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Extracorporeal Carbon Dioxide Removal With the Hemolung in Patients With Acute Respiratory Failure: A Multicenter Retrospective Cohort Study*

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OBJECTIVES: Extracorporeal carbon dioxide removal ($ECCO_2R$) devices are effective in reducing hypercapnia and mechanical ventilation support but have not been shown to reduce mortality. This may be due to case selection, device performance, familiarity, or the management. The objective of this study is to investigate the effectiveness and safety of a single $ECCO_2R$ device (Hemolung) in patients with acute respiratory failure and identify variables associated with survival that could help case selection in clinical practice as well as future research.

DESIGN: Multicenter, multinational, retrospective review.

SETTING: Data from the Hemolung Registry between April 2013 and June 2021, where 57 ICUs contributed deidentified data.

PATIENTS: Patients with acute respiratory failure treated with the Hemolung. The characteristics of patients who survived to ICU discharge were compared with those who died. Multivariable logistical regression analysis was used to identify variables associated with ICU survival.

INTERVENTIONS: None.

MEASUREMENTS AND MAIN RESULTS: Of the 159 patients included, 65 (41%) survived to ICU discharge. The survival was highest in status asthmaticus (86%), followed by acute respiratory distress syndrome (ARDS) (52%) and COVID-19 ARDS (31%). All patients had a significant reduction in $Paco_2$ and improvement in pH with reduction in mechanical ventilation support. Patients who died were older, had a lower Pao_2:Fio_2 (P/F) and higher use of adjunctive therapies. There was no difference in the complications between patients who survived to those who died. Multivariable regression analysis showed non-COVID-19 ARDS, age less than 65 years, and P/F at initiation of $ECCO_2R$ to be independently associated with survival to ICU discharge (P/F 100–200 vs <100: odds ratio, 6.57; 95% CI, 2.03–21.33).

CONCLUSIONS: Significant improvement in hypercapnic acidosis along with reduction in ventilation supports was noted within 4 hours of initiating $ECCO_2R$. Non-COVID-19 ARDS, age, and P/F at commencement of $ECCO_2R$ were independently associated with survival.

KEY WORDS: acute respiratory failure; extracorporeal carbon dioxide removal; hypercapnia; respiratory acidosis; survival

Reducing tidal volume and driving pressures is known to improve survival in mechanically ventilated patients (1, 2). Such lung protective ventilation strategies may cause hypercapnic acidosis in some patients. Several recent studies have shown that acute hypercapnia, especially when associated with acidosis, is associated with an increased risk of mortality and morbidity (3–7). Low-flow extracorporeal carbon dioxide removal ($ECCO_2R$)

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KEY POINTS

Question: What is the effectiveness and safety of a single $ECCO_2R$ device (Hemolung) in patients with acute respiratory failure and what are the characteristics associated with survival?

Findings: Significant improvement in hypercapnic acidosis was noted within 4 hours of initiation $ECCO_2R$. COVID-19 ARDS, age, and P/F ratio at the commencement of $ECCO_2R$ were independently associated with ICU survival.

Meaning: This study provides insights into patient selection for future clinical trials as well as real world use of $ECCO_2R$.

devices are currently used to correct hypercapnia and hypercapnic acidosis while instituting lung protective ventilation (8–11).

Low-flow $ECCO_2R$ devices have been shown to be effective at removing carbon dioxide from blood (11–13). However, there are substantial differences in the CO_2 removal capacities of the $ECCO_2R$ devices used in recent studies, and the optimal blood flow required for clinical practice is yet to be defined (14–17). Although randomized controlled trials (RCTs) are now being published (8, 18, 19), the efficacy of $ECCO_2R$ devices in acute or acute on chronic hypercapnic respiratory failure is poorly understood. In part, this is because of the heterogeneity of the patient pathologies including those with acute and chronic hypercapnic acidosis (11, 14, 16, 20).

RCTs investigating $ECCO_2R$ in acute respiratory distress syndrome (ARDS) patients did not show a reduction in mortality (8, 18, 21). Indeed, the results of the recent RCTs provided conflicting results with the Xtravent study showing a benefit in terms of increase in ventilator-free days in patients with ARDS (Pao_2:FIO_2 [P/F] <150) (8), whereas the REST study showed potential harm with a reduction in ventilator-free days (18) in similar ARDS patients with P/F less than 150. It is likely that case selection, type of device used (arteriovenous vs venovenous $ECCO_2R$), device familiarity, or the management of the device contributed to the differences in the outcomes. Published data on $ECCO_2R$ devices suggest that variations in device performance can impact the complications including hemolysis and bleeding as well as the overall outcomes of the patients (22).

Given these factors, it is important to have $ECCO_2R$ device-specific performance and safety data that can help in selecting the most appropriate $ECCO_2R$ device to treat the clinical condition of the patient. To the best of our knowledge, there are no large studies that specifically investigated the performance of $ECCO_2R$ devices or patient characteristics to identify the factors that are independently associated with the survival of patients. Such data will inform case selection in routine practice as well as design of clinical trials.

The aim of this study was to investigate a single $ECCO_2R$ device (Hemolung, ALung Technologies, Pittsburgh, PA) in patients with acute respiratory failure and identify factors that are independently associated with survival of patients.

MATERIALS AND METHODS

This retrospective, multicenter, multinational study included patients treated with the Hemolung for acute respiratory failure and whose data were submitted to the Hemolung Registry between April 2013 and June 2021. Seventy centers provided data to the registry during the period, of which 57 centers had patients with acute respiratory failure.

Hemolung RAS Registry

The voluntary Hemolung Registry is maintained by ALung Technologies and includes deidentified patient data as well as device safety and performance data. The data available in the Registry included demographics, diagnosis, comorbidities, indications for the use of $ECCO_2R$, therapy course including the mechanical ventilation and $ECCO_2R$ settings, complications, and the outcome of the patients.

In the United States, the Hemolung was used under Food and Drug Administration Investigational Device Exemption or Emergency Use Authorization for COVID-19. Outside of the United States, Hemolung therapies were conducted in compliance with each country's or region's necessary approval for use at the discretion of the physician caring for the patient.

The Hemolung Registry Program collects deidentified standard of care data on patients treated with the Hemolung in a retrospective manner. There is no requirement to collect and report data outside of standard of care. Based on federal regulation 45 Code of Federal Regulations 46 and associated guidance, no

institutional review board review was necessary (and, thus, no number was assigned) because it did not fall under the board's guidelines as human subject research.

Aims and Objectives

1) To provide clinical characteristics of patients with acute lung injury treated with Hemolung.
2) Assess the efficacy of Hemolung on CO_2 clearance and reduction of mechanical ventilation support.
3) Safety of Hemolung.
4) Compare the characteristics of patients who died in ICU with those who survived and identify variables independently associated with survival to ICU discharge.

Inclusion Criteria. Patient data were included in the analysis if the following criteria were all met: 1) data were part of the ALung Registry, 2) patients were diagnosed with acute respiratory failure, and 3) ICU discharge status was known.

Exclusion Criteria. Patients with chronic lung conditions, such as chronic obstructive pulmonary disease, emphysema, pulmonary fibrosis, or cystic fibrosis, were excluded.

Outcomes

Primary Outcome. The primary outcome includes improvement in pH and $Paco_2$ during the first 36 hours of Hemolung therapy.

Secondary Outcomes.

1) Reduction in mechanical ventilation support including minute ventilation, respiratory rate, tidal volume, and peak inspiratory pressure with the use of Hemolung during the first 36 hours.
2) Survival to ICU discharge.
3) Safety and complications, which occurred throughout the entirety of Hemolung therapy.

Hemolung

The Hemolung (ALung Technologies) has been specifically designed and optimized for low-flow venovenous $ECCO_2R$. The Hemolung is composed of the catheter, disposable cartridge, and system controller. The Hemolung Catheter is a 15.5-Fr dual-lumen central venous catheter placed in either the femoral or jugular vein. The device removes up to 50% of basal metabolic CO_2 production at extracorporeal blood flows of 350–550 mL/min. Anticoagulation is required to prevent blood clotting during the therapy with a recommended target of an activated partial thromboplastin time (APTT) of 1.5–2 times the upper limit of normal range or equivalent. The recommended target for this study was defined as aPTT of 50–70 seconds based on the aPTT reported in previous studies (11, 23).

Statistical Analysis

Continuous variables are reported as mean ± SD or median (interquartile range), and categorical variables with counts and percentages. Descriptive two-sided *p* values (Wilcoxon rank-sum for continuous variables and Fisher exact for categorical variables) provided nominal statistical association measures. Data were grouped into time intervals of pre-Hemolung, 4–8 hours, and 16–35 hours on Hemolung. Linear models were constructed and summarized the values over time and change from baseline in pH, $Paco_2$, and ventilator settings. The estimates at each interval were summarized with two-sided 95% CIs and the change from baseline summarized with paired *t* test *p* values. A two-tailed *p* value of less than 0.05 indicated statistical significance for those analyses. Multivariate logistic regression models were used to identify variables independently associated with survival to ICU discharge. Some variables were categorized (body mass index >30, P/F split at 100 and 200, pH at 7.30, and $Paco_2$ at 70 mm Hg) to promote clinical interpretation. This may have reduced statistical power at the expense of clinical interpretation, and sensitivity analyses based on continuous data demonstrate that the modeling choice is robust in this regard. The use of multivariate logistic regression was used to control for correlations among the various risk factors. Given the exploratory nature of this study, *p* values for variables associated with ICU survival were not provided, and instead, study findings are provided as uni- and multivariable-controlled odds ratios with 95% CIs. The use of CIs rather than *p* values achieves the aim of correcting for multiple comparisons, and therefore, no additional correction was needed or applied. All analyses were performed using SAS Version 9.4 (SAS Institute, Cary, NC).

RESULTS

A total of 159 patients were included in the final analysis (**Supplemental Fig. 1**, http://links.lww.com/CCM/H315). Of the 159 patients, three patients were noninvasively ventilated, and one patient did not receive mechanical ventilation. The remaining patients were all invasively mechanically ventilated at the time

TABLE 1.
Patient Characteristics at the Time of Initiation of Hemolung

Variable	Estimate
Age (yr) (median [IQR]) ($n = 156$)	55.50 (44.50–64.00)
Sex (male:female; %) ($n = 156$)	106:50 (66.67:31.45)
Body mass index (median [IQR]) ($n = 151$)	28.1 (24.2–34.9)
Comorbidities, *n* (%) (*n = 159)*	
Congestive cardiac failure	5 (3.14)
Coronary artery disease	8 (5.03)
Pulmonary hypertension	5 (3.14)
Obstructive sleep apnea	8 (5.03)
Diabetes	39 (24.53)
Renal failure	16 (10.06)
Cirrhosis of liver	1 (0.63)
HIV infection	3 (1.89)
Admission diagnosis, n (%) ($n = 159$)	
Acute respiratory distress syndrome (non-COVID-19)	58 (36.48)
COVID-19	88 (55.35)
Status asthmaticus	7 (4.4)
Other	6 (3.77)
Arterial blood gases	
pH median (IQR) ($n = 155$)	7.23 (7.16–7.33)
Pa_{O_2} (mm Hg), median (IQR) ($n = 156$)	79.25 (67.5–100)
Pa_{CO_2} (mm Hg), median (IQR) ($n = 155$)	73.5 (60.00–90.00)
H_{CO_3} (mmol), median (IQR) ($n = 149$)	30 (24.60–35.80)
Sa_{O_2} (%), median (IQR) ($n = 151$)	94.50 (90.30–97.00)
F_{IO_2} (%), median (IQR) ($n = 148$)	75.00 (50–100.00)
Adjunctive therapies, *n* (%) ($n = 159$)	
Nonrespiratory[a]	19 (11.95)
Respiratory[b]	70 (44.02)
None	50 (31.45)
Not determined	20 (12.58)
Location, *n* (%)	
Europe	64 (40.25)
United States	90 (56.60)
Other	5 (3.14)

IQR = interquartile range.

[a]Nonrespiratory adjunctive therapies included: continuous renal replacement therapy, continuous venovenous hemodialysis, hemodialysis, convalescent plasma, left ventricular assist device/right ventricular assist device/biventricular assist device, plasmapheresis, and primasol.

[b]Respiratory adjunctive therapies included: extracorporeal membrane oxygenation, proning, lung recruitment maneuvers, inhaled epoprostenol, and inhaled nitric oxide.

of Hemolung therapy initiation. The characteristics of the patients included are presented in **Table 1**.

The changes in blood gases and the ventilator settings following the initiation of Hemolung are presented in **Supplemental Table 1** (http://links.lww.com/CCM/H315). A significant reduction in $Paco_2$, increase in pH with reduction in minute ventilation, and peak inspiratory pressure were noted at all the time intervals during the first 36 hours of therapy (Supplemental Table 1, http://links.lww.com/CCM/H315).

Overall, 65 of the 159 patients (41%) included in the study survived to ICU discharge. A comparison of the patients who died with those who survived to ICU discharge is presented in **Table 2**. Patients who survived to ICU discharge were younger and had higher P/F ratio (**Table 2**). The survival rate was different in various diagnostic categories, with highest rate of survival seen in status asthmaticus (86%; six out of seven patients), followed by ARDS patients (52%; 30 out of 58 patients) and lowest in COVID-19 ARDS patients (31%; 27 out of 88 patients).

The anticoagulation management of Hemolung differed between survivors and nonsurvivors, where a higher proportion of nonsurvivors did not receive the recommended target of anticoagulation (**Table 3**). There were no differences in blood gases, reduction in mechanical ventilator settings, Hemolung blood flow, or carbon dioxide removal rates between the survivors and nonsurvivors (**Supplemental Table 2**, http://links.lww.com/CCM/H315).

The rate of occurrence of complications did not differ significantly between survivors and nonsurvivors (**Table 4**). Multivariable logistic regression analysis showed pre-Hemolung P/F ratio, and the diagnosis at admission was independently associated with survival to ICU discharge. A P/F ratio more than 100, age less than 65 years, and non-COVID-19 ARDS were independently associated with increased survival to ICU discharge (**Table 5**). The discrimination of the model was good with an area under the curve of 0.83 (**Supplemental Fig. 2**, http://links.lww.com/CCM/H315).

DISCUSSION

Key Findings

This study showed correction of hypercapnia and improvement in pH along with a reduction in minute ventilation, respiratory rate, and tidal volumes with the use of Hemolung. Multivariable logistic regression analysis showed age, P/F ratio greater than 100 prior to initiation of Hemolung, and the diagnosis of non-COVID-19 ARDS to be independently associated with ICU survival.

Relationship With Previous Studies

The study further supports the findings from several other previous studies that low-flow $ECCO_2R$ devices such as Hemolung are effective in improving hypercapnia while reducing the lung injury due to invasive mechanical ventilation (8, 11, 14, 16, 20). The overall survival rate of patients in this study is about 41% and is comparable with other studies that used $ECCO_2R$ (8, 23, 24). The mortality observed in this study showed significant differences across the diagnostic categories with a very low survival in COVID-19 ARDS patients (31%).

Respiratory failure with COVID-19 ARDS during the first few months of the pandemic showed a very high mortality (>60%) especially in patients who required invasive mechanical ventilation (25). This was largely related to increased burden of the healthcare settings where ICU capacities exceeded the resources available including ICU beds, equipment, and appropriately trained critical care clinicians (26). However, in the settings where the healthcare system was not stressed, the outcomes were much better (27). Additionally, it took time to understand the nature of COVID-19 and develop potential therapies. The patients with COVID-19 ARDS included in this study were during the initial months of the pandemic. Thus, the high mortality noted in this study is likely to be reflective of the factors associated with an overburdened healthcare system and a poorly understood disease. A similar mortality was reported in other series where $ECCO_2R$ was used in COVID-19 ARDS patients (23).

This study showed that there are significant variations in management of anticoagulation. In this study, a higher proportion of nonsurvivors did not receive the recommended target of anticoagulation (approximately 23% of the patients had a lower target, and 24% had higher than the recommended anticoagulation target). Although these differences are significant between survivors and nonsurvivors, the targeted anticoagulation was not independently associated with ICU survival. Given the retrospective nature of our study,

TABLE 2.
Comparison of Demographic and Clinical Characteristics of Patients Who Died and Survived to Discharge From ICU

Variable	Survived to ICU Discharge, $n = 65$	Died in ICU, $n = 94$	p
Age (yr), median (IQR)	49.0 (38.0–61.0)	58.0 (49.0–65.0)	0.0054[a]
Males, *n* (%)	44 (67.7)	62 (66.0)	0.4545[b]
Body mass index, median (IQR)	28.1 (22.0–34.3)	28.2 (25.4–36.1)	0.0759[a]
Diagnosis, *n* (%)			
Acute respiratory distress syndrome	30 (46.2)	28 (29.8)	0.0040[b]
COVID-19	27 (41.5)	61 (64.9)	
Status asthmaticus	6 (9.2)	1 (1.1)	
Other	2 (3.1)	4 (4.3)	
Comorbidities, *n* (%)			
Congestive heart failure	1 (1.5)	4 (4.3)	0.6492[b]
Systemic hypertension	15 (23.1)	29 (30.9)	0.3675[b]
Coronary artery disease	2 (3.1)	6 (6.4)	0.4732[b]
Diabetes	12 (18.5)	27 (28.7)	0.1892[b]
HIV	1 (1.5)	2 (2.1)	> 0.999[b]
Obstructive sleep apnea	2 (3.1)	6 (6.4)	0.4732[b]
Renal failure	4 (6.2)	12 (12.8)	0.1936[b]
Cirrhosis of liver	1 (1.5)	0 (0.0)	0.4088[b]
Cancer	6 (9.2)	7 (7.4)	0.7717[b]
Pulmonary hypertension	2 (3.1)	3 (3.2)	1.0000[b]
Blood gases prior to initiation of Hemolung			
pH, median (IQR), $n = 155$	7.3 (7.2–7.3)	7.2 (7.2–7.3)	0.3067[a]
Pa_{O_2} (mm Hg), median (IQR), $n = 156$	84.0 (69.0–113.0)	76.0 (65.5–94.0)	0.0701[a]
Pa_{CO_2} (mm Hg), median (IQR), $n = 155$	70.0 (59.5–88.0)	75.9 (62.6–91.0)	0.3779[a]
H_{CO_3} (mmol), median (IQR), $n = 149$	29.3 (25.0–35.8)	30.6 (23.8–35.8)	0.9505[a]
Sa_{O_2} (%), median (IQR), $n = 141$	95.0 (92.0–98.0)	94.0 (90.0–97.0)	0.0431[a]
F_{IO_2} (%), median (IQR), $n = 148$	60.0 (50.0–75.0)	90.0 (60.0–100.0)	< 0.00011
P/F ratio, median (IQR), $n = 147$	135.0 (111.0–213.0)	106.0 (74.0–160.0)	0.0002[a]
Adjunct therapies, $n = 159$, *n* (%)			
Nonrespiratory[c]	6 (9.2)	13 (13.8)	0.0089[b]
Respiratory[d]	21 (32.3)	49 (52.1)	
None	30 (46.2)	20 (21.3)	
Not determined	8 (12.3)	12 (12.8)	
Duration of Hemolung therapy (d), median (IQR), $n = 158$	6.1 (4.9–9.0)	6.2 (2.8–9.3)	0.3130[a]
Respiratory assist system ICU length of stay (d), median (IQR), $n = 138$	31.5 (17.0–60.0)	19.0 (10.0–31.5)	< 0.00011

IQR = interquartile range.

[a]Wilcoxon rank-sum *p*.

[b]Fisher exact *p*.

[c]Nonrespiratory adjunctive therapies included: continuous renal replacement therapy, continuous venovenous hemodialysis, hemodialysis, convalescent plasma, ventricular assist devices, and plasmapheresis.

[d]Respiratory adjunctive therapies included: extracorporeal membrane oxygenation, prone ventilation, lung recruitment maneuvers, inhaled epoprostenol, and inhaled nitric oxide.

TABLE 3.
Comparison of Hemolung Management in Patients Who Died and Survived to Discharge From ICU

Variable	Survived to ICU Discharge, *n* = 65	Died in ICU, *n* = 94	*p*
Cannulation site (*n* = 159), *n* (%)			
Jugular	38 (58.5)	51 (54.3)	0.8887[a]
Femoral	26 (40.0)	41 (43.6)	
Subclavian	1 (1.5)	2 (2.1)	
Anticoagulation target (*n* = 159), *n* (%)			
Recommended target	28 (43.1)	22 (23.4)	0.0432[a]
Higher than recommended target	12 (18.5)	26 (27.7)	
Lower than recommended target	15 (23.1)	21 (22.3)	
Not determined	10 (15.4)	25 (26.6)	
Hemolung performance (*n* = 111)			
Blood flow (mL/min)	451.4 (427.1–491.6)	444.1 (379.8–495.2)	0.2087[b]
Sweep gas (L/min)	7.7 (5.0–9.8)	8.3 (5.0–9.7)	0.4824[b]

[a]Fisher exact *p*.
[b]Wilcoxon rank-sum *p*.

the reasons for this variation in anticoagulation targets cannot be elucidated. It is possible that clinicians targeted lower anticoagulation in clinical conditions where the risk of bleeding was high (28) and a higher target when the risk of equipment failure due to circuit thrombosis was high (10).

As the technological advances in extracorporeal therapies are rapidly evolving, it is important to examine the efficacy of the newer $ECCO_2R$ devices for selecting the appropriate device to meet the clinical needs of patients to ensure best possible outcomes. $ECCO_2R$ devices are unique and different from conventional extracorporeal membrane oxygenation (ECMO) devices that provide complete support of cardiorespiratory function. $ECCO_2R$ devices, on the contrary, have variable performance and complication profiles. Case selection, therefore, may have to be specifically tailored to the respective $ECCO_2R$ device.

The three RCTs that investigated $ECCO_2R$ in ARDS patients did not show a mortality benefit (8, 18, 21). It is important to note that none of these three RCTs reached the planned sample size as they were stopped at interim analyses. The $ECCO_2R$ device used nor the case selection in the study by Morris et al (21) reflects contemporary clinical practice. However, the Xtravent and REST trials used $ECCO_2R$ technology and case selection that are relevant to current practice (8, 18). These two studies used different $ECCO_2R$ devices with different CO_2 extraction capabilities, which may contribute to heterogeneity of results. While none of the studies showed a reduction in mortality with the use of $ECCO_2R$, Xtravent study showed that patients with a P/F ratio less than 150 had more ventilator-free days both at 28- and 60-day postrandomization. On the contrary, in the REST trial (18), use of $ECCO_2R$ reduced ventilator-free days. It is likely that the differences in the results are due to significant differences in the performance of iLA (used in the Xtravent study) compared with Hemolung (used in the REST Trial). Interventional lung assist (iLA AV, Novalung, Heilbronn, Germany) (8) had a higher blood flow (1300 mL/min vs 350–450 mL/min) and was likely to have cleared more carbon dioxide along with provision of oxygen. Our results suggest higher P/F ratios (>100) are independently associated with ICU survival.

Study Implications. The results of this study have implications for clinical application of Hemolung as well as future research.

Case Selection. This study further confirms that low-flow $ECCO_2R$ devices such as Hemolung can correct hypercapnic acidosis and allow mechanical ventilatory support to be reduced. It further defines the characteristics of patients who have a higher likelihood

TABLE 4.
Comparison of Hemolung Complications in Patients Who Died and Survived to Discharge From ICU

Variable	Survived to ICU Discharge, *n* = 65	Died in ICU, *n* = 94	*p*
Blood product use (*n* = 147), median (interquartile range)			
Packed red cells usage	1.0 (0.0–4.0)	0.0 (0.0–3.0)	0.3207[a]
Fresh frozen plasma usage	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.6861[a]
Platelets usage	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.3753[a]
Hemolung and therapy adverse event, *n* (%)			
Circuit thrombosis, *n* = 147	5 (7.7)	3 (3.2)	0.2733[b]
Cannulation complications, *n* = 148	0 (0.0)	1 (1.1)	1.0000[b]
Inability to initiate flow	1 (1.5)	3 (3.2)	0.6454[b]
Unable to obtain vascular access	1 (1.5)	1 (1.1)	1.0000[b]
Kinked guide wire	0 (0.0)	2 (2.1)	0.5136[b]
Air in circuit	0 (0.0)	1 (1.1)	1.0000[b]
Low blood flow	0 (0.0)	2 (2.1)	0.5136[b]
Bleeding cerebral	0 (0.0)	2 (2.1)	0.5136[b]
Bleeding noncerebral	6 (9.2)	6 (6.4)	0.5510[b]
Hemolysis	6 (9.2)	4 (4.3)	0.3190[b]
Hemodynamic instability	1 (1.5)	2 (2.1)	1.0000[b]
Thrombocytopenia	4 (6.2)	10 (10.6)	0.4022[b]
Liver failure	0 (0.0)	2 (2.1)	0.5136[b]
Anemia	2 (3.1)	11 (11.7)	0.0753[b]
Cardiopulmonary resuscitation	0 (0.0)	2 (2.1)	0.5136[b]
Disseminated intravascular coagulation	1 (1.5)	0 (0.0)	0.4088[b]

[a]Wilcoxon rank-sum *p*.
[b]Fisher exact *p*.

of survival based on the characteristics at the time of initiation of Hemolung. Although COVID-19 ARDS patients in this study had a high mortality, this study does not delineate if this was due to the disease process or due to overburdened healthcare systems due to the pandemic. This study showed that P/F ratio at the time of initiation of Hemolung was independently associated with survival. Patients who had P/F ratio greater than 100 had higher odds of survival to ICU discharge and are likely to benefit most with Hemolung. It is likely that patients who have P/F ratio less than 100 will need more intensive support such as ECMO to help in oxygenation as well as ventilation (29). The Hemolung is not designed to provide substantial levels of oxygenation. A recent study that investigated patients with COVID-19 ARDS showed that a treatment strategy that included ECMO reduced mortality, and ECMO was most effective in patients less than 65 years and P/F ratio less than 80 (risk ratio for mortality, 0.87 [0.84–0.91]). The effectiveness of ECMO in patients with P/F ratio of 120–149 was reduced (risk ratio for mortality, 1.05 [1.02–1.08]), suggesting that less severe ARDS patients with COVID-19 may not benefit as much with ECMO (30). Such patients may benefit from reduction of ventilator-induced lung injury with the use of low-flow $ECCO_2R$ devices.

Practice Variations. This study highlights that practice variation exists with the use of $ECCO_2R$ especially with the use of anticoagulation, where nearly 46% of the patients included had anticoagulation higher or lower than the recommended target. The unadjusted mortality was higher in patients who did not have recommended targets of anticoagulation. It was, however, not independently associated with mortality.

TABLE 5.
Predictors of ICU Survival in Multivariate Logistic Regression Analysis

Covariate	Unadjusted OR (95% CI) (LB–UB)	Adjusted[a] OR (95% CI) (LB–UB)
Age 1-yr increase from 65 yr	**0.97 (0.94–0.99)**	**0.96 (0.93–0.99)**
Body mass index ≥30 vs <30	0.85 (0.44–1.64)	1.76 (0.61–5.07)
P/F >200 vs <100	**6.25 (2.23–17.54)**	**6.70 (1.56–28.84)**
P/F category 100–200 vs <100	**3.70 (1.60–8.57)**	**6.57 (2.03–21.33)**
pH ≥7.30 vs <7.30	0.99 (0.49–1.98)	0.83 (0.22–3.08)
$Paco_2$ ≥70 vs <70	0.73 (0.38–1.39)	0.76 (0.24–2.38)
Diagnosis COVID-19 vs ARDS	**0.41 (0.21–0.82)**	**0.26 (0.08–0.81)**
Diagnosis other vs ARDS	0.47 (0.08–2.75)	0.40 (0.05–3.09)
Diagnosis asthmaticus vs ARDS	5.60 (0.63–49.45)	2.06 (0.19–22.97)
Diagnosis COVID-19 vs other	0.89 (0.15–5.13)	0.64 (0.08–5.14)
Diagnosis COVID-19 vs asthmaticus	0.07 (0.01–0.64)	0.12 (0.01–1.47)
Diagnosis other vs asthmaticus	0.08 (0.01–1.26)	0.19 (0.01–3.73)
Anticoagulation target recommended vs not recommended	2.22 (1.07–4.60)	2.37 (0.91–6.09)

ARDS = acute respiratory distress syndrome, OR = odds ratio, LB = lower bound, P/F = Pao_2:Fio_2, UB = upper bound.
[a]Adjusted for age (as a continuous variable), body mass index (dichotomized), diagnosis, anticoagulation target, baseline pH, and $Paco_2$.
Boldface values indicate statistical significance.

Strengths and Limitations

This study has several strengths. This is the first study to date that specifically aimed to identify the independent association of variables that could predict survival of patients. This is the largest retrospective study investigating a single $ECCO_2R$ device in patients with acute respiratory failure, thus reducing heterogeneity as reported in some studies (11, 16, 20). Although the REST trial had a larger number of patients, it did not reach the targeted sample size; thus, the inferences of the REST trial are not definitive. Our study included real-world data on both physiologic outcomes as well as patient centered outcomes, providing significant clinical insights on the efficacy of the device in removal of carbon dioxide, its safety, and efficacy. The results of this study are generalizable to centers using $ECCO_2R$ and can aid in case selection for routine clinical practice as well as in future RCTs.

Given the retrospective nature of this study, it has several limitations. The data available on blood gases and ventilator requirements were limited to the first 36 hours of the Hemolung. However, a similar time frame was reported in other studies (9), and it is very likely that the improvements in the gas exchange and mechanical ventilator settings would have persisted with the use of Hemolung as shown in other studies (11). The survival data were available to ICU discharge, and severity of illness scores such as Acute Physiology and Chronic Health Evaluation III, Sequential Organ Failure Assessment, or Simplified Acute Physiology Score were not available in a significant proportion of the patients included. Furthermore, only patients submitted to the registry were included, it is highly likely that more patients have received therapy, and this is likely to have resulted in selection bias.

CONCLUSIONS

A significant improvement in hypercapnic acidosis along with reduction in mechanical ventilation supports was seen within 4 hours of initiating Hemolung therapy. P/F ratio greater than 100 at the commencement of Hemolung, age, and non-COVID-19 ARDS was independently associated with ICU survival. These findings may assist in case selection to optimize clinical outcomes. $ECCO_2R$ clinical trials are needed to further evaluate risk to benefit ratio and long-term outcomes in appropriately selected patients.

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