Analysis of COVID-19 Patients With Acute Respiratory Distress Syndrome Managed With Extracorporeal Membrane Oxygenation at US Academic Centers

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Objective: This study analyzed the outcomes of COVID-19 patients with ARDS who were managed with extracorporeal membrane oxygenation (ECMO) across 155 US academic centers.

Summary Background Data: ECMO has been utilized in COVID-19 patients with acute respiratory distress syndrome (ARDS) and refractory hypoxemia. Early case series with the use of ECMO in these patients reported high mortality exceeding 90%.

Methods: Using ICD-10 codes, data of patients with COVID-19 with ARDS, managed with ECMO between April and September 2020, were analyzed using the Vizient clinical database. Outcomes measured included in-hospital mortality, hospital and ICU length of stay, and direct cost. For comparative purposes, the outcome of a subset of COVID-19 patients aged between 18 and 64 years and managed with versus without ECMO were examined.

Results: 1,182 patients with COVID-19 and ARDS received ECMO. In-hospital mortality was 45.9%, mean length of stay was 36.8 ± 24.9 days, and mean ICU stay was 29.1 ± 17.3 days. In-hospital mortality according to age group was 25.2% for 1 to 30 years; 42.2% for 31 to 50 years; 53.2% for 51 to 64 years; and 73.7% for $\geq$65 years. A subset analysis of COVID-19 patients, aged 18 to 64 years with ARDS requiring mechanical ventilation and managed with (n = 1113) vs without (n = 16,343) ECMO, showed relatively high in-hospital mortality for both groups (44.6% with ECMO vs 37.9% without ECMO).

Conclusions: In this large US study of patients with COVID-19 and ARDS managed with ECMO, the in-hospital mortality is high but much lower than initial reports. Future research is needed to evaluate which patients with COVID-19 and ARDS would benefit from ECMO.

Keywords: acute respiratory distress syndrome, ARDS, coronavirus, COVID-19, ECMO, extracorporeal membrane oxygenation

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February 2020 marked the first case of the coronavirus disease 2019 (COVID-19) in the United States (US).[1] As of January, 20, 2021, there have been more than 24 million cases and more than 400,000 deaths in the US.[2] The mortality associated with COVID-19 for patients presenting with respiratory failure or acute respiratory distress syndrome (ARDS) requiring mechanical ventilation is >50%.[3,4] While mechanical ventilation is a cornerstone for management of patients with ARDS, the risk of ventilator-induced lung injury remains a concern. In a subset of patients with severe ARDS who remain hypoxic and unresponsive to conventional therapy including prone positioning, corticosteroids, and paralysis, extracorporeal membrane oxygenation (ECMO) has been used at certain centers.[5] Unfortunately there is paucity of data for ECMO therapy in COVID-19 patients with severe ARDS. Preliminary small case series showed poor survival with mortality in excess of 90%.[6,7] The National Institute of Health (NIH) COVID-19 treatment guidelines state that there are insufficient data to recommend either for or against the routine use of ECMO for patients with COVID-19 and refractory hypoxemia.[8] There has been only a single large-scale, multicenter study to date reporting on 1032 COVID-19 patients who underwent ECMO in 36 countries.[9] The in-hospital mortality in 968 patients with final disposition was 39%.[9] This largest study to date provided provisional support for the use of ECMO in COVID-19-related respiratory failure.[9] The objective of our study was to analyze the outcomes of COVID-19 patients with ARDS managed with ECMO across US academic centers. We hypothesize that ECMO therapy in patients with COVID-19 and ARDS may be appropriate in selected patients.

METHODS

Data Source

The Vizient database is an administrative, clinical, and financial database for more than 650 academic, complex teaching and community hospitals in the US. The Vizient database is a collection of patient-level, discharge data extracted from hospital billing systems. It contains discharge information on in-patient hospital stay including patient demographics, comorbidities, length of hospital and intensive care unit (ICU) stay, in-hospital mortality, and direct hospitalization cost. Direct cost relates to the cost of care and is calculated by the total cost minus the indirect cost. The Vizient database is confined to index hospitalization data and thus has no information available on mortality or complications occurring after discharge. Approval for the use of the Vizient patient-level data in this study was obtained from Vizient, as well as approval and waiver of consent from the Institutional Review Board of the University of California, Irvine as exempted status.

Population and Cohort Identification

This study was a retrospective analysis of the Vizient clinical database for deidentified data of COVID-19 patients with a diagnosis

of ARDS or respiratory failure who underwent ECMO therapy between April 1, 2020 and September 31, 2020. This analysis was performed as of January 20, 2021. Patients with COVID-19 were identified using International Classification of Disease, Tenth edition (ICD-10) diagnosis code of U07.1. Patients with diagnoses of ARDS or acute respiratory failure were identified using ICD-10 diagnosis codes of J80, J960, J9601, J9600, and J9602. Patients who underwent ECMO were identified using ICD-10 procedural codes of 5A1522F, 5A1522G, 5A152H 5A15A2G, 5A15A2F, 5A15A2H. Patients needing respiratory intubation and mechanical ventilation were identified using ICD-10 procedural codes for the insertion of endotracheal airway (5A1955Z, 0B110F4, 0B113F4, 0BH13EZ, 0BH17EZ, and 0BH18EZ).

Demographics and Characteristics

Age, sex (self-reported), race/ethnicity (self-reported and confined to options provided by Vizient), and insurance payer types were analyzed. Pre-existing comorbidities were identified based on the Vizient Elixhauser comorbidity list to include uncomplicated and complicated hypertension, diabetes, obesity, coagulation deficiency, anemia, renal failure, congestive heart failure, and chronic pulmonary disease.

Outcomes

The primary outcome was in-hospital mortality. Secondary outcomes included length of hospital stay, length of ICU stay, and hospitalization direct cost. Outcomes were also analyzed according to age group of 1 to 30 years, 31 to 50 years, 51 to 64 years, and ≥65 years. For comparative purposes, a subset of the ECMO cohort limited to 18 to 64 years was compared to a similar cohort of patients with COVID-19 and ARDS who did not receive ECMO therapy.

Statistical Analysis

Descriptive statistics were calculated and expressed as mean ± standard deviation for continuous variable and absolute number and relative frequencies (%) of total for categorical variables. Proportional differences in patient characteristics between groups were analyzed using the Pearson's Chi-square test. Continuous variables were compared using Student *t* tests. Statistical analyses were performed using SAS 9.4 (SAS Institute Inc, Carey, NC). A *P* value of less than 0.05 was considered significant.

RESULTS

A total of 1182 COVID-19 patients with ARDS who underwent ECMO therapy from 155 US academic centers and their affiliates (range, 1–38 cases per center) were identified. The distribution of demographics and characteristics of COVID-19 patients who underwent ECMO stratified by in-hospital morality is presented in Table 1. The study cohort were 71.4% male gender, 38.4% Hispanic ethnicity, and 47.3% had commercial insurance payers. Of the entire cohort 11.4% were 1 to 30 years-old, 46.5% were 31 to 50 years-old, 37.2% were 51 to 64 years-old, and 4.8% were ≥65 years-old. The most common comorbidities were obesity (58.3%), hypertension (53.5%), and diabetes (36.0%). In unadjusted analyses, when compared with patients who survived, the patients who died were more likely to be male (72.9% vs 68.9%, $P = 0.04$); age 51 to 64 years (43.2% vs 32.2%, $P < 0.001$); age ≥65 years (7.8% vs 2.3%, $P < 0.001$), and more likely to have a coagulation deficiency (29.0%

TABLE 1. Summary of Characteristics of COVID-19 Patients With ARDS Who Were Managed With ECMO, Stratified According to In-hospital Mortality

	All Patients (N = 1182)	Survivors (n = 640)	Deceased (n = 542)	*P* Value†
Sex, no (%)				
Female	338 (28.6)	199 (31.1)	139 (25.6)	$P = 0.04$
Male	844 (71.4)	441 (68.9)	403 (72.9)	$P = 0.04$
Age group, no. (%)				
1–30	135 (11.4)	101 (15.8)	34 (6.3)	$P < 0.01$
31–50	550 (46.5)	318 (49.7)	232 (42.8)	$P = 0.01$
51–64	440 (37.2)	206 (32.2)	234 (43.2)	$P < 0.01$
≥ 65	57 (4.8)	15 (2.3)	42 (7.8)	$P < 0.01$
Race/ethnicity, no. (%)				
Caucasian	376 (31.8)	198 (30.9)	178 (32.8)	$P = 0.48$
African American	256 (21.7)	151 (23.6)	105 (19.4)	$P = 0.08$
Asian	62 (5.2)	39 (6.1)	23 (4.2)	$P = 0.15$
Other/unknown	488 (41.2)	252 (39.4)	236 (43.5)	$P < 0.01$
Hispanic*	502 (38.4)	270 (42.2)	232 (42.8)	$P = 0.83$
Payer no. (%)				
Commercial	559 (47.3)	305 (47.7)	254 (46.9)	$P = 0.79$
Medicare/Medicaid/State-assisted	490 (40.7)	268 (41.9)	222 (41.0)	$P = 0.75$
Existing comorbidities, no. (%)				
Obesity	689 (58.3)	394 (61.6)	295 (54.4)	$P = 0.01$
Hypertension	632 (53.5)	332 (51.9)	300 (55.4)	$P = 0.23$
Diabetes	425 (36.0)	217 (33.9)	208 (38.4)	$P = 0.11$
Anemia	279 (23.6)	158 (24.7)	121 (22.3)	$P = 0.34$
Coagulation deficiency	280 (23.7)	123 (19.2)	157 (29.0)	$P < 0.01$
Chronic pulmonary disease	211 (17.9)	102 (15.9)	109 (20.1)	$P = 0.06$
Renal failure	134 (11.3)	73 (11.4)	61 (11.2)	$P = 0.93$
Congestive heart failure	119 (10.1)	58 (9.1)	61 (11.3)	$P = 0.21$

Stated proportion represent the proportion of the characteristics for all patients, survivors or deceased.
†Chi-square tests.
*Including White Hispanic, Black Hispanic, Asian Hispanic, and other Hispanic.

TABLE 2. Outcomes of COVID-19 Adults With ARDS Who Were Managed With ECMO

Outcomes	Overall N = 1182
In-hospital mortality, n (%)	542 (45.9)
In-hospital mortality according to age group, n (%)	
1–30	34 of 135 (25.2)
31–50	232 of 550 (42.2)
51–64	234 of 440 (53.2)
≥ 65	42 of 57 (73.7)
Mean length of hospital stay (d)	36.8 ± 24.9
Mean length of ICU stay (d)	29.1 ± 17.3
Mean direct cost ($)	137,376 ± 103,496
Discharge status, n	
To another rehab or other facility	324 (27.4)
To home	194 (16.4)
To long-term care hospital	111 (9.4)
Expired	542 (45.9)
Unknown	2 (0.2)
Hospice	9 (0.8)

ARDS indicates acute respiratory distress syndrome.

vs 19.2%; $P < 0.01$). For the cohort of COVID-19 patients with ARDS who underwent ECMO therapy, other concomitant diagnoses included acidosis (42.6%), alkalosis (18.0%), fluid overload (33.5%), hypovolemia (15.1%), hypernatremia (55.5%), hyponatremia (33.5%), hypokalemia (36.9%), hyperkalemia (36.2%), malnutrition (26.4%), sepsis unspecified (12.6%), other sepsis (54.5%), encephalopathy (27.9%), and viral pneumonia (94.8%),

Outcomes

The outcomes for COVID-19 patients with ARDS who were managed with ECMO are presented in Table 2. The all-cause, in-hospital mortality rate was 45.9%. The mean length of stay was 36.8 ± 24.9 days. The mean length of ICU stay was 29.1 ± 17.3 days. The direct cost of hospitalization was $137,376 ± 103,496. Location of discharge status included rehabilitation, skilled nursing or other facility (27.4%), home (16.4%), long-term care facility (9.4%), hospice (0.8%), unknown (0.2%), and expired (45.9%)

Association of Age With In-hospital Mortality for COVID-19 Patients Who Underwent ECMO

The in-hospital mortality according to age group is presented in Figure 1. The in-hospital mortality according to age group was 25.2% for age 1 to 30 years; 42.2% for age 31 to 50 years; 53.2% for age 51 to 64 years; and 73.7% for age ≥65 years (Table 2).

COVID-19 Patients With ARDS on Mechanical Ventilation Managed With Versus Without ECMO

The subset analysis of COVID-19 patients with ARDS requiring mechanical ventilation, age between 18 to 64 years, managed with and without ECMO is presented in Table 3. For the group that was managed with ECMO (n = 1113), the in-hospital mortality rate was higher for patients managed with ECMO compared with patients not receiving ECMO (44.6% vs 37.9%, $P < .01$). When compared to patients not receiving ECMO, patients receiving ECMO had an increased mean length of stay (37.1 ± 24.9 days vs 23.1 ± 18.8 days, $P < 0.01$), and mean direct cost ($138,403 ± 99,173 vs $48,419 ± 44,799, $P < 0.01$).

DISCUSSION

In this large national cohort analysis of COVID-19 patients with ARDS who underwent ECMO therapy, the overall in-hospital mortality was 45.9% which is substantially lower than initial early reports.[6,7] Among patients with COVID-19 who underwent ECMO therapy, there was an increase in mortality with increasing age with the highest mortality among patients over 65 years old. In a subset analysis of COVID-19 patients with ARDS who were between 18–64 years, we found a high mortality rate for patients managed with and without ECMO therapy (44.6% vs. 37.9%, respectively). As ECMO is generally employed in patients that have failed aggressive ventilatory support, representing a sicker patient population when compared to non-ECMO patients, a relatively similar mortality between these groups may represent a number of lives saved. Our comparative analysis also demonstrated that the use of ECMO therapy significantly increase the length of stay as well as hospitalization cost and therefore selection for ECMO therapy should be taken within the context of available institutional resources.

Early reports of ECMO in management of COVID-19 patients demonstrated exceedingly high mortality.[6,7] In a pooled analysis of

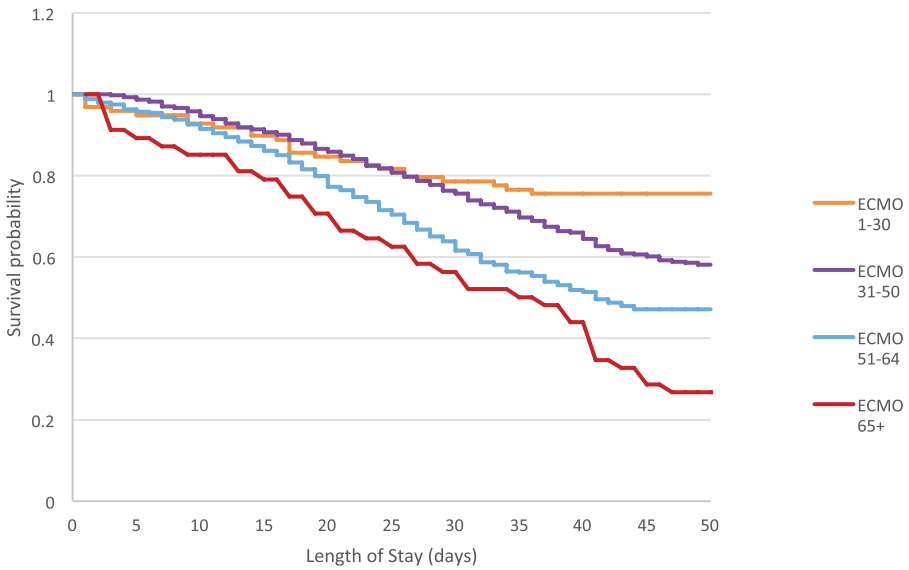

FIGURE 1. In-hospital mortality of COVID-19 patients with ARDS who underwent ECMO, according to age group.

TABLE 3. Characteristics and Outcomes for COVID-19 Patients With ARDS, Age Between 18 and 64 Years, Who Were Managed With Versus Without ECMO

Characteristics and Outcomes	Without ECMO (n = 16,343)	With ECMO* (n = 1113)	*P* Value*
Sex, no (%)			
Female	5789 (35.4)	315 (28.3)	$P<0.01$
Male	10,550 (64.6)	798 (71.7)	$P < 0.01$
Age group, no. (%)			
18–30	832 (5.1)	123 (11.1)	$P < 0.01$
31–50	5113 (31.3)	550 (49.4)	$P < 0.01$
51–64	10,398 (63.6)	440 (39.5)	$P < 0.01$
Race/ethnicity, no. (%)			
Caucasian	5773 (35.3)	348 (31.3)	$P < 0.01$
African American	4468 (27.3)	246 (22.1)	$P < 0.01$
Asian	625 (3.8)	53 (4.8)	$P = 0.12$
Other/unknown	5477 (33.5)	466 (41.9)	$P < 0.01$
Hispanic*	6335 (38.8)	478 (42.9)	$P < 0.01$
Existing comorbidities, no. (%)			
Obesity	7921 (48.5)	662 (59.5)	$P < 0.01$
Hypertension	10,046 (61.5)	584 (52.5)	$P < 0.01$
Diabetes	7434 (45.5)	400 (35.9)	$P < 0.01$
Anemia	4954 (30.3)	271 (24.3)	$P < 0.01$
Coagulation deficiency	2690 (16.5)	264 (23.7)	$P < 0.01$
Chronic pulmonary disease	2919 (17.9)	200 (18.0)	$P = 0.93$
Renal failure	3239 (19.8)	119 (10.7)	$P < 0.01$
Congestive heart failure	2113 (12.9)	105 (9.4)	$P < 0.01$
In-hospital mortality, n (%)	6191 (37.9)	497 (44.6)	$P < 0.01$
Mean length of stay (d)	23.1 ± 18.8	37.1 ± 24.9	$P < 0.01$
Mean direct cost ($)	$48{,}419 \pm 44{,}799$	$138{,}403 \pm 99{,}173$	$P < 0.01$

*Chi-squared or Student *t* tests with unequal variance.
ARDS indicates acute respiratory distress syndrome.

early reports, Henry et al. reported on 234 COVID-19 patients with ARDS; 17 underwent ECMO with a mortality rate of 94.1%.[6] The largest series to date was reported from the extracorporeal life support organization (ELSO) registry on 1,032 patients who underwent ECMO for management of ARDS related to COVID-19.[9] Their study reported a 39% mortality rate for patients with final disposition.[9] In the current study, the mortality rate for COVID-19 patients with ARDS managed with ECMO is relatively similar to that of the ELSO registry at 45.9%. One major difference worth noting is the ELSO registry likely included higher volume ECMO centers, whereas our study is inclusive of all academic centers performing ECMO for COVD-19 patients in the US. In our analysis, 36 of 155 centers performed only a single case of ECMO for COVID-19 as of the time of our analysis. The low volume in many of these US centers may explain the higher in-hospital mortality in our study compared to that of the ELSO registry.

There are several limitations to this study. This is a retrospective study of an administrative database that is reliant on the accuracy and input of data, documentation of appropriate and consistent diagnosis and procedural codes, and is subject to misclassification and missing data. Furthermore, the Vizient database is limited to in-hospital mortality, without follow-up data thus underrepresents the true mortality rate. The Vizient database also lacks pertinent clinical information including ventilator status, radiologic evaluations and laboratory tests to determine the extent and severity of ARDS. Without these additional data, it would not be possible to find a similar group of COVID-19 patients with severe ARDS and refractory hypoxemia for comparative purposes. In other words, the ECMO vs. non-ECMO groups are not similar as the ECMO group is a much sicker patient population. Our comparative analysis between groups was meant to provide comparative data on the high risk of death of COVID-19 patients with ARDS requiring mechanical ventilation with an understanding that this control group likely has a much lower severity of ARDS compared to the group of patients who were managed with ECMO therapy. Despite these limitations, this study is the largest US study to date reporting on the outcome of COVID-19 patients with ARDS and managed with ECMO. Our data showing >50% survival, supports the provision in the use of ECMO for COVID-19-related ARDS. Additionally, our study adds to the literature showing the use of ECMO in COVID-19 patients led to a substantial increase in cost and length of hospitalization. Therefore, these findings should be taken into consideration when deciding to use ECMO therapy during this and future pandemics.

CONCLUSIONS

In this large, US study of COVID-19 patients with ARDS who underwent ECMO therapy, the overall in-hospital mortality was 45.9% which is much lower than initial reports. Analysis of a subset of COVID-19 patients with ARDS managed with vs. without ECMO demonstrated a relatively high but similar mortality. This likely represents the efficacy of ECMO as a salvage therapy which is applied to patients who have failed conventional ventilatory support. Our findings refute previous reports of futility for ECMO therapy in the setting of COVID-19. Future research is needed to evaluate which subset of patients with COVID-19 would benefit from ECMO therapy.

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