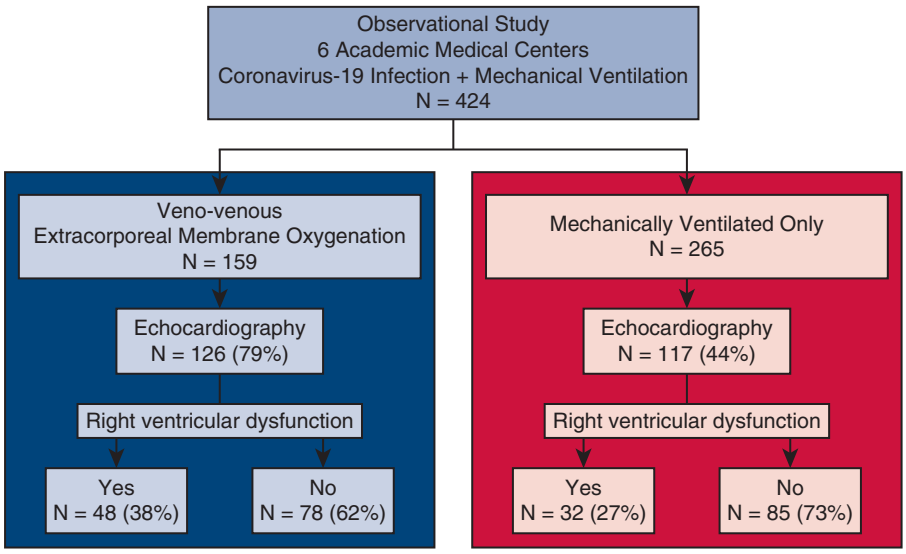

FIGURE 1. Study design flow diagram.

TABLE 1. Demographics of mechanically ventilated patients with COVID-19 based on extracorporeal membrane oxygenation status and presence of right ventricular dysfunction

Demographics of mechanically ventilated patients with COVID-19						
	ECMO (n = 126)			No ECMO (n = 117)		
	No RVD (n = 78)	RVD (n = 48)	*P* value	No RVD (n = 85)	RVD (n = 32)	*P* value
Age, y (mean, SD)	48.8 (11.4)	51.94 (9.5)	.189	59.6 (14.8)	63.2 (12.7)	.226
Female sex	24 (30.8%)	15 (31.2%)	1.00	30 (35.3%)	10 (31.2%)	.847
Race			.223			.383
Asian	1 (1.3%)	2 (4.2%)		6 (7.1%)	3 (9.4%)	
Black	14 (17.9%)	15 (31.2%)		19 (23.4%)	10 (31.2%)	
Other	17 (21.8%)	8 (16.7%)		36 (42.4%)	8 (25.0%)	
White	46 (59.0%)	23 (47.9%)		24 (28.2%)	11 (34.4%)	
BMI (mean, SD)	34.6 (8.7)	33.4 (6.9)	.441	32.8 (8.7)	29.7 (6.3)	.072
Insured	68 (87.2%)	40 (83.3%)	.736	75 (88.2%)	25 (78.1%)	.276
Distance traveled, miles (median, IQR)	41.5 (14.5, 82.5)	25.5 (10.0, 63.2)	.237	6.0 (3.0, 36.0)	5.0 (3.5, 9.5)	.573
Diabetes	32 (42.1%)	19 (40.4%)	1.00	40 (48.2%)	17 (53.1%)	.790
Cardiovascular disease	5 (6.7%) 3	7 (14.9%) 1	.241	20 (24.1%) 2	10 (31.2%) 0	.585
Hypertension	34 (44.7%)	25 (53.2%)	.468	48 (57.8%)	20 (62.5%)	.807
Chronic kidney disease	5 (6.6%)	4 (8.5%)	.965	16 (19.5%)	6 (18.8%)	1.00
Liver disease	1 (1.3%)	2 (4.3%)	.679	1 (1.2%)	1 (3.1%)	1.00
Obstructive sleep apnea	6 (8.0%)	7 (14.9%)	.368	14 (17.9%)	3 (9.4%)	.401
Interstitial lung disease	0	0	1.00	0	1 (3.2%)	.611
Chronic obstructive pulmonary disease	6 (7.9%)	3 (6.5%)	1.00	11 (13.4%)	5 (16.1%)	.947
Current smoker	4 (5.9%)	1 (2.4%)	.719	7 (9.5%)	2 (6.9%)	.979
ICU admission Apache II Score (median, SD)	15.2 (8.5)	14.9 (6.9)	.852	16.1 (7.0)	16.5 (7.8)	.777
ICU admission SOFA Score (median, SD)	7.9 (4.1)	7.0 (3.6)	.174	7.4 (2.9)	7.9 (3.5)	.417

ECMO, Extracorporeal membrane oxygenation; *RVD*, right ventricular dysfunction; *SD*, standard deviation; *BMI*, body mass index; *IQR*, interquartile range; *ICU*, intensive care unit; *SOFA*, Sequential Organ Failure Assessment.

of death in patients with RVD supported with ECMO (OR, 2.33; 95% CI, 1.05-5.28; $P = .04$). ICU admission measures of systemic illness and prediction of mortality were similar between RVD and non-RVD ECMO cohorts, as measured by SOFA and Apache II scores (Table 1).

When both ECMO and non-ECMO cohorts were stratified by the presence of RVD, baseline patient characteristics were similar (Table 1). ECMO-supported patients with RVD were more likely to require inotropes than ECMO-supported patients without RVD (66.7% vs 24.4%, $P < .001$); however, there were no significant differences in vasopressor or inhaled pulmonary vasodilator use, or duration of mechanical ventilation before ECMO cannulation (Table 2). There were no significant differences in receipt of blood transfusion ($P = .901$) or clotting complications (including deep venous thromboses and pulmonary emboli) ($P = .255$), although bleeding complications were significantly increased in ECMO-supported patients with RVD compared with ECMO-supported patients without RVD (77.1% vs 53.8%, $P = .015$). Use of investigational COVID-19 therapy, tracheostomy, and steroids was also similar between groups. There was no significant difference in rates of intracranial hemorrhage, stroke, or delirium. There was a trend toward increased rates of acute kidney injury in the RVD cohort, but this did not reach statistical significance (89.4% vs 73.1%, $P = .052$) There was no significant difference in days ventilated before ECMO, hours on ECMO, or duration of mechanical ventilation required during the hospital stay. Duration of mechanical ventilation before ECMO and total duration of mechanical ventilation were similar between ECMO-supported patients with and without RVD. Length of hospital admission (39.0 vs 37.0 days, $P = .603$) was not significantly different in ECMO-supported patients with and without RVD (Table 2). ECMO-supported patients with RVD demonstrated a significantly reduced survival to discharge compared with ECMO-supported patients without RVD (39.6% vs 64.1%, $P = .012$) (Table 2, Figure 2). Kaplan–Meier survival curves demonstrated a varying rate of survival over time, but these rates were not significantly different in the

TABLE 2. Hospitalization characteristics for mechanically ventilated patients with COVID-19 based on extracorporeal membrane oxygenation status and presence of right ventricular dysfunction

Hospitalization characteristics of mechanically ventilated patients with COVID-19						
	ECMO (n = 126)			No ECMO (n = 117)		
	No RVD (n = 78)	RVD (n = 48)	*P* value	No RVD (n = 85)	RVD (n = 32)	*P* value
Days intubated (median, IQR)	25.5 (11.2-40.8)	25.0 (12.0-49.0)	.590	16.0 (8.0-23.5)	15.5 (9.2-24.5)	.840
Days intubated pre-ECMO (median, IQR)	4.3 (1.0-6.5)	4.0 (3.0-7.0)	.300	-	-	-
ECMO hours (median, IQR)	396.0 (216.0-708.0)	528.0 (273.0-761.5)	.097	-	-	-
LV dysfunction	3 (3.8%)	11 (22.9%)	.003	5 (5.9%)	10 (31.2%)	<.001
Inotropes	19 (24.4%)	32 (66.7%)	<.001	13 (15.3%)	7 (21.9%)	.570
Vasopressors	75 (96.2%)	47 (97.9%)	.980	74 (87.1%)	30 (93.8%)	.486
Inhaled pulmonary vasodilators	37 (48.1%)	30 (62.5%)	.164	25 (29.4%)	7 (21.9%)	.560
Neuromuscular blockade	72 (92.3%)	46 (95.8%)	.680	38 (45.2%)	15 (46.9%)	1.00
Therapeutic anticoagulation	76 (97.4%)	48 (100.0%)	.701	51 (60.0%)	23 (71.9%)	.331
Steroids	57 (73.1%)	38 (79.2%)	.577	46 (54.1%)	14 (43.8%)	.438
Investigational COVID therapy	44 (56.4%)	29 (60.4%)	.797	57 (67.1%)	22 (68.8%)	1.00
Blood transfusion	63 (80.8%)	40 (83.3%)	.901	38 (44.7%)	12 (37.5%)	.622
Bleeding complication	42 (53.8%)	37 (77.1%)	.015	18 (21.2%)	6 (18.8%)	.974
Clotting complication	41 (52.6%)	31 (64.6%)	.255	25 (29.4%)	10 (31.2%)	1.00
Infectious complication	65 (83.3%)	42 (87.5%)	.705	64 (75.3%)	21 (65.6%)	.416
Acute kidney injury	57 (73.1%)	42 (89.4%)	.052	57 (67.1%)	24 (75.0%)	.545
Stroke	2 (2.6%)	5 (10.4%)	.142	11 (12.9%)	4 (12.5%)	1.00
Delirium	52 (66.7%)	28 (58.3%)	.451	48 (56.5%)	24 (75.0%)	.105
Length of stay, d (median, IQR)	39.0 (29.0-54.5)	37.0 (27.2-63.5)	.603	29.0 (21.0-40)	30.5 (18.8-46.8)	.515
Alive at discharge	50 (64.1%)	19 (39.6%)	.012	58 (68.2%)	21 (65.6%)	.962

ECMO, Extracorporeal membrane oxygenation; *RVD*, right ventricular dysfunction; *IQR*, interquartile range; *LV*, left ventricular.

ECMO cohort ($P = .08$) or no ECMO cohort ($P = .91$) in relation to RVD given censoring (Figure 3).

In contrast to those patients who required ECMO, the impact of RVD in the cohort who did not require ECMO support was less pronounced. In the 117 mechanically ventilated patients who were not cannulated for ECMO, there was neither a significant difference in survival related to RVD (68.2% vs 65.6%, $P = .962$) (Figure 2) nor were there significant differences in rates of in-hospital complications including duration of mechanical ventilation, length of stay, bleeding, or clotting complications (Table 2).

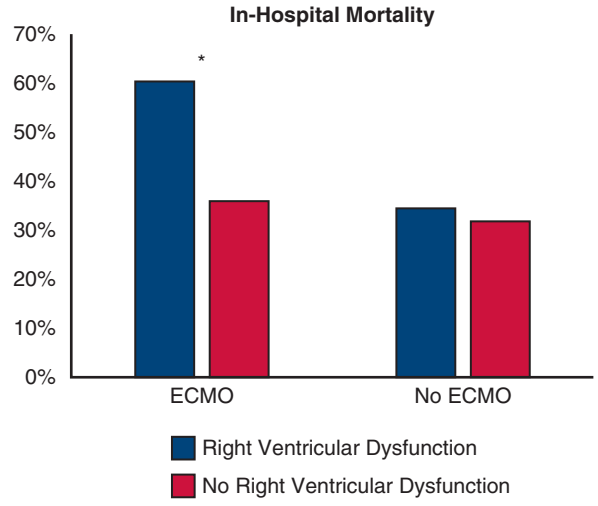

FIGURE 2. Percent in-hospital mortality for patients supported with ECMO and those not supported with ECMO, stratified by presence of RVD. *ECMO*, Extracorporeal membrane oxygenation.

An additional subgroup analysis was performed investigating the impact of single-site cannulation (right internal jugular dual lumen cannula) for VV-ECMO versus dual-site cannulation (right internal jugular return with common femoral venous drainage) (Figure 4) for VV-ECMO. Single-site cannulation was used in 34.1% (43/126) of ECMO-supported patients, and dual-site cannulation in 65.9% of patients (83/126). There were no significant differences in observed RVD between single-site and dual-site cannulation groups (39.5% vs 37.3%, $P = .963$). In-hospital survival was not significantly different between single-site cannulation and dual-site cannulation groups (58.1% vs 53.0%, $P = .719$).

DISCUSSION

We present data from the multicenter interdisciplinary ORACLE collaborative with a specific focus on

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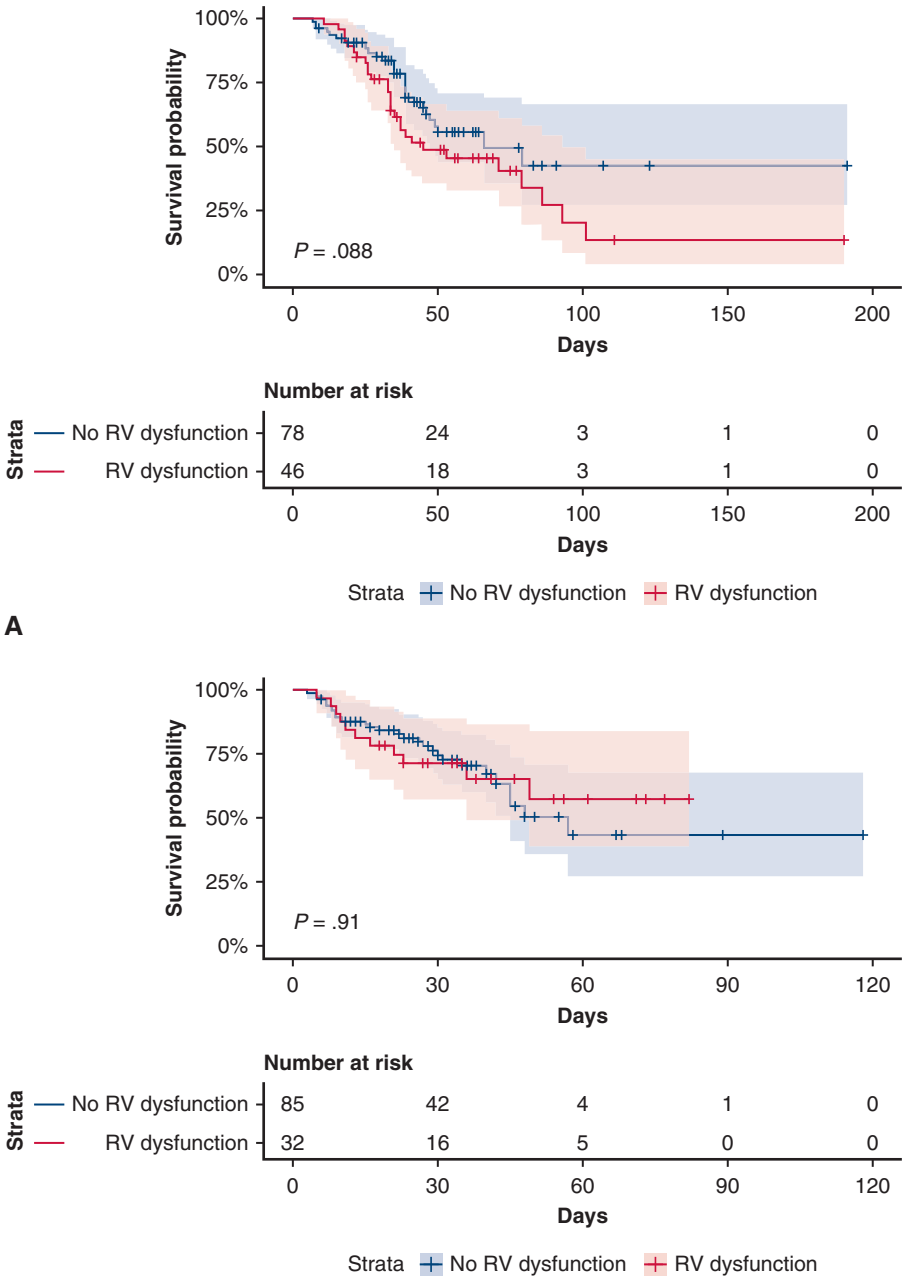

FIGURE 3. Kaplan–Meier survival curves representing the association between survival to discharge and RVD for (A) ECMO-supported patients and (B) patients supported with mechanical ventilation alone. Log-rank *P* values are shown for each comparison. *Shaded regions* denote 95% confidence intervals, with number at risk shown below each figure. *Hash* marks indicate events. *RV*, Right ventricle.

characterizing the incidence and impact of RVD in VV-ECMO–supported patients with COVID-19–associated ARDS during the first wave of this pandemic. This study has several key findings. First, we demonstrate a significant incidence of RVD in this cohort, with approximately 1 in 3 patients (32.6%) exhibiting some degree of RVD by echocardiography. The incidence of RVD in this cohort is similar to what is previously reported for patients requiring VV-ECMO for ARDS. Notably, we observed this cardiac dysfunction to be a predominantly isolated right-sided insult, with only 5.6% of ECMO-supported patients exhibiting biventricular dysfunction. Because a portion of patients had both RVD and LV dysfunction in the ECMO group, we investigated whether the increased mortality in the RVD ECMO group was associated with LV dysfunction. In a multiple logistic regression model with RVD and LV

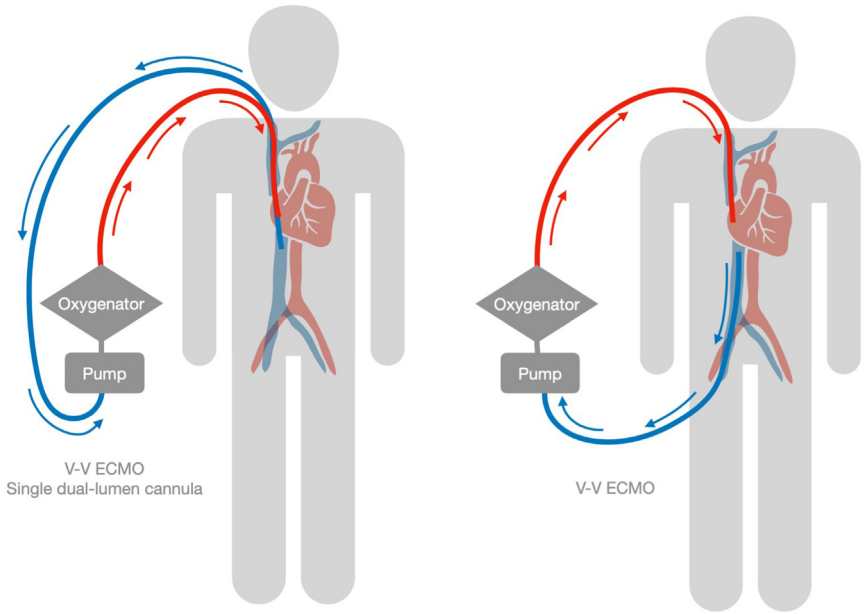

FIGURE 4. Visual representation of single-site (single dual lumen cannula, *left*) and dual-site (VV-ECMO, *right*) cannulation strategies. *VV-ECMO*, Veno-venous extracorporeal membrane oxygenation.

dysfunction, only RVD was significantly associated with increased odds of death before discharge. When we used of subset of only patients who did not have LV dysfunction, RVD was still significantly associated with mortality. Additional covariates could not be included because of the small sample size. Cannulation approach using a single-site versus a dual-site strategy was not associated with significant differences in in-hospital survival in this study.

As such, our findings are less suggestive of a global myocarditis phenotype that has been previously described[13,14] and favor right-sided dysfunction as the dominant ventricular dysfunction pattern in this disease process. Second, this multicenter study demonstrated increased in-hospital mortality associated with RVD on echocardiography in ECMO-supported patients (Figure 2). The observed increased mortality associated with RVD in VV-ECMO–supported patients has been suggested by multicenter studies,[30] Substantial clinical morbidity exists for patients with COVID-19 who require VV-ECMO support, regardless of RV function. ECMO-supported patients with RVD in this study demonstrated increased dependence on inotropes and increased bleeding complications. Patients with RVD did not have increased rates of clotting complications, stroke, vasopressor needs, progression to dialysis, duration of mechanical ventilation, or length of time on ECMO. Third, the present study suggests the association of RVD with increased mortality in COVID-19 ARDS may be limited to those who are supported with VV-ECMO, because there was no significant difference in clinical outcomes related to RVD in patients supported with mechanical ventilation alone (survival to discharge 68.2% vs 65.6%, $P = .962$). These findings provoke discussion on 2 central questions: (1) Is RVD a phenotype of another determinant of survival, such as degree of hypoxemia, or is it the cause of the survival difference? (2) Would protecting the RV with an RVAD with an oxygenator improve survival? The question of RVAD placement is particularly challenging because RVD is not always present at the time that mechanical circulatory support is initiated.

RV failure is often underrecognized in critical illness, particularly in the setting of ARDS, due in part to the difficulty of diagnosis by noninvasive means.[21] During the early wave of the COVID-19 pandemic, concern regarding the possibility of transmission to healthcare workers during diagnostic procedures such as echocardiography or use of Swan Ganz catheters likely resulted in an underrecognition of RVD, which has since been described in 27% to 40% of hospitalized patients with COVID-19, with some studies showing a 3-fold increase in mortality.[11,31-36] RVD has been shown to impact outcomes for ECMO-supported patients with ARDS before the COVID-19 pandemic; however, the implications of RV dysfunction in COVID-19–associated ARDS has not clearly been delineated. Mechanistically, the development of RVD in the setting of ARDS can be considered as a secondary result of pulmonary vasoconstriction in response to the combined hypoxemia, hypercapnia, and acidosis seen in these individuals. Furthermore, hypercoagulability and increased incidence of pulmonary embolism associated with COVID-19 may have contributed to increased incidence of RVD. This, coupled with the increased airway driving pressures often required by many of these patients to offset

pulmonary parenchymal fibrosis and reduced elasticity, leads to rapid onset of pulmonary arterial hypertension. This acute pulmonary hypertension results in a compensatory dilation of the RV as it shifts on the Frank-Starling curve to provide adequate contractility against the increased pulmonary resistance. These mechanistic details become increasingly important in the setting of COVID-19–associated ARDS, which has been associated with significant systemic effects including pulmonary interstitial inflammation and eventually fibrosis, which dramatically limit lung compliance and increase hypercoagulability. The results of the present study suggest that more liberal use of echocardiography in ECMO-supported patients with ARDS may aid in prognostication and could better guide therapeutic efforts.

Correction of these respiratory and metabolic derangements with the institution of VV-ECMO should offer RV protection from dysfunction. However, the presence of persistent RVD and inferior outcomes for patients with ARDS-associated RVD in prior studies suggests persistent RV-PA uncoupling due to inadequate gas exchange and metabolic correction, pulmonary vascular dysregulation, or macrovascular/microvascular thrombosis resulting in persistent pulmonary hypertension on ECMO. As a result, persistent RV dysfunction on ECMO is concerning for a more fixed uncoupling phenomenon or progression to chronic pulmonary hypertension in some individuals, which may be related to the association with increased inotropic support seen in our study.

The observed prevalence of RVD in COVID-19–associated ARDS, the risk for persistent RV-PA uncoupling, and the description of direct myocardial inflammatory manifestations of COVID-19 have prompted some centers to adopt more liberal use of right atrial to pulmonary artery ECMO (venopulmonary ECMO) configurations. These modifications to the ECMO circuit facilitate RV unloading and enhanced pulmonary arterial flow in an attempt to counteract these effects. Data from this approach are limited but promising, with centers demonstrating a 3-fold survival benefit for venopulmonary ECMO over maximal mechanical ventilation alone.[22,37] These single-center studies should be interpreted with caution because comparative studies of venopulmonary ECMO versus conventional VV-ECMO are lacking; however, they do promote a shift in the approach to ARDS from an isolated pulmonary parenchymal derangement to a mixed cardiopulmonary condition that may require a more tailored approach for patients with RVD.

The present study is supportive of prior small, single institution investigations that suggested reduced survival in ECMO-supported patients with RVD and expands on those analyses.[30] These findings highlight the importance of multi-institutional collaboratives, such as the ORACLE collaborative, in assessment of complex therapies for ARDS. Although RVD occurring in patients on ECMO support was numerically infrequent at any one institution within the collaborative, collectively this analysis allows for a more robust assessment of patient outcomes related to the condition across multiple medical institutions. These retrospective studies are important in providing a foundation for future, prospective studies in this arena to better delineate the roll of echocardiographic screening and RVD in VV-ECMO–supported patients with ARDS and the roll of medical optimization to mitigate the impact of RVD on morbidity and mortality in this cohort of patients.

Study Limitations

Our analysis has several limitations. Although the cohort included patients from 6 institutions across the United States, this was a retrospective observational study with the associated inherent weaknesses. In-hospital care of patients with COVID-19 ARDS and posthospitalization assessments were performed during a time when the healthcare system in this country was experiencing unique stressors and rapid evolution of the understanding of this novel disease. This includes the potential for variability in vasopressor use, anticoagulation, and other therapies within and between institutions. Furthermore, COVID-19–specific medical therapeutics, such as monoclonal antibodies, were not available during this era. In this analysis, we had insufficient sample size to explore site-level variation and their impact on outcomes. Additionally, patients with RVD were categorized dichotomously and based only on assessment by echocardiography rather than on severity of RVD. It must be acknowledged that because echocardiograms were performed on the basis of assessment of clinical need, and thus were not performed prospectively, their interpretation is subject to bias. A structured approach to repeat echocardiography was not performed to assess for recovery of RVD, and although board-certified echocardiographers interpreted these exams, there is likely some degree of heterogeneity in the strict criteria used. Finally, this study was a retrospective analysis of mechanically ventilated patients with COVID-19 supported with VV-ECMO during the first wave of the pandemic from March to August 2020; COVID-19 and its treatment continue to evolve.

CONCLUSIONS

This multicenter study demonstrates significant mortality associated with the presence of RVD in patients with COVID-19–associated ARDS supported with VV-ECMO. Of note, ventricular derangement in this cohort was predominantly characterized by isolated RVD, and the increased mortality appears limited to patients requiring ECMO support. These findings offer important insight into the management of COVID-19–associated ARDS.

Conflict of Interest Statement

The authors reported no conflicts of interest.

The *Journal* policy requires editors and reviewers to disclose conflicts of interest and to decline handling or reviewing manuscripts for which they may have a conflict of interest. The editors and reviewers of this article have no conflicts of interest.

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Key Words: COVID-19, extracorporeal membrane oxygenation, right ventricular dysfunction

TABLE E1. Demographics of mechanically ventilated patients with COVID-19 based on extracorporeal membrane oxygenation status

	Demographics of mechanically ventilated patients with COVID-19		
	ECMO (n = 126)	No ECMO (n = 117)	*P* value
Age, y (mean, SD)	49.8 (10.7)	60.6 (14.3)	<.001
Female sex	39 (31.0%)	40 (34.2%)	.688
Race			<.001
Asian	3 (2.4%)	9 (7.7%)	
Black	29 (23.0%)	29 (24.8%)	
Other	25 (19.8%)	44 (37.6%)	
White	69 (54.8%)	35 (29.9%)	
BMI (mean, SD)	34.1 (8.1)	32.0 (8.2)	.037
Insured	108 (85.7%)	100 (85.5%)	1.000
Distance traveled, miles (median, IQR)	34.5 (12.2-77.8)	6.0 (3.0-27.8)	<.001
Diabetes	51 (41.5%)	57 (49.6%)	.261
Cardiovascular disease	12 (9.8%)	30 (26.1%)	.002
Hypertension	59 (48.0%)	68 (59.1%)	.111
Chronic kidney disease	9 (7.3%)	22 (19.3%)	.011
Liver disease	3 (2.5%)	2 (1.8%)	1.000
Obstructive sleep apnea	13 (10.7%)	17 (15.5%)	.373
Interstitial lung disease	0 (0.0%)	1 (0.09%)	.969
Chronic obstructive pulmonary disease	9 (7.4%)	16 (14.2%)	.141
Current smoker	5 (4.6%)	9 (8.7%)	.347
ICU admission Apache II Score (median, SD)	15.2 (7.9)	16.2 (7.2)	.237
ICU admission SOFA Score (median, SD)	7.6 (3.9)	7.5 (3.1)	.925

ECMO, Extracorporeal membrane oxygenation; *SD*, standard deviation; *BMI*, body mass index; *IQR*, interquartile range; *ICU*, intensive care unit; *SOFA*, Sequential Organ Failure Assessment.

TABLE E2. Hospitalization outcomes for mechanically ventilated patients with COVID-19 based on extracorporeal membrane oxygenation status

	Hospital outcomes of mechanically ventilated patients with COVID-19		
	ECMO (n = 126)	No ECMO (n = 117)	*P* value
Days intubated (median, IQR)	25.0 (11.0-41.0)	16.0 (8.0-24.2)	.001
Days intubated pre-ECMO (median, SD)	4.5 (3.4)	-	-
ECMO, h (median, IQR)	452.0 (235.0-737.8)	-	-
LV dysfunction	14 (11.1%)	15 (12.8%)	.832
Inotropes	51 (40.5%)	20 (17.1%)	<.001
Vasopressors	122 (96.8%)	104 (88.9%)	.030
Inhaled pulmonary vasodilators	67 (53.6%)	32 (27.4%)	<.001
Neuromuscular blockade	118 (93.7%)	53 (45.7%)	<.001
Therapeutic anticoagulation	124 (98.4%)	74 (63.2%)	<.001
Steroids	95 (75.4%)	60 (51.3%)	<.001
Investigational COVID therapy	73 (57.9%)	79 (67.5%)	.159
Blood transfusion	103 (81.7%)	50 (42.7%)	<.001
Bleeding complication	79 (62.7%)	24 (20.5%)	<.001
Clotting complication	72 (57.1%)	35 (29.9%)	<.001
Acute kidney injury	99 (79.2%)	81 (69.2%)	.104
Stroke	7 (5.6%)	15 (12.8%)	.080
Delirium	80 (63.5%)	72 (61.5%)	.856
Length of stay, d (median, IQR)	39.0 (27.8-56.2)	29.0 (20.0-40.0)	<.001
Alive at discharge	69 (54.8%)	79 (67.5%)	.057

ECMO, Extracorporeal membrane oxygenation; *IQR*, interquartile range; *SD*, standard deviation; *LV*, left ventricular.