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Extracorporeal membrane oxygenation for respiratory failure in phases of COVID-19 variants

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Abstract

Background: Adaptive mutations of the severe acute respiratory syndrome-related coronavirus (SARS-CoV-2) virus have emerged throughout the coronavirus disease 2019 (COVID-19) pandemic. The characterization of outcomes in patients requiring extracorporeal membrane oxygenation (ECMO) for severe respiratory distress from COVID-19 during the peak prevalence of different variants is not well known.

Methods: There were 131 patients with laboratory-confirmed SARS-CoV-2 infection supported by ECMO at two referral centers within a large healthcare system. Three predominant variant phase time windows (Pre-Alpha, Alpha, and Delta) were determined by a change-point analyzer based on random population sampling and viral genome sequencing. Patient demographics and outcomes were compared.

Results: The average age of patients was 46.9 ± 10.5 years and 70.2% (92/131) were male. Patients cannulated for ECMO during the Delta variant wave were younger compared to earlier Pre-Alpha (39.3 ± 7.8 vs. 48.0 ± 11.1 years) and Alpha phases (39.3 ± 7.8 vs. 47.2 ± 7.7 years) ($p < .01$). The predominantly affected race in the Pre-Alpha phase was Hispanic (52.2%; 47/90), while in Alpha (61.5%; 16/26) and Delta (40%; 6/15) variant waves, most patients were White ($p < .01$). Most patients received a tracheostomy (82.4%; 108/131) with a trend toward early intervention in later phases compared to Pre-Alpha ($p < .01$). There was no significant difference between the duration of ECMO, mechanical support, intensive care unit (ICU) length of stay (LOS), or hospital LOS over the three variant phases. The in-hospital mortality was overall 41.5% (54/131) and was also similar. Six-month survival of patients who survived to discharge was 92.2% (71/77).

Conclusions: There was no significant difference in survival or time on ECMO support in patients during the peak prevalence of the three variants.

KEYWORDS
acute respiratory distress syndrome, extracorporeal membrane oxygenation; circulatory support

1 | BACKGROUND

The global effect of coronavirus disease 2019 (COVID-19) has continued to evolve as adaptive mutations in the severe acute respiratory syndrome-related coronavirus (SARS-CoV-2) virus genome emerges. These mutations could alter the pathogenicity of the disease and creates challenges in the development of vaccines and drugs. Four major variants of SARS-CoV-2 have been designated by the World Health Organization (WHO) as variants of concern: Alpha, Beta, Gamma, and Delta.[1,2] A recent meta-analysis found that Beta and Delta variants are associated with a higher risk of hospitalization, ICU admission, and mortality, with the Delta variant having the highest relative risk of severe illness and mortality.[3] The use of extracorporeal membrane oxygenation (ECMO) for patients with severe acute respiratory distress syndrome (ARDS) from COVID-19 who have failed conventional mechanical ventilatory strategies has been described in multiple studies throughout the course of the pandemic.[4–11] Besides limited reports in Europe that have described conflicting trends of patient outcomes on ECMO for COVID-19 ARDS over the course of the pandemic,[12–14] little is known about the characteristics or trends between the eras of SARS-CoV-2 variants at their peak prevalence in the United States. The goal of this study is to describe the outcomes of patients who were placed on ECMO for severe COVID-19 during different variants phases within a single healthcare system.

2 | METHODS

2.1 | Study design

We conducted a retrospective analysis of 131 patients with laboratory-confirmed COVID-19, all of whom were placed on ECMO between April 2020 to November 2021 at two referral centers within a single healthcare system for severe respiratory failure refractory to conventional mechanical ventilatory strategies. Patients still on ECMO at the time of this study were excluded. Patients were further categorized into three predominant variant phases (Pre-Alpha, Alpha, and Delta) based on the date of their first positive COVID-19 test. For the purposes of this study, Pre-Alpha will be defined as viral lineages that were not classified by the WHO as a distinct variant of interest or concern. Alpha is defined as the B.1.1.7 variant and Delta as the B.1.617.2 variant.[2] Variant wave time windows were determined by a change-point analyzer based on random population sampling and COVID-19 sequencing predominantly in the central Texas area within the Baylor Scott & White System. Besides the aforementioned three predominant phases, other minor variants of interest or concern were present in small proportions as represented in the Supporting Information: Figure. The study was approved by the Institutional Review Board and the requirement for informed consent was waived due to the retrospective nature of this study.

2.2 | Patient management

Critical care and daily ECMO were managed by the treatment team at each center. Multidisciplinary team management included medical and surgical intensivists, cardiothoracic surgeons, ECMO specialists, infectious disease specialists, nephrologists, and other consultants as indicated. The clinical indications for ECMO, ECMO settings, and weaning strategies were guided by a system-wide ECMO protocol established by the Baylor Scott & White ECMO Governance Council.[10]

2.3 | Outcome measures

The primary endpoints were in-hospital mortality at the ECMO facility and duration of ECMO support. Secondary outcomes included death after withdrawal of care on ECMO, successful ECMO decannulation, rate of recannulation, rate of tracheostomy, duration of time from ECMO to tracheostomy, length of extracorporeal life support (ECLS), duration of mechanical ventilatory support, length of stay (LOS) in the intensive care unit (ICU), length of stay at ECMO referral center, discharge disposition, postdischarge survival, rates of in-hospital complications, secondary infections, and concurrent ECMO and COVID treatment therapies.

Death after decannulation and the percentage of patients requiring recannulation were calculated from the number of patients who underwent ECMO decannulation. Total continuous ventilatory days, ICU LOS, and total LOS were determined from patients who survived to discharge. The length of ECLS in patients who required recannulation was calculated from the total additive length of time they were on ECMO. Bleeding was defined as new acute blood loss anemia requiring transfusion. Postdischarge survival was determined by a review of hospital medical records and systematic obituary searches using a previously validated protocol.[15]

2.4 | Statistical analysis

Continuous variables were presented as the mean ± standard deviation (SD) or median with interquartile range (IQR) as appropriate, and categorical variables as proportions, unless otherwise specified. Depending on the type of data, Student's t test, unequal variance t test, Mann–Whitney U test, Fisher's exact test, or χ^2 test were used. Kaplan–Meier analysis was used with the log-rank test to determine differences in survival rate between the two groups. A p value of less than .05 was considered statistically significant, and no adjustments were made for multiple comparisons. All statistical analyses were performed using SAS (Statistical Analysis System Institute, Cary, NC).

3 | RESULTS

3.1 | Patients

Between April 2020 and October 2021, there were 131 patients placed on ECMO for COVID-19 ARDS. Based on sequencing patterns, the three variant phases were defined as: Pre-Alpha (before March 14, 2021; $n = 90$), Alpha (March 15, 2021 to July 4, 2021; $n = 26$), and Delta (July 5, 2021 to November 17, 2021); $n = 15$) (Supporting Information: Figure). The baseline demographics and comorbidities of patients are characterized in Table 1. The average age of the entire cohort was 46.9 ± 10.5 years and predominantly male (70.2%; 92/131). However, patients cannulated for ECMO during the Delta variant phase were significantly younger compared to earlier Pre-Alpha (39.3 ± 7.8 vs. 48.0 ± 11.1 years) and Alpha phases (39.3 ± 7.8 vs. 47.2 ± 7.7 years) ($p = .01$). The predominantly affected race in the Pre-Alpha phase was Hispanic (52.2%; 47/90), while in Alpha (61.5%; 16/26) and Delta (40%; 6/15), most patients were White ($p < .01$). In all variant phases, most patients were obese (body mass index [BMI] 35.5 ± 8.4 kg/m^2) and the most common comorbidity was hypertension (36.6%; 48/131).

3.2 | Pre-ECMO characteristics

The median duration of time from reported onset of symptoms was 6 (IQR: 6) days to hospitalization, 10 (IQR: 11) days to intubation, and 16 (IQR: 14) days to ECMO cannulation. These values were similar across all variant phases. There were 82.4% (108/131) patients who were paralyzed and 62.6% (82/131) who were proned before ECMO initiation. The average arterial oxygen partial pressure to fractional inspired oxygen (P/F) ratio was 90.0 ± 38.7 Most patients were cannulated with venovenous ECMO (96.2%; 126/131) (Supporting Information: Table 1).

TABLE 1 Demographics and baseline comorbidities of patients with COVID-19 ARDS undergoing ECMO therapy

	All ($n = 131$)	Pre-Alpha ($n = 90$)	Alpha ($n = 26$)	Delta ($n = 15$)	p Value
Age	46.86 ± 10.50	48.02 ± 11.12	47.23 ± 7.71	39.26 ± 7.84	.01
Gender					
Male	92 (70.23%)	64 (71.11%)	18 (69.23%)	10 (66.67%)	.93
Race					.00
White	47 (35.88%)	25 (27.78%)	16 (61.54%)	6 (40.00%)	
Black	21 (16.03%)	16 (17.78%)	1 (3.85%)	4 (26.67%)	
Hispanic	58 (44.27%)	47 (52.22%)	9 (34.62%)	2 (13.33%)	
Asian	1 (0.76%)	0 (0.00%)	0 (0.00%)	1 (6.67%)	
Middle Eastern/North African	0	0 (0.00%)	0 (0.00%)	0 (0.00%)	
Native Pacific Islander	1 0.76%)	1 (1.11%)	0 (0.00%)	0 (0.00%)	
Other		1 (1.11%)	0 (0.00%)	0 (0.00%)	
Unknown		0 (0.00%)	0 (0.00%)	2 (13.33%)	
BMI	35.52 ± 8.44	35.22 ± 8.29	36.78 ± 10.03	35.08 ± 6.38	.70
HTN	48 (36.64%)	35 (38.89%)	9 (34.62%)	4 (26.67%)	.64
Diabetes	35 (26.72%)	29 (32.22%)	5 (19.23%)	1 (6.67%)	.07
HLD	26 (19.85%)	18 (20.00%)	5 (19.23%)	3 (20.00%)	1.00
COPD	3 (2.29%)	3 (3.33%)	0 (0.00%)	0 (0.00%)	.72
Coronary artery disease	6 (4.58%)	6 (6.67%)	0 (0.00%)	0 (0.00%)	.33
Active smoker	5 (3.82%)	2 (2.22%)	2 (7.69%)	1 (6.67%)	.37
Cancer	6 (4.58%)	6 (6.67%)	0 (0.00%)	0 (0.00%)	.33
Immunosuppression	7 (5.34%)	7 (7.78%)	0 (0.00%)	0 (0.00%)	.18
Renal failure	3 (2.29%)	3 (3.33%)	0 (0.00%)	0 (0.00%)	.72

Note: Continuous variables are expressed either as mean ± standard deviation.

Abbreviations: ARDS, acute respiratory distress syndrome; BMI, body mass index; COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus disease 2019; ECMO, extracorporeal membrane oxygenation; HLD, hyperlipidemia; HTN, hypertension.

3.3 | Concurrent therapies and complications on ECMO

While on ECMO for COVID-19, 48.1% (63/131) patients required continuous renal replacement therapy and 24.4% (32/131) required chest tube placement. While most patients were still being treated with Remdesevir in all three variant phases, there was a trend toward decreased use of convalescent plasma (Pre-Alpha 43.3%; Alpha 15.4%; Delta 6.7%; $p < .01$). There was no difference in stroke, new-onset renal failure, hemorrhagic complications, secondary infections, or ECMO complications between the three phases (Supporting Information: Table 2).

3.4 | Outcomes

The in-hospital mortality was overall 41.5% (54/131) and similar between all three variant phases. Six-month survival of patients who were discharged alive to the last follow-up was 92.2% (71/77) (Figure 1). This was similar between all three groups (Figure 2). Life supporting therapies including ECMO were withdrawn from 36.6% (48/131) of patients due to the futility of care. The remaining 63.4% (83/131) of patients were decannulated; however, 9.6% (8/83) of these patients required recannulation. There were 12 patients who did not survive after being decannulated from ECMO (14.5%; 12/83). In all phases, most patients required tracheostomy (82.4%; 108/131); however, there was a trend toward a shorter duration of time from ECMO to tracheostomy in the more recent Alpha and Delta phases compared to the earliest Pre-Alpha phase (Pre-Alpha 8.5 ± 9.6 vs. Alpha 1.9 ± 3.1 vs. Delta 2.6 ± 2.5 days; $p < .01$). There was no significant difference between the duration of ECLS, mechanical support, ICU LOS, or hospital LOS over the three variant phases (Table 2). Of the patients discharged alive, 62.3% (48/77) were discharged to a long-term assisted care, rehabilitation, or skilled nursing facility, 16.9% (13/77) were transferred back to their referring hospital for continued ventilatory weaning and care, and 20.8% (16/77) were discharged home from the ECMO referral center. Overall, the average length of time when patients were first admitted to a hospital to their arrival home was 111.4 ± 105.8 days.

4 | COMMENT

Two years ago, our center published its early ECMO experience in the COVID-19 ARDS patient population.[10] The pandemic has continued to progress with the evolution of adaptive mutations in the SARS-CoV-2 virus. This study serves as an update to our previous report and contributes to the growing body of evidence in this specific indication for ECMO. We present the outcomes of patients with severe COVID-19 ARDS requiring ECMO support during time frames of different variants of SARS-CoV-2 at their peak prevalence. There was no significant difference in duration of ECLS or in-hospital mortality within the Pre-Alpha, Alpha, and Delta variant waves; however, patients placed on ECMO were younger in the more recent phases and were more likely to be of White ethnicity. The most recent emergence of the Omicron variant is a sobering reminder of the continued challenges we face with the pandemic. Therefore, the continued evaluation of COVID-19 outcomes remains relevant.

During the initial phase of the pandemic, the genomic diversity of SARS-CoV-2 was reportedly low.[16] In December of 2020, the alpha variant was first detected in the United Kingdom.[17] Preliminary data suggested that this variant was more transmissible than previous variants.[18,19] Studies describing the clinical severity of the alpha variant have been inconsistent. A large, matched cohort study using community data in Europe found that the alpha variant was associated with an increased risk of death

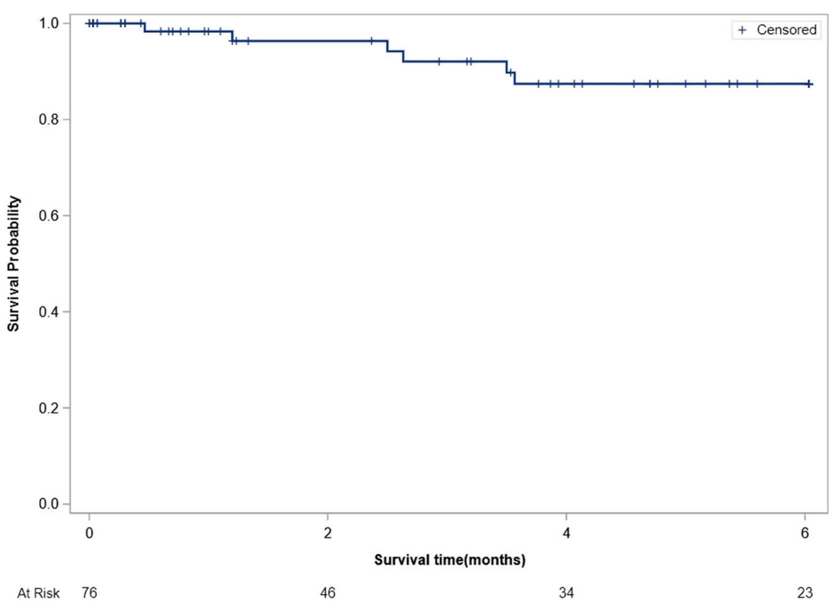

FIGURE 1 Kaplan–Meier curve survival of all coronavirus disease 2019 patients who underwent extracorporeal membrane oxygenation and survived to discharge.

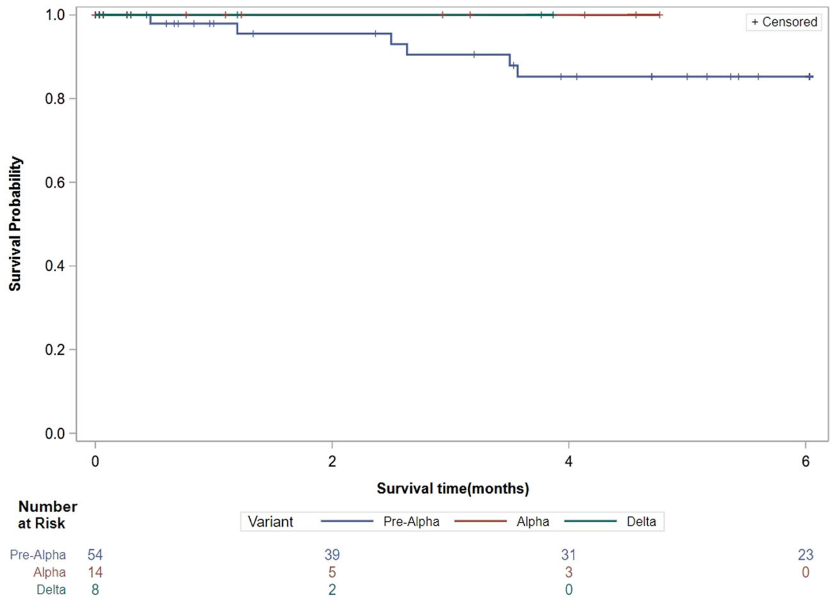

FIGURE 2 Kaplan–Meier survival curve differentiated by variant phases in patients who tested positive for coronavirus disease 2019 and survived to discharge after extracorporeal membrane oxygenation cannulation.

TABLE 2 Outcomes of patients on ECMO therapy

	All (*n* = 131)	Pre-Alpha (*n* = 90)	Alpha (*n* = 26)	Delta (*n* = 15)	*p* Value
Decannulated from ECMO	83 (63.36)	58 (64.44)	16 (61.54)	9 (60.00)	.93
Withdrawn from ECMO	48 (36.64)	32 (35.56)	10 (38.46)	6 (40.00)	.93
Required recannulation	8 (9.64)	7 (12.07)	0 (0)	1 (11.11)	.37
Death after decannulation	12 (14.46)	10 (17.24)	2 (12.5)	0 (0)	.52
Tracheostomy	108 (82.44)	72 (80.00)	23 (88.46)	13 (87.67)	.57
Time from ECMO to tracheostomy (days)	2.5 [6]	4 [12.5]	1 [1]	2 [2]	<.01
Duration of ECLS	22.5 [36]	25 [32]	19 [47]	7 [39]	.19
Duration of mechanical ventilatory support	36 [41]	39 [38]	30 [30]	25 [41]	.05
In-hospital mortality	54 (41.54%)	36 (40.00%)	12 (46.15%)	6 (42.86%)	.89
Length of stay in ICU	41 [41]	41 [42]	43 [58]	27 [30]	.05
Length of stay at ECMO referral center	22.5 [36]	25 [32]	19 [47]	7 [39]	.19
Discharge disposition					.27
Home	16 (20.78)	12 (22.22)	2 (14.29)	2 (22.00)	
Rehabilitation facility	9 (11.69)	8 (14.82)	1 (7.14)	0 (0)	
LTAC	36 (46.75)	23 (42.59)	8 (57.14)	5 (56.00)	
SNF	3 (3.90)	1 (1.85)	0 (0)	2 (22.00)	
Transferred to referring hospital	13 (16.88)	10 (18.52)	3 (21.43)	0 (0)	

Note: Continuous variables are expressed either as median [interquartile range] or mean ± standard deviation.

Abbreviations: ECLS, extracorporeal life support; ECMO, extracorporeal membrane oxygenation; ICU, intensive care unit; LTAC, long-term assisted care; SNF, skilled nursing facility.

with a hazard ratio between 1.32 and 2.04.[20] A smaller retrospective study at a single site hospital similarly demonstrated a significantly higher risk of death or transfer to the ICU.[21] Another multicenter study showed that while the alpha variant was more transmissible, there was no increased disease severity.[19] There have been no studies to the authors' knowledge that have examined the specific outcomes of patients with severe ARDS from the alpha variant of COVID-19 requiring ECMO therapy. Our study did not demonstrate a significant difference in duration of ECLS and in-hospital mortality during the peak prevalence of the alpha variant within our regional healthcare system compared to the other two variants.

The delta variant was designated a variant of concern by the WHO in May 2021.[17] Studies characterizing the clinical implications of this variant remain sparse. A large cohort study from a national database in England showed that compared to alpha, the delta variant was associated with an increased relative risk of hospitalization compared to the alpha variant.[22] Another study based on national surveillance data in Singapore similarly found that the delta variant was associated with increased severity of COVID-19 infection and higher viral load.[23] In our cohort, there was again no difference between outcomes of patients who underwent ECMO therapy for COVID-19 during the peak prevalence of the delta variant compared to others. However, patients who were cannulated for ECMO during this time were significantly younger compared to previous variant phases.

Several studies globally have reported the progression of outcomes in ECMO patients from COVID-19 throughout the pandemic. Data from the EuroECMO survey demonstrated increasing mortality with decreased weaning and survival in the second wave of the pandemic.[13] Similarly, an observational study in France demonstrated longer periods of noninvasive ventilation and worse pulmonary status before ECMO implantation.[14] In Germany, the overall hospital mortality also increased throughout the course of the pandemic.[12] A recent report published by the Extracorporeal Life Support Organization Registry (ELSO) found that in-hospital mortality 90 days after ECMO initiation for COVID-19 after May 1, 2020 was 52% compared to 37% before that date.[24] This corresponds in our data set to the midpoint of the alpha variant phase; however, the in-hospital mortality of our patient cohort was not statistically different between the three variant phases. The overall in-hospital mortality in our cohort of patients was 41%, which remains relatively consistent with our previous study.[10,11] With the growing body of literature, reported survival among different centers is highly variable.[4–9] The ELSO report further showed that mortality approached 60% in late-adopting centers with less experience. A large multicenter study addressing ECMO center experience in the pediatric population demonstrated that ECMO therapy at centers with high case volumes was associated with improved patient survival.[25] This is not entirely surprising, given the fact that ECMO is a resource-intense therapy requiring interdisciplinary team training on intensive care and clinical management, as well as the eligibility criteria.[26,27] As the pandemic progresses, utilization of centers of experience to optimize outcomes for patients while providing adequate training and guidance for building up newer ECMO programs to improve access to therapy is imperative.

Studies evaluating the long-term quality of life outcomes of patients who have recovered from ECMO-supported COVID-19 should be pursued.[28] Reports on non-ECMO patients hospitalized for COVID-19 have shown that a significant proportion of patients remained symptomatic with fatigue, muscle weakness, difficulty sleeping, and psychiatric disturbances as well as physically compromised at 6 months after discharge.[29] Furthermore, multiple studies have demonstrated a decline in healthcare-related quality of life between 12 months to 3 years after decannulation from VV-ECMO for any reason.[30–32] Our study shows that across all time points in the pandemic, the majority of patients were either discharged from the ECMO facility to an assisted facility or back to the referring hospital for ongoing ventilatory weaning and rehabilitation. On average, the duration of time from initial hospital admission for COVID-19 to when patients were able to return home was around 3 months. This reinforces the magnitude of debilitation and length of recovery patients with severe ARDS from COVID-19 face if they survive the acute phase. Moreover, most patients in our cohort underwent tracheostomy. Duration from initiation of ECMO to tracheostomy significantly decreased over the course of the pandemic, which agrees with other groups who advocate for an early tracheostomy to decrease sedation requirements and improve pulmonary toilet in anticipation of the prolonged disease process.[9,33]

4.1 | Limitations

This study is subject to all limitations inherent to any retrospective observational study. In addition, our study is limited to a single healthcare system, so the generalizability of this data is unknown. As the pandemic progressed, the management of COVID-19 has evolved. Importantly, the cohort size within the three variant phases is variable, with this study being performed at the tail end of the delta wave. There are significantly fewer patients in the alpha and delta wave with significant variances in outcomes making it difficult to conclude that the results are not influenced by the small sample size. Several patients in our system who were cannulated during the delta predominant phase remained on ECMO and were excluded from this study. Further studies at later time points will be needed to capture complete data throughout the entire time period of delta variant predominance as well as extend the surveillance period into the predominant Omicron phase. Finally, the viral strain of SARS-CoV-2 that patients were affected by is not exactly known as genomic testing was not performed on all patients included in our cohort. Rather, our study is based on the likelihood of patients being affected by a particular strain based on the correlation of their first positive COVID-19 test to the most prevalent viral lineage at the time based on random population sampling.

5 | CONCLUSION

This report presents the outcomes of COVID-19 patients on ECMO from a large healthcare system with multiple ECMO referral centers throughout the different variant predominant phases of the pandemic. Our data did not identify significantly different survival or duration of ECLS throughout the three predominant variant phases within this region. However, there was a trend toward younger patients of White ethnicity as the pandemic progressed. Further studies are necessary to reinforce or refute our findings and better characterize outcomes between different variants.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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