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Original Research Article

The role of ECMO in COVID-19 acute respiratory failure: Defining risk factors for mortality

Jared Gallaher [a,*], Lauren Raff [a], Andrew Schneider [a], Trista Reid [a], Melissa B. Miller [b], Olivia Boddie [a], Anthony Charles [a]

[a] University of North Carolina at Chapel Hill School of Medicine, Department of Surgery, Chapel Hill, NC, USA
[b] University of North Carolina at Chapel Hill School of Medicine, Department of Pathology and Laboratory Medicine, Chapel Hill, NC, USA

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ABSTRACT

Background: Veno-venous extracorporeal membrane oxygenation (VV ECMO) utilization increased substantially during the COVID-19 pandemic, but without patient selection criteria.
Methods: We conducted a retrospective review of all adult patients with COVID-19-associated ARDS placed on VV ECMO at our institution from April 2020 through June 2022.
Results: 162 patients were included (n = 95 Pre-Delta; n = 58 Delta; n = 9 Omicron). The frequency of ECMO duration greater than three weeks was variable by pandemic period (17% pre-Delta, 41% Delta, 22% Omicron, p = 0.003). In-hospital mortality was 60.5%. Age ≥50 years (RR 1.28, 95% CI 1.01, 1.62), ≥7 days of respiratory support (1.39, 95% CI 1.05, 1.83) and pre-cannulation renal failure requiring dialysis (RR 1.42, 95% CI 1.13, 1.78) were associated with mortality.
Conclusions: In this cohort of VV ECMO patients with COVID-19, older age, a longer duration of pre-ECMO respiratory support, and pre-ECMO renal failure all increased the risk of mortality by approximately 30%.

1. Introduction

The novel SARS-CoV-2 disease (COVID-19), in the most severe cases, can lead to acute respiratory distress syndrome (ARDS). After the failure of maximal ventilatory therapy, extracorporeal membrane oxygenation (ECMO) may be considered as a rescue therapy.[1] While simple in concept, ECMO is complex in its execution, requiring trained staff and specialist equipment, and has a high burden of complications. ECMO is not a therapeutic modality; it simply supports patients with failing lungs, providing time for lung recovery or—exceptionally— serving as a bridge to lung transplantation.[2]

Early in the COVID pandemic, concerns about the high mortality rate observed in COVID-19 patients requiring ECMO support were raised.[3] However, subsequent observational cohort studies, including one from the Extracorporeal Life Support Organization (ELSO) registry, reported outcomes for patients with COVID-19 receiving ECMO that were comparable to ECMO-supported patients with non-COVID-19-related ARDS.[4–6] However, there has been a significant variance in reported outcomes from various ECMO centers in the United States (US) and Europe.

Prior to the pandemic, the role of careful patient selection on ECMO outcomes was relatively well established. However, with changes in COVID-19 management and virulence, patient selection for ECMO has become more challenging.[7–9] In addition, the duration of ECMO support in the absence of clear improvement in lung recovery has been controversial. We, therefore, sought to evaluate all COVID-19 patients presenting to our high-volume quaternary care institution that progressed to ECMO support. We examined patient characteristics and changes in ECMO-related COVID-19 mortality over the pandemic period while accounting for differing pandemic periods based on COVID-19 variants.

2. Methods

We performed a retrospective study of all COVID-19 patients cannulated for veno-venous (VV) ECMO at the University of North Carolina (UNC) Medical Center (UNCMC). UNCMC is a quaternary academic medical center located in Chapel Hill, NC, with approximately 900 inpatient beds. The UNC ECMO program includes neonatal, pediatric, and adult cardiac and respiratory failure patients. Adult patients placed on VV ECMO for respiratory failure are cannulated and managed by

* Corresponding author. 4006 Burnett Womack Building, CB# 7228, Chapel Hill, NC, 27599, USA.
E-mail address: jared_gallaher@med.unc.edu (J. Gallaher).

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trauma/critical care surgeons in the Surgical Intensive Care Unit (SICU). We previously published a description of our VV ECMO management protocol.[9] In general, patient management was consistent throughout the pandemic and the decision to cannulate a patient was made by the on-call ECMO surgeon within the guidelines and recommendation of ELSO. Data was collected using chart reviews by a research assistant and reviewed by an ECMO surgeon.

We included patients from April 1, 2020, through June 30, 2022. All patients with COVID-19-associated ARDS cannulated for VV ECMO were included in the analysis, including patients <18 years old who were greater than 50 kg in weight and managed by the adult team. We recorded each patient's clinical history from the electronic medical record. The Charlson Comorbidity Index (CCI) was used to compare medical comorbidities.[10]

The primary outcome of this study was to identify pre-cannulation risk factors associated with in-hospital mortality after VV ECMO for COVID-19 ARDS. We initially examined patients based on the time of presentation relative to the dominant circulating variant during the pandemic. We categorized patients into the Pre-Delta Period, Delta Period, and Omicron Period. The transition from the Pre-Delta to the Delta period was defined as a diagnosis on June 10, 2021, when the Delta variant rapidly increased in its proportion of new COVID-19 cases at UNCMC.[11] The Omicron period was similarly defined, beginning on December 10, 2021. During December 2021 and January 2022, there was substantial overlap in of patients with either Delta or Omicron infections. Starting in December 2021, all ECMO patients who had routine admission COVID-19 testing also had SARS-CoV-2 genomic sequencing performed if the viral load was sufficient. Consequently, to better examine the potential effects of different variant infections, any patients with confirmed Omicron infection or those who did not have variant data were included in the Omicron Period for analysis, while patients with confirmed Delta infection during the Omicron Period were included in the Delta Period.

We used bivariate analysis to compare patients based on period presentation (three categories). We utilized Chi-squared tests to compare categorical variables and ANOVA (analysis of variance) for continuous variables with a normal distribution. For continuous variables with a non-normal distribution, we used a Kruskal-Wallis test to compare medians. Means are reported with standard deviations (SD) and medians with interquartile ranges (IQR). We then used a similar strategy to compare patients based on whether they survived to hospital discharge.

Using variables identified on bivariate analysis, we modeled pre-cannulation predictors of in-hospital mortality after VV ECMO for COVID-19 using a modified Poisson regression model.[12,13] Initially, the model was fit with statistically significant variables from the bivariate analysis. Variables were removed stepwise if they did not significantly contribute to mortality in our multivariable model. We also tested whether there was a better model fit after adding a polynomial term. The final model is reported with adjusted risk ratios (RR) and a 95% confidence interval.

We performed all statistical analyses with Stata/SE 17.0 (Stata- Corp LP, College Station, TX). The University of North Carolina Institutional Review Board approved this study (#19–3513 and #20–2448) and waived the need for informed consent.

3. Results

A total of 162 patients were cannulated for VV ECMO during the study period, with 95 patients cannulated during the Pre-Delta period, 58 patients during the Delta period, and 9 during the Omicron period. A total of 18 patients were cannulated during the Omicron period, but 9 were confirmed to be Delta by viral genomic sequencing and were included in the Delta group. (Fig. 1).

A comparison of patients, stratified by period, is shown in Table 1. Notable differences included a much higher median age in the Pre-Delta period at 50 years (IQR 42–58) compared to 42 years (IQR 36–48) and 49 years (IQR 43–51, $p < 0.001$) in the Delta and Omicron periods, respectively. Hispanic whites comprised 37% of all patients in the pre-Delta period compared to only 21% in the Delta period ($p = 0.006$). African Americans also represented a higher proportion of patients early in the pandemic at 28% Pre-Delta compared to 12% during the Delta period. The median BMI was consistently high at over 36 kg/m2 in each period ($p = 0.4$), as shown in Fig. 2. The prevalence of diabetes mellitus was variable at over 25% ($p = 0.031$) for all patients but highest during the Pre-Delta ($n = 38$, 40%) and Omicron periods ($n = 6$, 67%). The Charlson Comorbidity Index was low across all cohorts. Fewer patients were insured in the Pre-Delta period at 66% compared to 83% during

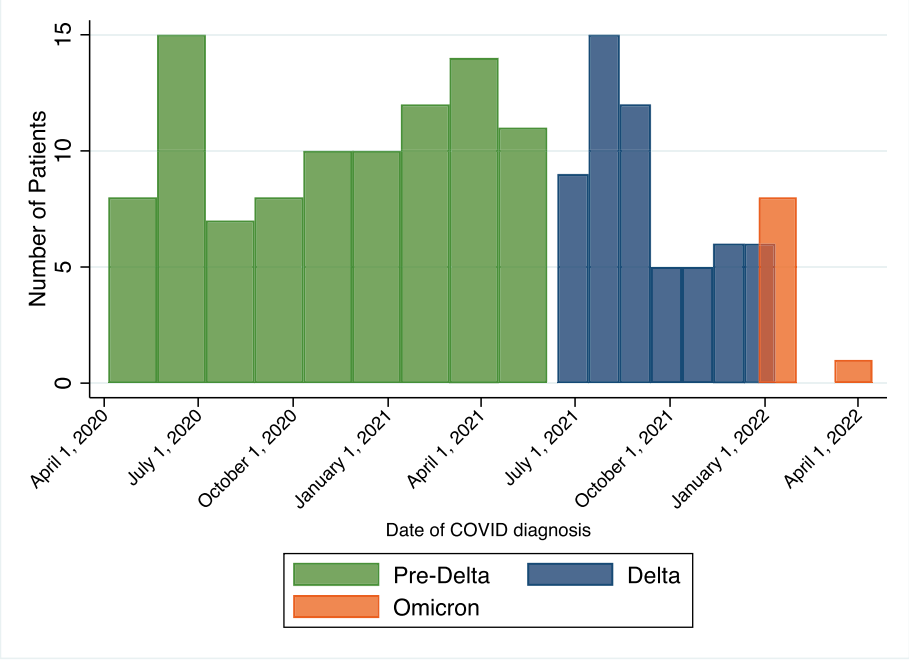

Fig. 1. Changes in COVID-19 ECMO patient volume by pandemic period.

Table 1
A comparison of COVID-19 patients placed on VV ECMO, stratified by time period of presentation.

	Pre-Delta (n = 95)	Delta (n = 58)	Omicron (n = 9)	*p* value
Patient Age (years)				
Median (IQR)	50.0 (42.0–58.0)	42.0 (36.0–48.0)	49.0 (43.0–51.0)	<0.001
Gender: N (%)				
Female	31 (33)	18 (31)	2 (22)	0.8
Male	64 (67)	40 (69)	7 (78)	
Race: N (%)				
African American	27 (28)	7 (12)	1 (11)	0.006
Hispanic White	35 (37)	12 (21)	4 (44)	
Non-Hispanic White	30 (32)	36 (62)	4 (44)	
Other	3 (3)	3 (5)	0 (0)	
BMI at hospital admission (kg/m2)				
Median (IQR)	36.2 (10.3)	36.8 (9.1)	41.0 (9.3)	0.4
Diabetes?				
Yes: N (%)	38 (40)	15 (26)	6 (67)	0.031
Charlson Comorbidity Score				
0	29 (31)	35 (60)	0 (0)	<0.001
1	35 (37)	20 (34)	7 (78)	
2	20 (21)	3 (5)	2 (22)	
3	5 (5)	0 (0)	0 (0)	
4	6 (6)	0 (0)	0 (0)	
Insurance status				
Self-Pay	32 (34)	10 (17)	4 (44)	0.050
Insured	63 (66)	48 (83)	5 (56)	
Vaccinated against COVID-19 prior to admission?				
Yes: N % ()	0 (0)	1 (2)	1 (11)	0.043
Transferred to UNCH?				
Yes: N (%)	82 (86)	57 (98)	9 (100)	0.027
Crude In-Hospital Mortality: N (%)	64 (67)	29 (50)	5 (56)	0.10

Table 2
A comparison of ECMO related outcomes, stratified by time period of presentation.

	Pre-Delta (n = 95)	Delta (n = 58)	Omicron (n = 9)	*p* value
Time on ECMO (days)				
Median (IQR)	14 (7-18)	17 (11-28)	9 (7-19)	0.008
On ECMO for Greater than 3 weeks?				
Yes: N (%)	16 (17)	24 (41)	2 (22)	0.003
Tracheostomy Performed on ECMO?				
Yes: N (%)	52 (55)	48 (83)	6 (67)	0.001
Number of ECMO circuit changes: N (%)				
0	62 (65)	31 (53)	6 (67)	0.3
1	27 (28)	16 (28)	2 (22)	
2	6 (6)	7 (12)	1 (11)	
3	0 (0)	2 (3)	0 (0)	
4	0 (0)	2 (3)	0 (0)	
CRRT while on ECMO?				
Yes: N (%)	34 (36)	26 (45)	5 (62)	0.2
Other Complications: N (%)				
Cerebrovascular accident	4 (4)	2 (3)	1 (11)	0.4
Liver Failure	3 (3)	6 (10)	1 (11)	0.1
Deep Vein Thrombosis or Pulmonary Embolism	2 (2)	1 (2)	0 (0)	1.00
Bleeding Complications: N (%)				
Cannulation site	18 (19)	8 (14)	1 (11)	0.7
Trachesostomy	19 (20)	17 (29)	3 (33)	0.3
Oropharynx	29 (31)	16 (28)	1 (11)	0.6
Gastrointestinal	16 (17)	2 (3)	0 (0)	0.026
Number of Blood Product Units Transfused on ECMO: Median (IQR)				
Packed Red Blood Cells	6 (3-12)	8 (2-14)	3 (0–7)	0.1
Platelets	1 (0–4)	0 (0–4)	0 (0–3)	0.8
Fresh Frozen Plasma	0 (0–0)	0 (0–0)	0 (0–0)	0.2

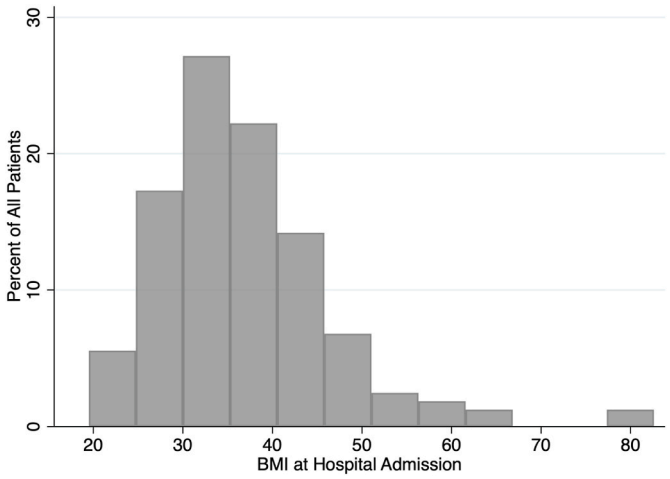

Fig. 2. Distribution of patient body mass index (BMI) at the time of ECMO cannulation.

Delta (p = 0.050). Vaccination was rare, with only 2 patients fully vaccinated at the time of cannulation. Crude in-hospital mortality was statistically similar between the cohorts at 67% (n = 64/95) during the Pre-Delta period, 50% (n = 29/58) in the Delta period, and 56% (n = 5/9, p = 0.1) during the Omicron period.

Table 2 compares patients based on ECMO-related outcomes, stratified by the presentation period. During the Pre-Delta period, the median duration was 14 days (IQR 7–18) compared to 17 days (IQR 11–28) during Delta and 9 days (IQR 7–19, p = 0.008) during Omicron. The proportion of patients who were on ECMO for three weeks or greater increased significantly throughout the pandemic, with only 17% (n = 16) during the Pre-Delta period compared to 41% (n = 24) in the Delta period and 22% (n = 2, p = 0.003) in the Omicron cohort. The need for renal replacement therapy (CRRT) during ECMO was common in over 35% of patients but similar across the periods (p = 0.2). Other complications, including cerebrovascular accidents, liver failure, and thromboembolic events, were not common in any group. Bleeding complications were common but were primarily bleeding at cannula sites or tracheostomy sites with no differences between the cohorts except for gastrointestinal bleeding. Median total blood transfusions while on ECMO for packed red blood cells, platelets, and fresh frozen plasma were similar.

Total crude in-hospital mortality was 60.5% (n = 98/162). Table 3 compares differences in patient characteristics stratified by hospital survival. The mean age was significantly higher among patients who died at 48.5 years (SD 10.9) compared to 41.9 years (SD 10.4, p < 0.001) in survivors. For patients <50 years old, crude in-hospital mortality was 52.0% (n = 52/100) and for patients ≥50 years, it was 74.2% (n = 46/62). Notably, there were no differences in gender composition, race, BMI, diabetes, Charlson Comorbidity Index, respiratory comorbidities, insurance status, or COVID-19 vaccination status related to mortality.

Time from diagnosis to ECMO (10 days vs. 13.5 days, p = 0.025) and time from hospital admission to ECMO (7.0 days vs. 10.0 days, p = 0.001) were significantly higher in non-survivors. Pre-cannulation renal failure was less common among those who survived (8% vs. 26%, p = 0.006). The median Pao2:Fio2 ratio was approximately 70 in both groups (p = 0.4). The median number of days of NIPPV before intubation was statistically similar between the two groups (2.5 vs. 4.0, p = 0.1) but the median number of days from intubation to ECMO was significantly lower among those who survived (2.0 days vs. 3.0 days, p = 0.043). When the total number of days requiring NIPPV and intubation were combined, the median total days of respiratory support were significantly lower in the survival group (6.0 vs. 8.0 days, p = 0.005).

Upon modeling, three factors were associated with an increased risk of in-hospital mortality. Age ≥50 years had a RR of death of 1.28 (95% CI 1.01, 1.62). Total days (≥7 days) of respiratory support (NIPPV + mechanical ventilation with intubation) had a RR of 1.39 (95% CI 1.05, 1.83) and pre-cannulation renal failure requiring dialysis had a RR of

Table 3
A comparison of characteristics between patients who survived to hospital discharge and those who did not. NIPPV = Noninvasive positive-pressure ventilation.

	Survived to Discharge (n = 64)	Died in Hospital (n = 98)	*p*-value
Patient Age (years)			
Mean (SD)	41.9 (10.4)	48.5 (10.9)	<0.001
Gender: N (%)			
Male	42 (66)	69 (70)	0.6
Female	22 (34)	29 (30)	
Race: N (%)			
Black	13 (20)	22 (22)	0.2
Hispanic White	21 (33)	30 (31)	
Non-Hispanic White	30 (47)	40 (41)	
Other	0 (0)	6 (6)	
BMI at hospital admission			
Median (IQR)	36.0 (30.4–44.7)	34.3 (30.2–39.9)	0.1
Diabetes?			
Yes: N (%)	27 (42)	32 (33)	0.2
Charleson Comorbidity Index: N (%)			
0	28 (44)	36 (37)	0.5
1	26 (41)	36 (37)	
2	8 (12)	17 (17)	
3	1 (2)	4 (4)	
4	1 (2)	5 (5)	
Patient Respiratory Comorbidities: N (%)			
Asthma	6 (9)	6 (6)	0.5
COPD	2 (3)	3 (3)	1.00
OSA	6 (9)	9 (9)	1.00
Smoker	4 (6)	10 (10)	0.6
Insurance status: N (%)			
Self-Pay	14 (22)	32 (33)	0.1
Insured	50 (78)	66 (67)	
Vaccinated against COVID-19 prior to admission?			
Yes: N (%)	0 (0)	2 (2)	0.5
Transferred to UNCH?			
Yes: N (%)	64 (100)	84 (86)	<0.001
Time from Diagnosis to ECMO (days)			
Median (IQR)	10.0 (6.0–17.0)	13.5 (10.0–17.0)	0.025
Time from Hospital Admission to ECMO (days)			
Median (IQR)	7.0 (3.0–11.5)	10.0 (7.0–14.0)	0.001
Organ Failure Prior to Cannulation: N (%)			
Renal	5 (8)	25 (26)	0.006
Cardiac arrest with ROSC	2 (3)	8 (8)	0.3
P:F ratio at cannulation			
Median (IQR)	67 (56–80)	71 (60–80)	0.4
Evidence of barotrauma at cannulation?			
Yes: N (%)	11 (17)	26 (27)	0.2
Received NIPPV?			
Yes: N (%)	54 (87)	83 (90)	0.6
Days of NIPPV prior to intubation			
Median (IQR)	2.5 (0.5–6.0)	4.0 (1.0–8.0)	0.1
Time from Intubation to ECMO (days)			
Median (IQR)	2.0 (0.5–4.0)	3.0 (1.0–5.0)	0.043
Total Days of NIPPV and Intubation Prior to ECMO (days)			
Median (IQR)	6.0 (2.0–8.5)	8.0 (4.0–12.0)	0.005

1.42 (95% CI 1.13, 1.78). A total of 45 patients (27.8%) had at least two of these factors, while 11 (6.8%) had all three. The RR of death if a patient had any two factors was 1.54 (95% CI 1.22, 1.95). Among the 11 patients with all three factors, 9 died (82%). Notably, the pandemic period was not a significant contributor to the adjusted mortality.

4. Discussion

In this study, we report one of the largest single-institution experiences with VV ECMO for patients with severe ARDS secondary to COVID-19 infection. Throughout the pandemic, certain patient factors were predictive of mortality after VV ECMO, including older age, length of respiratory support, and the need for dialysis before cannulation. Independently, each increased the risk of death by over 30%. Patients with at least two factors had a more than 50% increased risk of death. Notably, gender, race, insurance status, medical comorbidity, and BMI were not associated with increased mortality. We also found significant differences in patient characteristics across different pandemic periods, especially in age, with a higher proportion of older patients placed on VV ECMO early in the pandemic. ECMO duration also increased in the Delta period, with more than 40% of patients on ECMO for greater than three weeks compared to only 17% pre-Delta. The number of patients requiring ECMO during the Omicron period decreased dramatically.

Globally, respiratory ECMO use increased significantly during the COVID-19 pandemic. As of July 2022, almost 15,000 COVID-19 cases are reported on the ELSO Dashboard, eclipsing the total number of pre-pandemic ECMO cannulations.[14] The widespread use of this expensive resource, especially during a pandemic, has led to important questions about appropriate indications and the ideal patient population when there is high demand.[15,16]

One emerging theme of published data has been the effect of age on survival. In our patient cohort, age was a significant predictor of mortality, with an age of 50 years or older increasing the adjusted risk of death by 30%. Crude mortality was close to 50% for patients under the age of 50 but nearly 75% for those over the age of 50. Hall et al. found similar findings in their multi-institutional US study of 505 COVID-19 ECMO patients, showed that the median age was significantly lower in survivors, 44 vs. 51 years ($p < 0.001$).[17] A similar multi-institutional study from Paris of 302 COVID-19 patients also demonstrated that approximately 50 years of age was a meaningful age threshold for significantly increased mortality.[18] Lastly, an early analysis of the first 1035 patients in the ELSO registry provided evidence that older age was associated with higher mortality, with every age group over 50 having a higher hazard ratio for mortality compared to patients under the age of 40 years.[19] Current ELSO guidelines for adult respiratory ECMO do not include age as a contraindication for cannulation but acknowledge that older age increases the risk of death.[20] With the currently available evidence, ECMO clinicians must give substantial weight to a patient's age starting at 50 years, especially in the presence of other risk factors.

In addition to age, seven or more total days of respiratory support had a similar association with mortality in our study. Patients who died also had a longer time from diagnosis to cannulation and from hospitalization to cannulation, although this was not significant in our model. While there is limited published data on this relationship for COVID-19 patients placed on VV ECMO, another US institutional study showed that mortality was 100% in patients that were mechanically ventilated for greater than 7 days and who did not receive a lung transplant.[21] Lebreton et al. also demonstrated a significant relationship between the duration of intubation and mortality, finding that each decrease in the number of ventilation days had an odds ratio of 0.91 (95% CI 0.84, 0.99).[18] Unfortunately, during the COVID-19 pandemic, calculating ventilation days is often more complicated due to a very high proportion of patients managed with prolonged NIPPV prior to intubation. Our study found that the duration of respiratory support, including NIPPV and mechanical ventilation, significantly predicted mortality over seven days. Current ELSO guidelines recommend using seven days of high-setting ventilatory support as a relative contraindication for ECMO support but do not include NIPPV.[20] However, our data suggest that the duration of NIPPV should also be considered, especially in higher risk patients.

Pre-cannulation renal failure requiring dialysis is not a contraindication to ECMO support and was not considered in decision-making by our center during the pandemic. However, it was a significant predictor of mortality in our cohort, independent of age or respiratory support duration. A recent German study of COVID-19 ECMO patients found that renal failure was much more common among non-survivors compared to survivors at 73% versus 33% ($p < 0.001$).[22] In addition, data from France also found that patients with a lower renal component of the Sequential Organ Failure Assessment (SOFA) score pre-ECMO had a lower risk of mortality.18 Although dialysis can easily be provided to

patients while on ECMO, pre-cannulation renal failure may signify greater systemic disease severity and affect prognosis. There is insufficient evidence to include renal failure as a contraindication to ECMO, but like older age, it should be considered in the presence of other adverse prognostic factors, especially if resources are limited. Consistent with other recent reports, BMI was not associated with mortality in our cohort and should not be considered a contraindication for ECMO in COVID-19 patients.[23–25]

Reported outcomes after ECMO for COVID-19 have been variable. While the ELSO registry reported mortality of approximately 40% for VV ECMO patients in 2020, recent large single-institution studies have shown much greater variability. These reports have ranged from 54% mortality in France18, 50% in Germany,[22] 46% in Italy,[26] 74% in Poland,[27] and 60% at our center. Differences in patient characteristics during various pandemic periods may explain the heterogeneity of published ECMO-associated outcomes. For example, early in the pandemic, our patient cohort's median age was significantly higher than in the Delta period, consistent with multi-center data from France.[28] Pre-vaccination, older patients comprised a larger proportion of patients with COVID-19-associated ARDS, which may have biased some centers towards placing relatively older patients on ECMO before evidence on clinical outcomes was available. In contrast, other centers may have been more cautious due to limited resources.[29] In addition to the strong correlation between age and survival, we also found that older patients did not tolerate a longer ECMO duration due to multi-organ failure and sepsis. Our data suggest that a longer duration of ECMO may have benefited some patients later in the pandemic and that firm cut-offs for ECMO duration for COVID-19 should be re-examined.[30]

Differences in COVID-19 variant characteristics, including clinical severity and rapidly changing population immunity due to vaccination and infection, make comparisons across different pandemic periods difficult.[31] It also made patient selection more challenging due to changing demographics of patients affected by the virus. Outside of age and ECMO duration, the primary differences in patient characteristics in our cohort were race and insurance status, but neither contributed to mortality in our analysis. Early in the pandemic, African Americans and Hispanic Whites comprised a much higher proportion of our ECMO cohort compared to later periods which shifted towards insured, non-Hispanic Whites. This finding is consistent with published US data that minority racial and ethnic groups were disproportionally affected by COVID-19, especially in 2020, with a higher risk of infection, hospitalization, and death.[32] The other notable difference was the dramatic decrease in ECMO volume during the Omicron period. Despite rapidly increasing case numbers, the number of patients cannulated for ECMO during the Omicron period was relatively low, with several patients confirmed to be infected with a Delta variant. While our Omicron sample is small, our findings are consistent with evidence that Omicron has a higher case-to-hospitalization ratio than previous variants and may lead to substantially lower rates of ARDS.[33,34] At high volume ECMO centers like ours, ECMO utilization may be a helpful indicator of disease severity as the pandemic evolves.

Our study is limited by its retrospective, single-institution design, which may limit generalizability to other centers. Patient selection criteria were not formally changed during the pandemic, but our results are biased by the patients referred to our center, which trended younger during the Delta period. However, this is one of the largest single-institution cohorts published and restricting our data to our center allowed for a controlled sample of patients with management consistency throughout the pandemic with a complete data set. Working at a single institution also allowed us to partner with the clinical laboratory to perform viral genomic sequencing, which was especially important during the Delta to Omicron transition. Our sample size may limit the ability to identify less common risk factors for mortality.

5. Conclusion

In this large cohort of VV ECMO patients with ARDS secondary to COVID-19, age ≥50 years, a duration of 7 or more days of total respiratory support, and pre-ECMO renal failure requiring dialysis all increased the risk of mortality by approximately 30%. More data is needed on the appropriate duration of ECMO support for COVID-19, especially for younger patients, as some patients appeared to benefit from an extended duration later in the pandemic. Careful consideration of ECMO candidates older than 50 years or with a prolonged course of critical illness is imperative.

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Declaration of competing interest

The authors have no conflict of interest to disclose. The authors have no financial relationships to disclose.

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