CHEST

Extracorporeal Membrane Oxygenation for Refractory Asthma Exacerbations With Respiratory Failure

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BACKGROUND: Asthma exacerbations with respiratory failure (AERF) are associated with hospital mortality of 7% to 15%. Extracorporeal membrane oxygenation (ECMO) has been used as a salvage therapy for refractory AERF, but controlled studies showing its association with mortality have not been performed.

RESEARCH QUESTION: Is treatment with ECMO associated with lower mortality in refractory AERF compared with standard care?

STUDY DESIGN AND METHODS: This is a retrospective, epidemiologic, observational cohort study using a national, administrative data set from 2010 to 2020 that includes 25% of US hospitalizations. People were included if they were admitted to an ECMO-capable hospital with an asthma exacerbation, and were treated with short-acting bronchodilators, systemic corticosteroids, and invasive ventilation. People were excluded for age < 18 years, no ICU stay, nonasthma chronic lung disease, COVID-19, or multiple admissions. The main exposure was ECMO vs No ECMO. The primary outcome was hospital mortality. Key secondary outcomes were ICU length of stay (LOS), hospital LOS, time receiving invasive ventilation, and total hospital costs.

RESULTS: The study analyzed 13,714 patients with AERF, including 127 with ECMO and 13,587 with No ECMO. ECMO was associated with reduced mortality in the covariate-adjusted (OR, 0.33; 95% CI, 0.17-0.64; $P = .001$), propensity score-adjusted (OR, 0.36; 95% CI, 0.16-0.81; $P = .01$), and propensity score-matched models (OR, 0.48; 95% CI, 0.24-0.98; $P = .04$) vs No ECMO. Sensitivity analyses showed that mortality reduction related to ECMO ranged from OR 0.34 to 0.61. ECMO was also associated with increased hospital costs in all three models ($P < .0001$ for all) vs No ECMO, but not with decreased ICU LOS, hospital LOS, or time receiving invasive ventilation.

INTERPRETATION: ECMO was associated with lower mortality and higher hospital costs, suggesting that it may be an important salvage therapy for refractory AERF following confirmatory clinical trials.

CHEST 2023; 163(1):38-51

KEY WORDS: asthma; extracorporeal membrane oxygenation; mechanical ventilation; respiratory failure

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ABBREVIATIONS: AERF = asthma exacerbation with respiratory failure; $ECCO_2R$ = extracorporeal CO_2 removal; *ECMO* = extracorporeal membrane oxygenation; LOS = length of stay; SMD = standardized mean difference; VILI = ventilator-induced lung injury; vvECMO = venovenous extracorporeal membrane oxygenation; vaECMO = venoarterial extracorporeal membrane oxygenation

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Take-home Points

Study Question. Is extracorporeal membrane oxygenation (ECMO) associated with lower mortality in refractory asthma exacerbations with respiratory failure?

Results. ECMO was associated with lower mortality and higher costs and appears to be safe in refractory asthma exacerbations requiring invasive ventilation, compared with patients treated without ECMO.

Interpretation. This is the first controlled study showing that ECMO has the potential to become an important, lifesaving, salvage therapy for people with refractory asthma exacerbations.

Asthma exacerbations kill 180,000 people globally every year, including more than 3,500 people in the United States.[1] These deaths include people admitted to the hospital with respiratory failure (AERF) requiring invasive mechanical ventilation, of whom 7% to 15% will die.[2-4] The tragedy of fatal asthma is worsened by the fact that the underlying pathophysiology of airway obstruction is completely reversible, and because many deaths occur in younger people with years of remaining productive life.[5,6]

Standard and adjunctive therapies for AERF include high-dose bronchodilators, corticosteroids, magnesium sulfate, heliox, ketamine, and inhaled volatile anesthetics.[5,7-10] Despite these therapies, ventilator pressures and blood P_{CO_2} remain elevated in many people, increasing the risk of spontaneous pneumothorax, respiratory acidosis, hemodynamic instability, ventilator-induced lung injury (VILI), and multiorgan system failure.[10-12] Deep sedation, neuromuscular blockade, and hypoventilation are recommended to decrease ventilator pressures through a strategy known as permissive hypercapnia.[10,13] But despite this combined approach, some patients with refractory AERF continue to have high ventilator pressures, poorly controlled hypercarbic respiratory acidosis, and persistent hemodynamic instability that increase the risk of death.[10-13]

Extracorporeal membrane oxygenation (ECMO) is a form of life support that has been used in refractory AERF to remove CO_2 and support oxygenation so that ventilator pressures can be reduced.[12,14-16] There are no formal criteria to guide the use of ECMO in refractory AERF, but the presence of persistently high ventilator pressures, uncontrolled respiratory acidosis, or hemodynamic instability have been suggested as justification to initiate ECMO.[9-12,17,18] Although the impact of ECMO for refractory AERF has been examined in case reports, case series, and registry studies,[10-12] no study has investigated the association of ECMO with mortality compared to standard care without ECMO. Accordingly, this study was designed to test the hypothesis that ECMO is associated with reduced mortality in refractory AERF treated with short-acting bronchodilators, systemic corticosteroids, and invasive mechanical ventilation.

Study Design and Methods

Study Design

This was a retrospective, epidemiologic, observational cohort study evaluating patient data voluntarily submitted to the Premier Perspective database between January 1, 2010 and December 31, 2020. The database used for this study includes 14,411,494 patients from 1,017 US hospitals that include primarily nonprofit, nongovernmental teaching hospitals throughout the United States. The database includes patient-level data on demographics, comorbidities, diagnostic and therapeutic services, laboratory tests performed, patient disposition, and clinical outcomes.[19-21] It also includes information on hospital size, region, urban or rural location, teaching hospital status, and physician specialty. *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) and *Tenth Revision* (ICD-10-CM) codes are available in the database as present on admission (POA) and present on discharge (POD). The database does not contain laboratory test results, ventilator settings, or ventilator pressures. The Colorado Multiple Institutional Review Board (COMIRB) approved this study (COMIRB 21-4056). Primary data are available from Premier Inc.

Study Population

Patients were included if they were admitted to the hospital between January 1, 2010 and December 31, 2020 with a primary diagnosis of asthma or asthma exacerbation, or a primary diagnosis of respiratory failure and a secondary diagnosis of asthma or asthma exacerbation (e-Table 1). The study adapted this design from the asthma and COPD literature.[22-24] Patients were included if they were admitted to an ECMO-capable hospital defined by the use of venovenous ECMO (vvECMO) or venoarterial ECMO (vaECMO) billing codes for any disease (e-Table 1). Included patients were required to be treated with inhaled short-acting bronchodilator medications (ie, albuterol

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Part of this article was presented in abstract form at the 2022 ATS International Conference, May 13-18, 2022, San Francisco, CA.

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DOI: https://doi.org/10.1016/j.chest.2022.09.029

or ipratropium) and systemic corticosteroids (ie, prednisone, methylprednisolone, dexamethasone, or hydrocortisone), and to be treated with invasive mechanical ventilation during their hospitalization. The study excluded patients who were < 18 years old, did not have an ICU stay, had nonasthma chronic lung diseases (ie, COPD, interstitial lung disease, or cystic fibrosis), or were admitted with COVID-19. Further, if there were multiple admissions, a single admission was selected randomly for patients in the single admission cohorts, whereas multiple admissions per patient were allowed in the multiple admission cohorts.

Measurements

Patients were divided into ECMO and No ECMO groups, based on use of billing codes for vvECMO or vaECMO during their hospitalization (e-Table 1). The primary outcome was hospital mortality. Key secondary outcomes included ICU length of stay (LOS), hospital LOS, length of invasive mechanical ventilation, and total hospital costs. The study also examined adverse effects related to ECMO including hemorrhage, neurologic or cardiac complications, infections, or pneumothorax (e-Table 1).

Statistics

The study was designed to determine the association of ECMO with primary, secondary, and safety outcomes. Statistical analysis was performed using methodology previous described, with modifications in selection of variables and development of the propensity score.[22,24-26] Patient and setting characteristics were compared between ECMO and No ECMO groups on the basis of standardized (mean) differences (SMDs), using simple average of variances to identify large differences.[27,28] Differences in outcomes were analyzed with covariate-adjusted, propensity score-adjusted, and propensity score-matched models.

Variables used to create the covariate-adjusted model and the propensity score included sociodemographic data; prior all-cause and asthma admissions; admission year; transfers from acute care hospitals; obesity; comorbidities in the combined comorbidity score other than pulmonary, HIV/AIDS, and dementia[29]; critical illness-related diagnoses; and therapies. These models also included setting characteristics such as hospital bed size, urban/rural location, geographic region, teaching/nonteaching hospital status, and physician specialty. A nonparsimonious approach using logistic regression was used to develop a propensity score to predict treatment with ECMO.[30,31] Differences in primary and key secondary outcomes between groups were analyzed by covariate-adjusted analysis, propensity score-adjusted analysis, and propensity score-matched analysis, using a 1:2 matching of ECMO to No ECMO patients. Each patient in the ECMO group was matched with two patients from the No ECMO group to the nearest fifth decimal point. Clustering of patients within hospitals was accounted for in the models for outcomes using generalized estimating equations. For mortality, a logit model (binomial distribution/logit link) and linear probability model (binomial distribution/identity link) were used, respectively, to estimate ORs and absolute risk reduction. For secondary outcomes, a Poisson model (Poisson distribution/log link) and linear model (normal distribution/identity link) were used, respectively, to estimate the ratio of (Poisson) means and mean difference.

Several sensitivity analyses were performed to determine whether the results in the primary cohort were robust, and to assess the influences from patient and setting characteristics. In the primary single admission cohort, differences in mortality were further explored in patients admitted to an ECMO-capable hospital and started on ECMO within the first 7 days, and in patients admitted to both ECMO-capable and -incapable hospitals without a time restriction. Analyses were repeated in a multiple admission cohort that included all admissions, so that differences in mortality could be assessed on the admission level. All tests were two-sided. $P < .05$ was considered significant, and SMD > 0.2 was considered large.[27,28] SAS version 9.4 (SAS Institute) was used for all analyses.

Results

After applying inclusion and exclusion criteria, 13,714 people with AERF from 499 hospitals were evaluated, including 127 in the ECMO group and 13,587 in the No ECMO group (Fig 1). In the full cohort, ECMO patients were younger, less likely to be female, more likely to have a principal diagnosis of asthma, and more likely to be admitted during later years of the study when ECMO cases were more common, compared with the No ECMO group (Fig 2A, Table 1). Forty percent of ECMO patients (51 of 127) were transferred from an outside acute care hospital, compared with only 13% in the No ECMO group (1,723 of 13,587). ECMO patients also had more nonseptic shock and acute kidney failure POA vs the No ECMO group (Table 1).

ECMO patients were more likely to be admitted to large (> 500 bed) teaching hospitals, compared with the No ECMO group (Table 2). ECMO patients were also more likely to be cared for by a pulmonologist or surgeon, and less likely to be cared for by an internist or hospitalist (Table 2). Treatment given to ECMO patients was substantially different from treatment given to No ECMO patients. For example, ECMO patients were more likely to receive antibiotics, continuous neuromuscular blockade, IV magnesium sulfate, heliox, inhaled anesthetics, loop diuretics, aminophylline, IV bicarbonate (HCO_3^-), vasopressors, and renal replacement therapy (Table 2). In contrast, a lower percentage of ECMO patients were treated with noninvasive ventilation vs the No ECMO group. Of 127 ECMO patients, 105 (83%) were treated with vvECMO, 8 (6%) were treated with vaECMO, and 14 (11%) were treated with both vvECMO and vaECMO. ECMO was started at a median of hospital day 1, a mean of hospital day 2.5, and a range of 1 to 19 days (Fig 2B). Seventy-four percent of patients (94 of 127) were started on ECMO in the first 2 days and 94% (120 of 127) were started in the first week of hospitalization. Once started, ECMO was continued for a median of 1.0 day, a mean of 4.0 days, and a range of 1 to 49 days. Overall mortality was 11.2% (n = 1,540/13,714) in the full cohort.

Covariate-Adjusted Model

In the covariate-adjusted model for patients with AERF admitted to an ECMO-capable hospital, treatment with

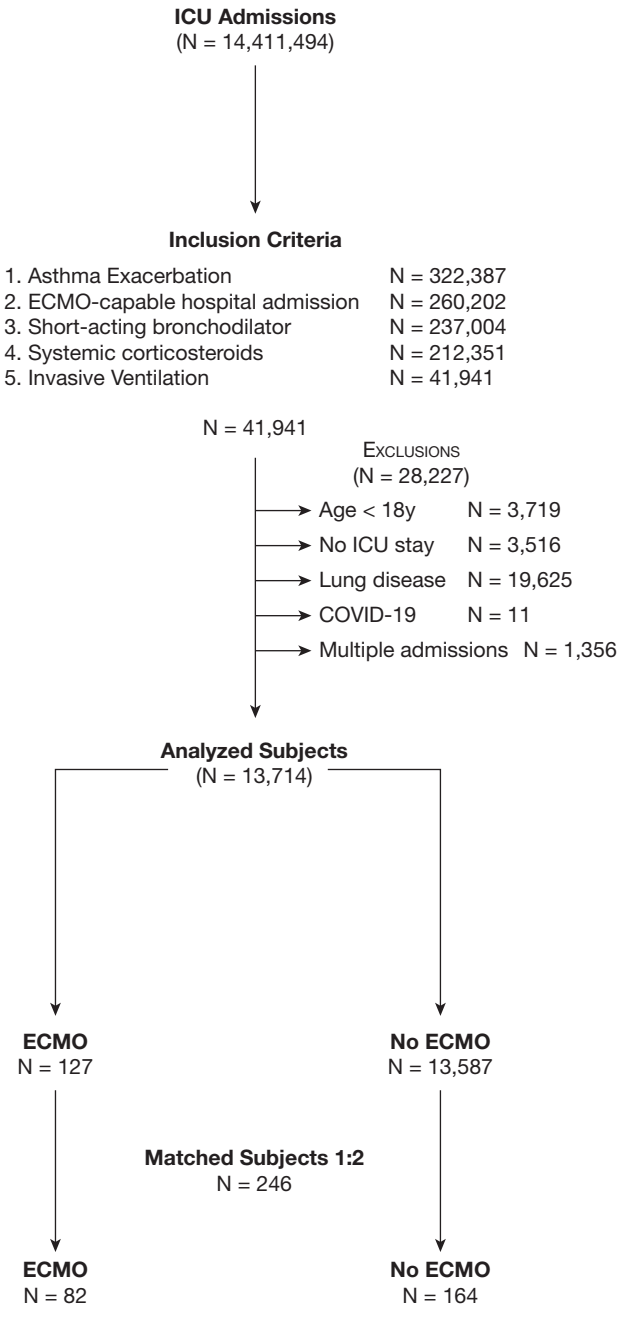


Figure 1 – *Study flow diagram. Flow diagram showing inclusion and exclusion criteria and analyzed patients. ECMO = extracorporeal membrane oxygenation.*

ECMO was associated with lower mortality (OR, 0.33; 95% CI, 0.17-0.64; $P = .001$) (Fig 3) and higher total hospital costs (ratio, 1.50; 95% CI, 1.31-1.71; $P < .0001$) (Fig 4) vs patients in the No ECMO group. ECMO was not associated with differences in ICU LOS, hospital LOS, or length of invasive mechanical ventilation, compared with the No ECMO group (Fig 4).

Propensity Score-Adjusted and -Matched Models

In the propensity score-adjusted model, ECMO was associated with reduced odds of mortality (OR, 0.36; 95% CI, 0.16-0.81; $P = .01$) (Fig 3) and higher mean total hospital costs (ratio, 1.79; 95% CI, 1.49-2.14; $P < .0001$) (Fig 4), compared with the No ECMO group. ECMO was not associated with differences in hospital LOS or length of invasive mechanical ventilation, but in this model ECMO was associated with increased ICU LOS (ratio, 1.25; 95% CI, 1.02-1.54; $P = 0.03$), compared with No ECMO patients (Fig 4).

The propensity score-matched sample achieved a high degree of covariate balance after matching one ECMO patient with two No ECMO patients (Tables 1, 2). In the propensity score-matched model, ECMO was associated with a mortality of 14.6% vs 26.2% in the No ECMO group, which equated to an absolute risk reduction of 11.6% (95% CI, 1.38%-21.79%; $P = .03$) (Table 3), and reduced odds of mortality (OR, 0.48; 95% CI, 0.24-0.98; $P = .04$) (Fig 3). ECMO was also associated with increased mean total hospital costs (ratio, 1.59; 95% CI, 1.32-1.91; $P < .0001$), which equated to an increase in total hospital costs by $113,789 per patient (95% CI, $65,968-$161,611; $P < .0001$), compared with the No ECMO group (Table 3, Fig 4). In contrast, ECMO was not associated with differences in ICU LOS, hospital LOS, or length of invasive mechanical ventilation (Fig 4, Table 3).

Sensitivity Analyses

Ninety-four percent of patients (120 of 127) were started on ECMO within the first 7 days after admission (Fig 2B). A sensitivity analysis was performed on patients admitted to an ECMO-capable hospital and started on ECMO within the first 7 hospital days, because patients started on ECMO later (ie, > hospital day 7) may be different from those started earlier (ie, ≤ hospital day 7). In this cohort, ECMO was associated with reduced odds of mortality in the covariate-adjusted model (OR, 0.48; 95% CI, 0.23-0.98; $P = .04$), but not in the propensity score-adjusted model (OR, 0.47; 95% CI, 0.21-1.05; $P = .07$) or the propensity score-matched model (OR, 0.61; 95% CI, 0.28-1.33; $P = .22$) (Fig 3).

The CESAR (Conventional Ventilatory Support vs Extracorporeal Membrane Oxygenation for Severe Adult Respiratory Failure) trial for ECMO in ARDS identified differences between ECMO and non-ECMO centers in adherence to lung-protective ventilator strategies, suggesting that institutional differences in

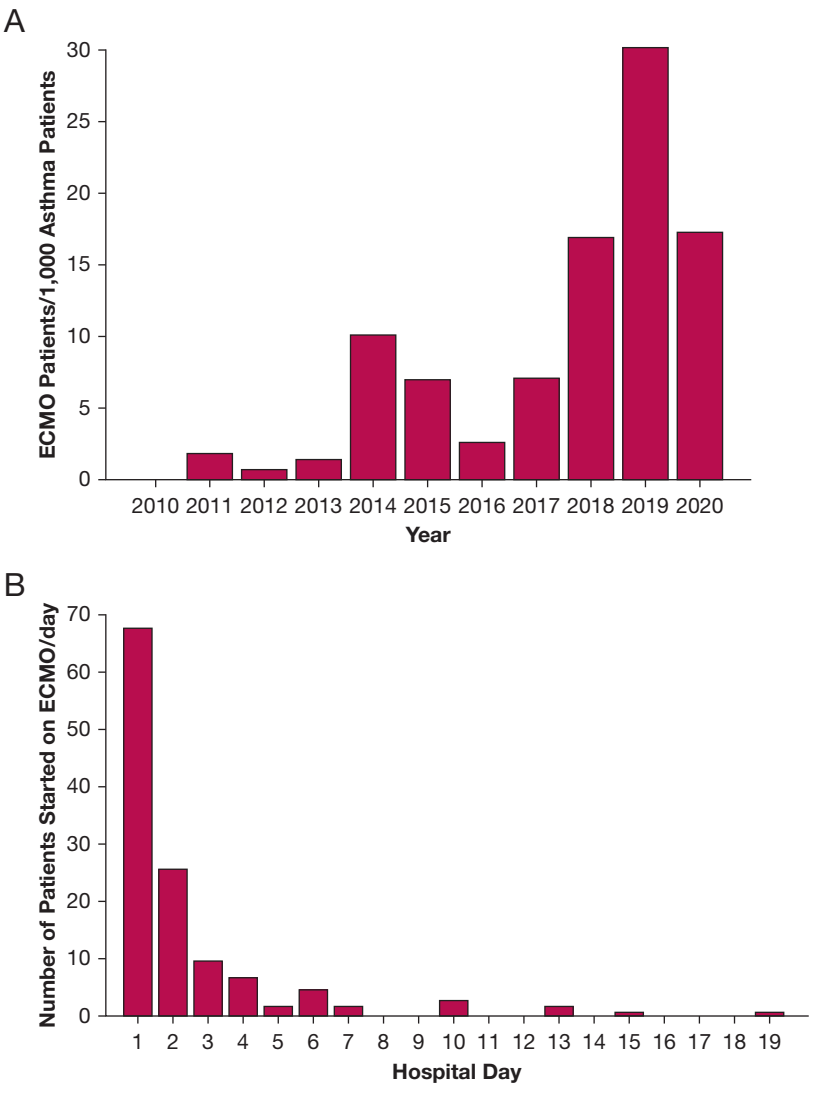


Figure 2 – *Extracorporeal membrane oxygenation (ECMO) use during asthma exacerbations with respiratory failure (AERF). A, Number of patients with AERF per 1,000 treated with ECMO from 2010 through 2020. B, Number of study patients started on ECMO by hospital day.*

treatment may impact outcomes.[32,33] On the basis of these observations, the primary study analysis was restricted to ECMO-capable hospitals. We also performed a sensitivity analysis that included patients from 499 ECMO-capable hospitals and 377 hospitals that do not perform ECMO. In this all-hospital cohort, ECMO was associated with lower mortality in the covariate-adjusted model (OR, 0.35; 95% CI, 0.19-0.67; $P = .002$) and the propensity score-adjusted model (OR, 0.39; 95% CI, 0.18-0.87; $P = .02$), but not in the propensity score matched model (OR, 0.56; 95% CI, 0.27-1.16; $P = .12$) (Fig 3).

To examine the association of ECMO with mortality on the admission level, primary and sensitivity analyses were repeated in cohorts that included all admissions between 2010 and 2020. In these analyses, ECMO continued to be associated with decreased mortality, with effect sizes similar to the single admission cohorts (Fig 3).

Adverse Effects

The propensity score matched sample in the single admission cohort was used to identify adverse effects with large differences between ECMO and No ECMO groups. Hemorrhage occurred in 11.0% (9 of 82) of ECMO patients vs 1.2% (2 of 164) of No ECMO patients (SMD, 0.416), including increased hemorrhage from the GI and respiratory passages (Table 4). Brain death was not detected in patients treated with ECMO but occurred in 4.9% (8 of 164) of the No ECMO group (SMD, –0.320). There were no differences in cardiac arrest between groups, which occurred in 11.0% (9 of 82) of ECMO patients and 14.0% (23 of 164) of No ECMO patients (SMD, –0.092) (Table 4). Group

TABLE 1] Patient Characteristics

Characteristic	Full Cohort			Propensity Score-Matched Sample		
	ECMO (n = 127)	No ECMO (n = 13,587)	SMD	ECMO (n = 82)	No ECMO (n = 164)	SMD
Age, mean (SD), y	38.0 (13.3)	46.0 (17.4)	−0.519	39.0 (14.0)	37.9 (14.4)	0.073
Sex, No. (%)						
Females	69 (54.3)	8,725 (64.2)	−0.202	45 (54.9)	78 (47.6)	0.147
Race, No. (%)						
White	58 (45.7)	6,723 (49.5)	−0.076	39 (47.6)	69 (42.1)	0.111
Black	44 (34.6)	4,477 (33.0)	0.036	26 (31.7)	58 (35.4)	−0.078
Asian	1 (0.8)	310 (2.3)	−0.122	1 (1.2)	5 (3.0)	−0.127
Other/unknown	24 (18.9)	2,077 (15.3)	0.096	16 (19.5)	32 (19.5)	0.000
Primary insurance, No. (%)						
Medicare	12 (9.4)	3,734 (27.5)	−0.478	10 (12.2)	19 (11.6)	0.019
Medicaid	65 (51.2)	3,938 (29.0)	0.465	35 (42.7)	70 (42.7)	0.000
Private	37 (29.1)	3,474 (25.6)	0.080	27 (32.9)	57 (34.8)	−0.039
Self-pay/other	13 (10.2)	2,441 (18.0)	−0.223	10 (12.2)	18 (11.0)	0.038
Principal diagnosis, No. (%)						
Asthma	54 (42.5)	3,892 (28.6)	0.293	38 (46.3)	70 (42.7)	0.074
Acute respiratory failure	73 (57.5)	9,695 (71.4)	−0.293	44 (53.7)	94 (57.3)	−0.074
All-cause admissions ≤ 12 mo, No. (%)						
0	90 (70.9)	7,617 (56.1)	0.311	56 (68.3)	117 (71.3)	−0.067
1	12 (9.4)	1,601 (11.8)	−0.076	8 (9.8)	15 (9.1)	0.021
2	5 (3.9)	1,042 (7.7)	−0.160	3 (3.7)	3 (1.8)	0.112
≥ 3	20 (15.7)	3,327 (24.5)	−0.219	15 (18.3)	29 (17.7)	0.016
Asthma admissions ≤ 12 mo, No. (%)						
0	104 (81.9)	10,868 (80.0)	0.048	66 (80.5)	133 (81.1)	−0.015
1	11 (8.7)	1,282 (9.4)	−0.027	6 (7.3)	13 (7.9)	−0.023
2	5 (3.9)	570 (4.2)	−0.013	4 (4.9)	7 (4.3)	0.029
≥ 3	7 (5.5)	867 (6.4)	−0.037	6 (7.3)	11 (6.7)	0.024
Admission year, No. (%)						
2010-2017	44 (34.6)	9,991 (73.5)	−0.848	35 (42.7)	64 (39.0)	0.074
2018-2020	83 (65.4)	3,596 (26.5)	0.848	47 (57.3)	100 (61.0)	−0.074
Transfers, No. (%)						
Acute care hospital transfer	51 (40.2)	1,723 (12.7)	0.656	27 (32.9)	57 (34.8)	−0.039
Comorbidities (present on admission), No. (%)						
Obesity	44 (34.6)	4,169 (30.7)	0.085	29 (35.4)	56 (34.1)	0.026
Metastatic disease	1 (0.8)	145 (1.1)	−0.029	1 (1.2)	1 (0.6)	0.064
Congestive heart failure	16 (12.6)	2,371 (17.5)	−0.136	12 (14.6)	18 (11.0)	0.110
Dementia	0 (0.0)	168 (1.2)	−0.158	0 (0.0)	1 (0.6)	−0.111
Renal disease	7 (5.5)	1,403 (10.3)	−0.179	4 (4.9)	9 (5.5)	−0.028
Weight loss	9 (7.1)	574 (4.2)	0.124	5 (6.1)	8 (4.9)	0.053
Hemiplegia	3 (2.4)	275 (2.0)	0.023	1 (1.2)	4 (2.4)	−0.091
Alcohol	7 (5.5)	610 (4.5)	0.047	6 (7.3)	9 (5.5)	0.075
Tumor	1 (0.8)	236 (1.7)	−0.085	1 (1.2)	1 (0.6)	0.064

(Continued)

TABLE 1] *(Continued)*

Characteristic	Full Cohort			Propensity Score-Matched Sample		
	ECMO (n = 127)	No ECMO (n = 13,587)	SMD	ECMO (n = 82)	No ECMO (n = 164)	SMD
Arrhythmia	29 (22.8)	2,892 (21.3)	0.037	19 (23.2)	45 (27.4)	−0.098
Pulmonary	127 (100.0)	13,587 (100.0)	…	82 (100.0)	164 (100.0)	…
Coagulopathy	12 (9.4)	575 (4.2)	0.208	7 (8.5)	11 (6.7)	0.069
Diabetes	7 (5.5)	1,235 (9.1)	−0.138	5 (6.1)	10 (6.1)	0.000
Anemia	22 (17.3)	2,217 (16.3)	0.027	17 (20.7)	30 (18.3)	0.062
Electrolytes	80 (63.0)	6,661 (49.0)	0.284	52 (63.4)	102 (62.2)	0.025
Liver	2 (1.6)	392 (2.9)	−0.089	2 (2.4)	2 (1.2)	0.091
Peripheral vascular disease	3 (2.4)	221 (1.6)	0.053	3 (3.7)	5 (3.0)	0.034
Psychosis	1 (0.8)	651 (4.8)	−0.245	0 (0.0)	1 (0.6)	−0.111
Pulmonary circulation	6 (4.7)	1,013 (7.5)	−0.114	5 (6.1)	7 (4.3)	0.083
HIV/AIDS	0 (0.0)	63 (0.5)	−0.097	0 (0.0)	0 (0.0)	…
Hypertension	51 (40.2)	6,486 (47.7)	−0.153	32 (39.0)	69 (42.1)	−0.062
Combined comorbidity score,[a] No. (%)						
≤ 1	38 (29.9)	4,829 (35.5)	−0.120	26 (31.7)	47 (28.7)	0.066
2-3	62 (48.8)	5,757 (42.4)	0.130	36 (43.9)	89 (54.3)	−0.208
≥ 4	27 (21.3)	3,001 (22.1)	−0.020	20 (24.4)	28 (17.1)	0.181
Critical illness-related diagnoses, No. (%)						
Severe sepsis without shock	2 (1.6)	97 (0.7)	0.081	2 (2.4)	2 (1.2)	0.091
Severe sepsis with shock	4 (3.1)	86 (0.6)	0.186	4 (4.9)	3 (1.8)	0.170
Shock (nonseptic)	15 (11.8)	540 (4.0)	0.294	11 (13.4)	15 (9.1)	0.135
Acute kidney failure	32 (25.2)	2,343 (17.2)	0.195	23 (28.0)	46 (28.0)	0.000

ECMO = extracorporeal membrane oxygenation; SMD = standardized (mean) difference, using simple average of variances.
[a]Variables included in the combined comorbidity score: metastatic disease, congestive heart failure, dementia, renal disease, weight loss, hemiplegia, alcohol, tumor, anemia, electrolytes, liver, peripheral vascular disease, psychosis, pulmonary circulation, HIV/AIDS, and hypertension.

differences in arrhythmia, pneumothorax, catheter or surgical site infections were small (Table 4).

Discussion

ECMO has increasingly been used as a salvage treatment for a range of severe respiratory and cardiac diseases,[15] but the difficulty of performing randomized controlled trials in the setting of extreme critical illness has made it challenging to generate high-quality, supporting evidence.[15] ECMO is seen as a potential therapeutic bridge for refractory AERF, because of its ability to remove blood CO_2 and improve oxygenation, allowing ventilator settings and pressures to be decreased until extreme airway obstruction abates.[14,15] Even with these potential benefits, studies of ECMO for refractory AERF have been limited to case reports, case series and registry studies that lack critical control subjects.[4,10-12] This is the first controlled study to examine the association of ECMO with mortality in AERF. Results showed that ECMO was associated with a substantial reduction of mortality and increase in total hospital costs in patients with AERF underscoring the potential importance of this infrequently used salvage therapy.

Use of ECMO was associated with a reduction in mortality ranging from OR 0.33 to OR 0.61 (corresponding to a reduction in mortality from 39% to 67%), depending on the cohort and analytic model used (Fig 3). This range exceeds the 31% improvement in 6-month survival without disability for ARDS patients treated with ECMO in the CESAR trial,[33] and the 24% reduction in mortality observed in the EOLIA (ECMO to Rescue Lung Injury in Severe ARDS) trial.[32] Mortality in the ECMO-treated group was 14.6% in the propensity score-matched sample of the current study, which was lower than the approximately 16.5% mortality reported by studies using data from the

TABLE 2] Setting and Treatment Characteristics

Characteristic	Full Cohort			Propensity Score-Matched Sample		
	ECMO (n = 127)	No ECMO (n = 13,587)		ECMO (n = 82)	No ECMO (n = 164)	
	No. (%)	No. (%)	SMD	No. (%)	No. (%)	SMD
No. of beds						
< 100	1 (0.8)	112 (0.8)	−0.004	1 (1.2)	1 (0.6)	0.064
100-199	2 (1.6)	1,125 (8.3)	−0.314	2 (2.4)	3 (1.8)	0.042
200-299	3 (2.4)	2,073 (15.3)	−0.467	2 (2.4)	5 (3.0)	−0.037
301-399	14 (11.0)	2,318 (17.1)	−0.174	9 (11.0)	19 (11.6)	−0.019
401-499	18 (14.2)	2,279 (16.8)	−0.072	12 (14.6)	27 (16.5)	−0.051
> 500	89 (70.1)	5,680 (41.8)	0.594	56 (68.3)	109 (66.5)	0.039
Patient population						
Urban	119 (93.7)	12,689 (93.4)	0.0123	79 (96.3)	158 (96.3)	0.000
Rural	8 (6.3)	898 (6.6)	−0.0123	3 (3.7)	6 (3.7)	0.000
Region						
South	41 (32.3)	6,105 (44.9)	−0.262	30 (36.6)	64 (39.0)	−0.050
Midwest	16 (12.6)	2,768 (20.4)	−0.211	12 (14.6)	27 (16.5)	−0.051
Northeast	44 (34.6)	2,085 (15.3)	0.457	23 (28.0)	46 (28.0)	0.000
West	26 (20.5)	2,629 (19.3)	0.028	17 (20.7)	27 (16.5)	0.110
Teaching status						
Nonteaching	20 (15.7)	6,251 (46.0)	−0.693	17 (20.7)	35 (21.3)	−0.015
Teaching	107 (84.3)	7,336 (54.0)	0.693	65 (79.3)	129 (78.7)	0.015
Physician specialty						
Internal medicine or hospitalist	57 (44.9)	8,828 (65.0)	−0.412	37 (45.1)	68 (41.5)	0.074
Family or general medicine	5 (3.9)	780 (5.7)	−0.084	4 (4.9)	5 (3.0)	0.094
Pulmonary medicine	21 (16.5)	1,300 (9.6)	0.208	13 (15.9)	31 (18.9)	−0.081
Surgery (cardiovascular, thoracic, vascular, or abdominal)	11 (8.7)	33 (0.2)	0.417	4 (4.9)	7 (4.3)	0.029
Anesthesiology	2 (1.6)	34 (0.3)	0.140	0 (0.0)	1 (0.6)	−0.111
Cardiovascular	4 (3.1)	84 (0.6)	0.187	1 (1.2)	2 (1.2)	0.000
Critical care or intensivist	12 (9.4)	826 (6.1)	0.126	10 (12.2)	18 (11.0)	0.038
Other	15 (11.8)	1,702 (12.5)	−0.022	13 (15.9)	32 (19.5)	−0.096
Therapies and tests						
vvECMO	105 (82.7)	…	…	68 (82.9)	…	…
vaECMO	8 (6.3)	…	…	5 (6.1)	…	…
vvECMO and vaECMO	14 (11.0)	…	…	9 (11.0)	…	…
Noninvasive ventilation	40 (31.5)	5,493 (40.4)	−0.187	27 (32.9)	46 (28.0)	0.106
Antibiotic	121 (95.3)	11,180 (82.3)	0.421	78 (95.1)	159 (97.0)	−0.094
Continuous neuromuscular blockade[a]	77 (60.6)	1,442 (10.6)	1.225	44 (53.7)	94 (57.3)	−0.074
Intermittent neuromuscular blockade[a]	36 (28.3)	4,383 (32.3)	−0.085	27 (32.9)	52 (31.7)	0.026
IV magnesium sulfate	96 (75.6)	8,001 (58.9)	0.362	61 (74.4)	128 (78.0)	−0.086
Aminophylline	9 (7.1)	315 (2.3)	0.227	5 (6.1)	17 (10.4)	−0.156
Ketamine	72 (56.7)	2,482 (18.3)	0.865	43 (52.4)	83 (50.6)	0.037
IV HCO_3^-	76 (59.8)	2,464 (18.1)	0.946	50 (61.0)	94 (57.3)	0.074
Heliox	10 (7.9)	387 (2.8)	0.225	8 (9.8)	15 (9.1)	0.021
Inhaled anesthetics[a]	6 (4.7)	165 (1.2)	0.208	2 (2.4)	11 (6.7)	−0.205

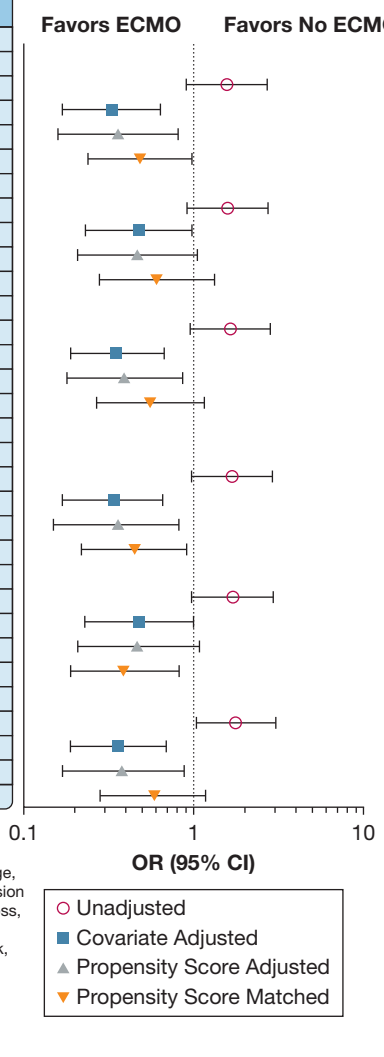
(Continued)

TABLE 2] *(Continued)*

Characteristic	Full Cohort			Propensity Score-Matched Sample		
	ECMO (n = 127)	No ECMO (n = 13,587)		ECMO (n = 82)	No ECMO (n = 164)	
	No. (%)	No. (%)	SMD	No. (%)	No. (%)	SMD
Vasopressors[a]	108 (85.0)	4,833 (35.6)	1.172	69 (84.1)	143 (87.2)	−0.087
Loop diuretics[a]	88 (69.3)	5,329 (39.2)	0.633	54 (65.9)	107 (65.2)	0.013
Renal replacement therapy	30 (23.6)	702 (5.2)	0.545	17 (20.7)	20 (12.2)	0.232
Brain natriuretic peptide	47 (37.0)	6,487 (47.7)	−0.21856	31 (37.8)	65 (39.6)	−0.038
Troponin	66 (52.0)	9,629 (70.9)	−0.39581	43 (52.4)	96 (58.5)	−0.123

ECMO = extracorporeal membrane oxygenation; SMD = standardized (mean) difference, using simple average of variances; vaECMO = venoarterial ECMO; vvECMO = venovenous ECMO.
[a]Inhaled anesthetics include isoflurane, sevoflurane, or desflurane; continuous neuromuscular blockers include use of ≥ 50 mg cisatracurium, ≥ 84 mg vecuronium, ≥ 84 mg pancuronium, ≥ 400 mg atracurium, or ≥ 800 mg rocuronium in any 24-h period; intermittent neuromuscular blockers include use of < 50 mg cisatracurium, < 84 mg vecuronium, < 84 mg pancuronium, < 400 mg atracurium, or < 800 mg rocuronium in any 24-h period; loop diuretics include furosemide, bumetanide, or torsemide; vasopressors include IV epinephrine, norepinephrine, or phenylephrine.

	No. ECMO Treated/Total	Mortality OR (95% CI)[2]	*P*-value[2]
SINGLE ADMISSION COHORTS			
ECMO-Capable Hospitals (PRIMARY COHORT)			
Full cohort, unadjusted	127/13,714	1.57 (0.91, 2.71)	.10
Full cohort, covariate adjusted[1]	127/13,714	0.33 (0.17, 0.64)	.001
Full cohort, propensity score adjusted[1]	127/13,714	0.36 (0.16, 0.81)	.01
Propensity score matched[1]	82/246	0.48 (0.24, 0.98)	.04
ECMO-Capable Hospitals and ECMO Initiation ≤ 7 Days			
Full cohort, unadjusted	120/13,707	1.59 (0.92, 2.75)	.10
Full cohort, covariate adjusted[1]	120/13,707	0.48 (0.23, 0.98)	.04
Full cohort, propensity score adjusted[1]	120/13,707	0.47 (0.21, 1.05)	.07
Propensity score matched[1]	84/252	0.61 (0.28, 1.33)	.22
All Hospitals			
Full cohort, unadjusted	127/17,346	1.65 (0.96, 2.84)	.07
Full cohort, covariate adjusted[1]	127/17,346	0.35 (0.19, 0.67)	.002
Full cohort, propensity score adjusted[1]	127/17,346	0.39 (0.18, 0.87)	.02
Propensity score matched[1]	98/294	0.56 (0.27, 1.16)	.12
MULTIPLE ADMISSION COHORTS			
ECMO-Capable Hospitals			
Full cohort, unadjusted	128/15,070	1.69 (0.98, 2.91)	.06
Full cohort, covariate adjusted[1]	128/15,070	0.34 (0.17, 0.66)	.001
Full cohort, propensity score adjusted[1]	128/15,070	0.36 (0.15, 0.82)	.02
Propensity score matched[1]	93/279	0.45 (0.22, 0.91)	.03
ECMO-Capable Hospitals and ECMO Initiation ≤ 7 Days			
Full cohort, unadjusted	121/15,063	1.70 (0.98, 2.95)	.06
Full cohort, covariate adjusted[1]	121/15,063	0.48 (0.23, 1.00)	.049
Full cohort, propensity score adjusted[1]	121/15,063	0.47 (0.21, 1.08)	.08
Propensity score matched[1]	84/252	0.39 (0.19, 0.82)	.01
All Hospitals			
Full cohort, unadjusted	128/19,010	1.77 (1.03, 3.05)	.04
Full cohort, covariate adjusted[1]	128/19,010	0.36 (0.19, 0.69)	.002
Full cohort, propensity score adjusted[1]	128/19,010	0.38 ((0.17, 0.88)	.02
Propensity score matched[1]	98/294	0.58 (0.28, 1.17)	.13



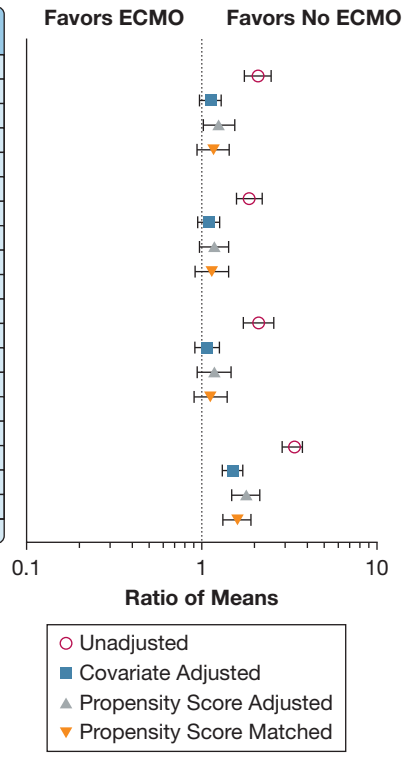
Abbreviations: ECMO = extracorporeal membrane oxygenation; OR = odds ratio; CI = confidence interval

[1]Variables included in covariate-adjusted analysis and creation of the propensity score listed in Tables 1 and 2 are: age, sex, race, primary insurance, data query criteria, all-cause hospital admissions, all-cause asthma admissions, admission year group, transfer from an acute care hospital, obesity, metastatic disease, congestive heart failure, renal, weight loss, hemiplegia, alcohol, tumor, anemia, electrolytes, liver, peripheral vascular disease, psychosis, pulmonary circulation, hypertension, combined comorbidity score, severe sepsis without shock, severe sepsis with shock, non-septic shock, acute kidney failure, number of hospital beds, urban or rural patient population, regions, hospital teaching status, attending physician specialty, noninvasive ventilation, antibiotic, continuous neuromuscular blockade, intermittent neuromuscular blockade, intravenous magnesium sulfate, aminophylline, ketamine, intravenous bicarbonate, heliox, inhaled anesthetics, vasopressors, loop diuretics, renal replacement therapy, brain natriuretic peptide, and troponin.

[2]Adjusted for hospital clustering

Figure 3 – *Mortality associated with extracorporeal membrane oxygenation (ECMO) for asthma exacerbations with respiratory failure. Left: Association of ECMO with mortality in the unadjusted, covariate-adjusted, propensity score-adjusted, and propensity score-matched analyses of the primary and sensitivity cohorts. Right: Results that favor ECMO or No ECMO groups, based on ORs and 95% CIs.*

	No. ECMO Treated/Total	Ratio[2,3] (95% CI)	*P*-value[3]
ICU LOS, days			
Full cohort, unadjusted	127/13,714	2.10 (1.76, 2.51)	< .0001
Full cohort, covariate adjusted[1]	127/13,714	1.12 (0.97, 1.29)	.11
Full cohort, propensity score adjusted[1]	127/13,714	1.25 (1.02, 1.54)	.03
Propensity score matched[1]	82/246	1.17 (0.94, 1.44)	.15
Hospital LOS, days			
Full cohort, unadjusted	127/13,714	1.87 (1.58, 2.22)	< .0001
Full cohort, covariate adjusted[1]	127/13,714	1.10 (0.95, 1.27)	.21
Full cohort, propensity score adjusted[1]	127/13,714	1.18 (0.98, 1.42)	.08
Propensity score matched[1]	82/246	1.14 (0.92, 1.42)	.23
Length of Invasive Mechanical Ventilation, days			
Full cohort, unadjusted	127/13,714	2.12 (1.74, 2.58)	< .0001
Full cohort, covariate adjusted[1]	127/13,714	1.07 (0.91, 1.26)	.40
Full cohort, propensity score adjusted[1]	127/13,714	1.18 (0.94, 1.47)	.16
Propensity score matched[1]	82/246	1.12 (0.90, 1.39)	.30
Total Hospital Cost, $			
Full cohort, unadjusted	127/13,714	3.29 (2.87, 3.76)	< .0001
Full cohort, covariate adjusted[1]	127/13,714	1.50 (1.31, 1.71)	< .0001
Full cohort, propensity score adjusted[1]	127/13,714	1.79 (1.49, 2.14)	< .0001
Propensity score matched[1]	82/246	1.59 (1.32, 1.91)	< .0001



Abbreviations: ECMO = extracorporeal membrane oxygenation; LOS= length of stay; CI = confidence interval

[1]Variables included in covariate-adjusted analysis and creation of the propensity score listed in Tables 1 and 2 are age, sex, race, primary insurance, principal diagnosis, all-cause hospital admissions, all-cause asthma admissions, admission year group, transfer from an acute care hospital, obesity, metastatic disease, congestive heart failure, renal, weight loss, hemiplegia, alcohol, tumor, anemia, electrolytes, liver, peripheral vascular disease, psychosis, pulmonary circulation, hypertension, combined comorbidity score, severe sepsis without shock, severe sepsis with shock, non-septic shock, acute kidney failure, number of hospital beds, urban or rural patient population, regions, hospital teaching status, attending physician specialty, noninvasive ventilation, antibiotic, continuous neuromuscular blockade, intermittent neuromuscular blockade, intravenous magnesium sulfate, aminophylline, ketamine, intravenous bicarbonate, heliox, inhaled anesthetics, vasopressors, loop diuretics, renal replacement therapy, brain natriuretic peptide, and troponin.

[2]Ratio of (Poisson) means using trimmed data at + 3 standard deviations

[3]Adjusted for hospital clustering

Figure 4 – *Key secondary outcomes associated with extracorporeal membrane oxygenation (ECMO) for asthma exacerbations with respiratory failure. Left: Association of ECMO with ICU length of stay (LOS), hospital LOS, time receiving mechanical ventilation, and total hospital costs in the unadjusted, covariate-adjusted, propensity score-adjusted, and propensity score-matched analyses of the primary cohort. Right: Results that favor ECMO or No ECMO groups based on ratios of means and 95% CIs.*

Extracorporeal Life Support (ELSO) Registry.[11,12] This difference may be related to advances in ECMO technology and/or ventilator management that have occurred since the period of the registry studies (1986-2016), compared with the current study, which included patients from 2010 to 2020.[11,12]

The beneficial effects of ECMO are hypothesized to derive from its ability to allow physicians to decrease the intensity of ventilator support, which is a prime cause of VILI and multiorgan system failure.[15,34] Yeo et al[12] showed that survival of AERF patients treated with ECMO was related to lower F_{IO_2} and positive end-expiratory pressure (PEEP) before and after ECMO was started, lower driving pressures after starting ECMO, and a shorter length of ECMO treatment, suggesting that initiation of ECMO before VILI begins may improve survival. Our study found that ECMO was typically started for AERF in the first several hospital days and continued for a median of 1 and mean of 4 days, supporting the notion that early initiation and short courses may have contributed to mortality benefits seen with ECMO.

Reduction of high levels of CO_2 has also been postulated to contribute to the benefits of ECMO, because it decreases the need for high levels of ventilator support, reduces right ventricular afterload, and may prevent hypercarbia-related immunosuppression and capillary leak.[15,35-37] This hypothesis is supported by data from patients with ARDS in the EOLIA trial, in which the mortality benefit of ECMO was concentrated in patients who qualified for the trial on the basis of the presence of hypercarbic respiratory acidosis.[32] Laboratory results are not available in the Premier database, preventing us from knowing the level of hypercarbia before or after initiation of ECMO. But hypercarbia is nearly a defining feature of refractory AERF, and many ECMO patients in our study were treated with IV HCO_3^- and/or renal replacement therapy, suggesting the presence of

TABLE 3] Outcomes Associated With ECMO: Propensity-Matched Model[a]

Study Group	Marginal Risk	Absolute Risk Reduction (95% CI)[b]	*P* Value[b]
Mortality, %			
ECMO	14.6	11.6 (1.4 to 21.8)	.03
No ECMO	26.2		
	Marginal Mean	Mean Difference (95% CI)[b]	
ICU LOS, d			
ECMO	10.11	1.44 (−0.60 to 3.48)	.17
No ECMO	8.67		
Hospital LOS, d			
ECMO	13.96	1.73 (−1.16 to 4.63)	.24
No ECMO	12.23		
Total length of invasive ventilation, d			
ECMO	9.51	1.02 (−0.99 to 3.03)	.32
No ECMO	8.49		
Total hospital cost, $			
ECMO	306,699	113,789 (65,968 to 161,611)	< .0001
No ECMO	192,909		

ECMO = extracorporeal membrane oxygenation; LOS = length of stay.
[a]Variables included in creation of the propensity score listed in Tables 1 and 2 are as follows: age, sex, race, primary insurance, data query criteria, all-cause hospital admissions, all-cause asthma admissions, admission year group, transfer from an acute care hospital, obesity, metastatic disease, congestive heart failure, renal disease, weight loss, hemiplegia, alcohol, tumor, anemia, electrolytes, liver disease, peripheral vascular disease, psychosis, pulmonary circulation, hypertension, combined comorbidity score, severe sepsis without shock, severe sepsis with shock, nonseptic shock, acute kidney failure, number of hospital beds, urban or rural patient population, regions, hospital teaching status, attending physician specialty, noninvasive ventilation, antibiotic, continuous neuromuscular blockade, intermittent neuromuscular blockade, IV magnesium sulfate, aminophylline, ketamine, IV HCO_3^-, heliox, inhaled anesthetics, vasopressors, loop diuretics, renal replacement therapy, brain natriuretic peptide, and troponin.
[b]Adjusted for hospital clustering.

TABLE 4] Adverse Effects Associated With ECMO: Propensity Score-Matched Sample

	ECMO (n = 82)	No ECMO (n = 164)	
Adverse Effect	No. (%)	No. (%)	SMD
Hemorrhage			
GI	3 (3.7)	0 (0.0)	0.276
Respiratory passages	6 (7.3)	1 (0.6)	0.349
Procedure site	0 (0.0)	1 (0.6)	0.111
Hemorrhage overall	9 (11.0)	2 (1.2)	0.416
Neurologic			
Intracerebral hemorrhage	0 (0.0)	1 (0.6)	−0.111
Brain death	0 (0.0)	8 (4.9)	−0.320
Neurologic overall	0 (0.0)	8 (4.9)	−0.320
Cardiac			
Arrhythmia	6 (7.3)	7 (4.3)	0.131
Cardiac arrest	9 (11.0)	23 (14.0)	−0.092
Cardiac overall	15 (18.3)	28 (17.1)	0.032
Infection			
Catheter or surgical site	1 (1.2)	0 (0.0)	0.157
Pulmonary			
Spontaneous or iatrogenic pneumothorax	4 (4.9)	7 (4.3)	0.029

ECMO = extracorporeal membrane oxygenation; SMD = standardized (mean) difference, using simple average of variances.

significant respiratory acidosis that would have been corrected by ECMO.

ECMO is an expensive, resource-intensive therapy that substantially adds to the costs and risks of care.[14,15] Our study confirmed this perception by showing that ECMO was associated with an increase in hospital expenses of almost $114,000 per patient, which extrapolates to an increased cost of $11.4 million per 100 patients treated. Given the younger age of our study population (~39 years), the potential of ECMO to prevent 36 years of life lost per person before age 75 may well be worth the cost. Adverse effects related to ECMO were limited to hemorrhage, suggesting that ECMO also has a reasonable safety profile given the approximately 26% risk of death from refractory AERF in the No ECMO group.

This study has several limitations that need to be considered when interpreting the results. First, study inclusion criteria could not be designed on the basis of the presence of high ventilator pressures or hypercarbic respiratory acidosis, because the database does not contain ventilator measurements or blood gas results. Instead, the study included and adjusted patients on the basis of indirect measures of asthma severity used in other asthma and COPD studies,[22-24] including the need for invasive mechanical ventilation, IV magnesium sulfate, heliox, inhaled volatile anesthetics, ketamine, IV HCO_3^-, intermittent and continuous neuromuscular blockade, renal replacement therapy, or shock. Second, confounding by indication, in which a measured or unmeasured variable independently affects the exposure and outcome, cannot be totally eliminated. This concern was addressed by including only patients receiving invasive mechanical ventilation, by excluding patients with conditions that could influence the choice of ECMO or mortality, and by using covariate adjustment, propensity score adjustment, and propensity score matching. Several sensitivity analyses were also used to examine the association between ECMO and mortality, with similar results. We cannot know why certain patients with AERF were treated with ECMO whereas others were not. However, use of ECMO for AERF during the study period was a rare event, so it is likely that most patients with AERF were not being considered for ECMO. Nonetheless, selection bias remains a possibility. Finally, inclusion of patients transferred from acute care hospitals (~40%) and the distribution of ECMO start days (hospital days 1-19) made it impossible to restrict the study to a specific ECMO exposure period. These considerations also made it difficult to adjust for immortal time bias, which is a possibility.

Interpretation

The most important message from this study is that ECMO, as practiced today, was associated with lower mortality and higher costs, and appears to be safe in refractory AERF. On the basis of 11.2% mortality for the total cohort, reported mortality for ventilated patients with AERF ranging from 7% to 15%,[2-4] and the percentage of No ECMO patients treated with continuous neuromuscular blockade (ie, 10.6%), up to 15% of patients with AERF may be eligible for ECMO each year. These results may also be relevant for low-flow, extracorporeal CO_2 removal ($ECCO_2R$) systems that use smaller catheters and lower blood flow rates, and can be added to renal replacement therapy systems.[38,39]

We wish to emphasize that although this is the largest controlled study to address the impact of ECMO for people with AERF, the results may still be subject to bias as listed previously, and therefore should only be considered hypothesis generating. A randomized clinical trial would be necessary to definitively determine the efficacy of ECMO for AERF requiring mechanical ventilation. Needless to say, any clinical trial would need to optimize standard and adjunctive therapies for AERF before enrollment, including permissive hypercapnia. Patients could then be considered for ECMO for persistently elevated plateau pressures (eg, $\geq$ 32 cm H_2O), which would account for intrinsic PEEP, high pulmonary driving pressures (eg, > 15-18 cm H_2O),[40,41] hemodynamic instability (eg, need for vasopressor support), severe hypercarbic respiratory acidosis (eg, pH < 7.2 and $Paco_2$ > 100 mm Hg), low Pao_2:Fio_2 ratios such as were used in the EOLIA study for ARDS,[32] or a life-threatening condition due to barotrauma.[9-12,17,18] If found to be clinically effective through controlled trials, innovations such as ECMO and $ECCO_2R$ may pave the way for CO_2 reduction to become a more standard, accessible, and less costly therapy for refractory AERF. In the interim, providers could consider early consultation for ECMO or transfer to an ECMO-capable center, based on their clinical judgment.[11,12,18]

Acknowledgments

Author contributions: R. W. V., S.-J. M., and J. K. Z. had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study design and concept: R. W. V., S.-J. M., and J. K. Z.; acquisition of data: R. R. A.; analysis and interpretation of data: R. W. V., S.-J. M., J. K. Z., P. M. H., T. H. K., A. K., P. D. S., R. R. A., M. D. A., P. M. R., M. M., E. L. B., and M. E. M.; drafting of the manuscript: R. W. V., J. K. Z., and S.-J. M.; critical revision of the manuscript for important intellectual content: R. W. V., S.-J. M., J. K. Z., P. M. H., T. H. K., A. K., P. D. S., R. R. A., M. D. A., P. M. R., M. M., E. L. B., and M. E. M.; statistical analysis: S.-J. M., R. R. A., M. E. M, and R. W. V.; administrative, technical, or material support: P. M. H., T. H. K., A. K., P. D. S., R. R. A., M. D. A., P. M. R., M. M., and E. L. B.; study supervision: R. W. V., J. K. Z., and S.-J. M.

Funding/support: This study was funded by a K. Louise Coulter Pulmonary Research and Health Sciences Fellowship Award to J. K. Z. and R. W. V., and by a University of Colorado Reserve Account for R. W. V.

Financial/nonfinancial disclosures: None declared.

Role of sponsors: The sponsors had no role in the design of the study, the collection and analysis of the data, or the preparation of the manuscript.

Other contributions: The authors extend appreciation to Patricia B. Koff, MEd, for critical reading of the manuscript and to Dr Sunita Sharma, MD, for insights on the study.

Additional information: The e-Table is available online under "Supplementary Data."

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