Online Data Supplement

Extracorporeal Membrane Oxygenation in Patients with Severe Respiratory Failure from COVID-19

Study of the Treatment and Outcomes in Critically Ill Patients with COVID-19

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SUPPLEMENTAL METHODS

Data Collection and Validation
Data were collected using REDCap, a secure, HIPAA-compliant, web-based application. Wherever possible, data were captured using checkboxes rather than manual entry to minimize keystroke errors. For data that required keystroke entry (e.g., laboratory values), we implemented validation ranges to flag potential errors in real-time. We also implemented automated data validation rules to flag errors in dates (e.g., if the date of death was entered as being before the date of ICU admission). Finally, all data were manually reviewed, and values that appeared incongruent or out of range were manually validated by confirming the accuracy of the data with the collaborator who entered it.

Overview of Target Trial Emulation
We sought to determine whether critically ill patients with severe hypoxemic respiratory failure from COVID-19 treated with venovenous extracorporeal membrane oxygenation (ECMO) during the first seven days following admission to the intensive care unit (ICU) have improved survival compared to patients not treated with ECMO in the first seven days following ICU admission.

Eligibility Criteria for the Emulated Trial
We sought to emulate a hypothetical target trial in which patients are considered eligible if they meet each of the following criteria:

Inclusion criteria:
1. Adults (≥18 years old) with laboratory-confirmed COVID-19 who were admitted to a participating ICU between March 1 and July 1, 2020
2. Required mechanical ventilation and had severe hypoxemia, defined as PaO_2/FiO_2 ratio <100 mm Hg, either on the day of treatment assignment or the day before (additional details below)

Exclusion criteria:
1. Age >70 years old
2. Active malignancy, defined as any malignancy (other than non-melanoma skin cancer) treated in the prior year
3. Admitted to an ICU at a non-ECMO-capable hospital
4. Required venoarterial ECMO during the first seven days of ICU admission

Patients meeting these criteria were categorized in the ECMO-treated versus ECMO non-treated group on days one through seven after ICU admission. ICU day one was defined as the 24-hour period spanning from midnight to midnight on the day of ICU admission. Days two through seven were defined as the subsequent hospital days following ICU day one. Patients were followed until hospital discharge, death, or September 1, 2020 – the date on which the study database for the current analysis was locked. Thus, all patients had at least 60 days of in-hospital follow-up.

The primary analysis compares the survival among ECMO initiators versus non-initiators. Survival time was defined as the interval from ECMO initiation or non-initiation to death, censored at hospital discharge or the date of last follow-up. Hazard ratios and 95% confidence intervals (CIs) were estimated using a Cox model.

Target trial emulation
Overview. To emulate the above target trial using our observational data, we categorized eligible individuals into either the ECMO group or the non-ECMO group on ICU day one. We repeated the process for eligible individuals on days two through seven. This approach eliminates the potential for immortal time bias that would result from comparing those initiating ECMO at later time points (e.g., ICU day five) to those who did not initiate ECMO at earlier time points (e.g., ICU day one) [1,2]. The final estimates were obtained by pooling the data from the emulation of the nested target trials from days one through seven after ICU admission.

Nested target trial approach. A cloned copy of each patient was generated on each day the patient was eligible to be assigned to ECMO or no ECMO (i.e., if the patient was mechanically ventilated, had a PaO_2/FiO_2 ratio <100, and had not previously been assigned to ECMO). Each clone was categorized in the ECMO group or in the no ECMO group on the day of treatment assignment. Patients who initiated ECMO were assigned to the ECMO group and were removed from consideration of treatment assignment on the following days, whereas patients who did not initiate ECMO remained potentially eligible to be considered for treatment assignment on the following days. For example, a patient who initiated ECMO on ICU day one did not have clones on ICU days two through seven. The clones of a patient who initiated ECMO on ICU day three, meanwhile, appeared as an ECMO non-initiator on days one and two and as an ECMO initiator on day three. For both the ECMO and non-ECMO groups, survival time was calculated from the day of treatment assignment to the date of death, or censored at the time of discharge or the last day of follow up. Additionally, we conducted an analysis to assess the potential for effect modification according to day of ECMO initiation or non-initiation. We introduced an interaction term, which was the product of indicator for therapy initiation and day of the 'trial' (day 1-3 versus day 4-7, dichotomized due to the relatively small number patients on any given day).

Multivariable adjustment for confounding. We adjusted for confounding using a multivariable Cox model. The following covariates were pre-specified based on clinical judgment: age; sex; race; body mass index; hypertension; diabetes mellitus; coronary artery disease; congestive heart failure; chronic obstructive pulmonary disease; shock (defined as receipt of at least one vasopressor); suspected or confirmed secondary infection; the renal, liver, and coagulation components of the Sequential Organ Failure Assessment score [3,4]; and receipt of rescue therapies for hypoxemia (prone position ventilation, neuromuscular blockade, and inhaled vasodilators, each assessed separately). Acute severity of illness characteristics were assessed on the day of treatment assignment. Additional details are provided below. We used a robust (sandwich) variance estimator to account for potential replications of patients induced by our nested target trial approach, which results in conservative (wider) 95% CIs. In addition to the time-to-death analyses describe above, we also estimated the difference in the risk of 60-day mortality in ECMO-treated versus ECMO non-treated patients using the marginal probabilities from a logistic regression model.

Sensitivity Analyses. We also conducted a series of sensitivity analyses. First, we treated hospital discharge as a competing risk rather than as a censoring event. Second, as an alternative approach to eliminate immortal time bias, we matched each patient who initiated ECMO on day 1 with two randomly selected eligible control patients (PaO2/FiO2 ratio <100 mm Hg while receiving invasive mechanical ventilation) who did not initiate ECMO. We then repeated the process on days 2 through 7, with ECMO non-treated patients only being included once. Third, we limited our analysis to a more homogeneous group of patients with the following characteristics: <65 years old; absence of coronary artery disease, congestive heart failure, and COPD; mechanically ventilated and with a PaO2/FiO2 ratio <80 mm Hg; and receipt of at least one rescue therapy for hypoxemia (prone position ventilation, neuromuscular blockade, or inhaled vasodilators) prior to ECMO initiation or non-initiation. For each of the above analyses, we adjusted for confounding by indication using a multivariable Cox model, as described above. Finally, we performed two additional analyses similar to the primary analysis, but using alternative PaO_2/FiO_2 thresholds (<80 and <150 mm Hg) to define eligibility. Finally, to assess the potential for effect modification according to day of treatment assignment, we tested the significance of an interaction term (treatment assignment x day of treatment [defined as day 1-3 versus day 4-7]) introduced into the model. Analyses were performed using SAS software version 9.4 (SAS Institute).

List of model covariates

A. Baseline covariates

1) Age: 18-49; 50-59; 60-70
2) Male sex
3) Race: white versus non-white (including other/unknown)
4) Body mass index (kg/m^2): <40; ≥40; missing
5) Hypertension
6) Diabetes mellitus
7) Coronary artery disease
8) Congestive heart failure
9) Chronic obstructive pulmonary disease

B. Severity-of-illness covariates

10) PaO_2/FiO_2 ratio (<80; 80-99 mm Hg)
11) Shock: defined as ≥1 vasopressor
12) Secondary infection, defined as suspected or confirmed new infection other than COVID-19
13) Renal, liver, and coagulation components of the Sequential Organ Failure Assessment score [5]

	Categories		
	0*	**1**	**2-4†**
SOFA Renal	Cr<1.2 mg/dl	Cr 1.2-1.9 mg/dl	Cr ≥2 mg/dl or UOP<500‡ or acute RRT or ESRD
SOFA Liver (Bilirubin)	<1.2 mg/dl	1.2-1.9 mg/dl	≥2 mg/dl
SOFA Coagulation (Platelet count)	≥150 K/mm^3	100-149 K/mm^3	<100 K/mm^3

Abbreviations: Cr, creatinine (mg/dl); ESRD, end stage renal disease; RRT, renal replacement therapy; SOFA, Sequential Organ Failure Assessment; UOP, urine output.
*Missing data were categorized as 0.
†Renal, liver, and coagulation SOFA scores of 2, 3, or 4 were binned due to low frequency of events in categories "3" and "4".
‡If the UOP was missing, the category was assigned according to the Cr

C. Rescue therapies for hypoxemia

14) Prone position ventilation
15) Neuromuscular blockade
16) Inhaled vasodilators (including inhaled nitric oxide and inhaled prostacyclins)

Missing Data

The renal, liver, and coagulation components of the SOFA score were categorized as "0" if missing [6-8]. Other than body mass index, all other variables above had complete data. Body mass index was analyzed in three categories: <40; ≥40; missing.

SUPPLEMENTAL TABLES

Table E1. List of ECMO-Capable Participating Sites

Northeast
Beth Israel Deaconess Medical Center
Brigham and Women's Hospital
Cooper University Health Care
Hackensack Meridian Health Hackensack University Medical Center
Johns Hopkins Hospital
Massachusetts General Hospital
MedStar Georgetown University Hospital
Montefiore Medical Center
Mount Sinai Hospital
New York-Presbyterian/Weill Cornell Medical Center
New York University Langone Hospital
Rutgers/New Jersey Medical School
Rutgers/Robert Wood Johnson Medical School
Temple University Hospital
Thomas Jefferson University Hospital
Tufts Medical Center
University of Pennsylvania Health System
University of Pittsburgh Medical Center
Westchester Medical Center
Yale University Medical Center
South
Baylor College of Medicine, Houston
Baylor University Medical Center/Baylor Scott White and Health
Duke University Medical Center
Mayo Clinic, Florida
Ochsner Medical Center
Tulane Medical Center
University of Alabama-Birmingham Hospital
University of Florida Health-Gainesville
University of Miami Health System
University of North Carolina Hospitals
University of Texas Southwestern Medical Center
University of Virginia Health System
Midwest
Detroit Medical Center
Froedtert Hospital, Medical College of Wisconsin
Henry Ford Hospital, Henry Ford Health System
Indiana University Health Methodist Hospital
Northwestern Memorial Hospital
Mayo Clinic, Rochester
Rush University Medical Center
University Hospitals Cleveland Medical Center
University of Chicago Medical Center
University of Illinois Hospital and Health Sciences System
University of Kentucky Hospital
University of Michigan Hospital
University of Oklahoma Health Sciences Center
Washington University Medical Center
West
Mayo Clinic, Arizona
Oregon Health and Science University Hospital
Stanford Healthcare
University of California-Davis Medical Center
University of California-Los Angeles Medical Center
University of California-San Diego Medical Center
University of California-San Francisco Medical Center
UCHealth University of Colorado
University of Washington Medical Center

Table E2. Definitions of Baseline Characteristics, Comorbidities, Treatments, and Outcomes

Baseline Characteristics	
Home medications	Medications that the patient was taking at home within 1 week prior to admission. Does not include those started at an outside hospital if the patient was transferred.
Anticoagulation	Therapeutic anticoagulants, not including anti-platelet agents such as aspirin or clopidogrel
Immunosuppressant drugs	Chemotherapy (in the 30 days prior to admission), corticosteroids >10 mg prednisone/day (or equivalent), calcineurin inhibitors (systemic, not topical), mycophenolate mofetil, azathioprine, rituximab, other
Coexisting Conditions	
Active malignancy	Per chart review; active malignancy (other than non-melanoma skin cancer) treated in the past year. Defined as cancer of the lung, breast, colorectal, prostate, gastric, pancreatic, melanoma, ovarian, brain, or other
Asthma	Per chart review
Chronic kidney disease	Baseline eGFR< 60 on at least two consecutive values at least 12 weeks apart prior to hospital admission. If not available, defined as per chart review
Chronic liver disease	Cirrhosis, alcohol-related liver disease, nonalcoholic fatty liver disease, autoimmune hepatitis, hepatitis B or hepatitis C, primary biliary cirrhosis, or other
Chronic obstructive pulmonary disease	Per chart review
Congestive heart failure	Per chart review; heart failure with preserved versus reduced ejection fraction
Coronary artery disease	Per chart review; any history of angina, myocardial infarction, or coronary artery bypass graft surgery
Diabetes mellitus	Per chart review; insulin versus non-insulin dependent
End stage renal disease	Per chart review; on hemodialysis or peritoneal dialysis
History of alcohol abuse	Per chart review
Homelessness	Per chart review
Hypertension	Per chart review
Pregnancy	Per chart review
RESP Score	-22 to 15 points; lower score indicating higher probability of death. Constructed with 12 patient characteristics: age, immunocompromised status, days of mechanical ventilation, diagnosis, central nervous system dysfunction, acute associated non-pulmonary infection, neuromuscular blocking agents or nitric oxide use, bicarbonate infusion, cardiac arrest, PaCO2, and peak inspiratory pressure [9]
Smoking	Per chart review; does not include vaping or smoking of non-tobacco products. Non-smoker, former smoker, current smoker
Longitudinal Treatments Including ECMO-Specific Parameters*	
Extracorporeal membrane oxygenation	Venovenous, venoarterial, or veno-arterial-venous
FiO_2†	FiO_2 corresponding to the lowest PaO_2 during each 24 hour day (midnight to midnight)
Inhaled pulmonary vasodilators	Per chart review; either inhaled nitric oxide or epoprostenol; date of initiation collected.
Invasive mechanical ventilation	Invasive mechanical ventilation
Mode of mechanical ventilation	Per chart review; defined as volume control, pressure control, synchronized intermittent ventilation, or airway pressure release ventilation
Neuromuscular Blockade	Per chart review; date of initiation collected.
Renal replacement therapy	CRRT, intermittent hemodialysis, peritoneal dialysis, other
PaO_2†	Lowest PaO_2 available during each 24 hour day (midnight to midnight)
PEEP†	Highest PEEP available during each 24 hour day (midnight to midnight)
Plateau pressure	Per chart review
Prone Positioning	Per chart review; date of initiation collected.
Respiratory rate	Per chart review; rate set on ventilator
Therapeutic anticoagulation	Per chart review; date of initiation collected
Tidal volume	Per chart review; in ventilatory modes in which tidal volume was mandatory, set value was recorded, in modes in which tidal volume is not set, observed tidal volume was used
Vasopressors	Maximum number of vasopressors required each day
Outcomes‡	
Acute kidney injury requiring renal replacement therapy‡	Per chart review based on need for renal replacement therapy (RRT) in patients without end-stage renal disease (ESRD) on hospital admission.
Liberation from ECMO	Per chart review; successful decannulation of ECMO, does not include withdrawal of care or decannulation resulting in immediate patient death.
Liberation from Mechanical ventilation	Per chart review; successful extubation, does not include patients who had a tracheostomy placed, unless they subsequently did not require invasive mechanical support.

Major bleed	Per chart review; bleeding in a critical area or organ (e.g., intracranial, retroperitoneal, pericardial, or intramuscular bleeding with compartment syndrome) or bleeding requiring a procedural intervention (e.g., EGD or IR embolization)
Respiratory failure	Requirement for invasive mechanical ventilation
Pneumothorax requiring a chest tube placement	Per chart review.
Secondary Infection	Per chart review; suspected or confirmed new infection other than COVID-19 that developed after admission to the ICU. Pneumonia (including ventilator-associated), urosepsis, biliary sepsis, bacteremia, other
Shock	Requirement for 2 or more vasopressors
Thromboembolic event	Per chart review; deep venous thrombosis, pulmonary embolism, stroke, heparin-induced thrombocytopenia, other

Table E2 Legend. Abbreviations: FiO_2, fraction of inspired oxygen; PaO_2, partial pressure of oxygen.

*Longitudinal treatments were recorded daily for the first 14 days following admission to the ICU. If multiple values were present, the lowest PaO_2 available, along with the corresponding FiO_2 at the time, was recorded, while the highest PEEP on each day was recorded. If the patient had an outcome, the date of the outcome was recorded.
†Only applies to patients receiving invasive mechanical ventilation with an arterial blood gas available.
‡Outcomes were recorded for the first 28 days of ICU admission among ECMO patients.

Table E3. Characteristics of Patients who Received ECMO

Characteristic	All ECMO Patients (N=190)	ECMO 60-Day Survivors (N=127)	ECMO 60-Day Non-Survivors (N=63)	P-Value
Baseline Demographics				
Age (yr) – median (IQR)	49 (41-58)	47 (38-54)	53 (46-60)	0.002
18–39	45 (23.7)	35 (27.6)	10 (15.9)	
40–49	56 (29.5)	41 (32.3)	15 (23.8)	0.01
50–59	54 (28.4)	35 (27.6)	19 (30.2)	
60-70	35 (18.4)	16 (12.6)	19 (30.2)	
Male sex – no. (%)	137 (72.1)	86 (67.7)	51 (81.0)	0.06
Race – no. (%)				0.96
White	77 (40.7)	50 (39.4)	27 (43.6)	
Black	42 (22.2)	29 (22.8)	13 (21.0)	
Asian	15 (7.9)	11 (8.7)	4 (6.5)	
American Indian / Alaska Native	5 (2.7)	4 (3.2)	1 (1.6)	
Native Hawaiian or Other Pacific Islander	1 (0.5)	1 (0.8)	0 (0.0)	
More than one race	2 (1.1)	2 (1.6)	0 (0.0)	
Unknown/Not Reported	47 (24.9)	30 (23.6)	17 (27.4)	
Hispanic – no. (%)	62 (32.6)	40 (31.5)	22 (34.9)	0.80
Body mass index (kg/m^2) – median (IQR)	32.7 (29.1-38.0)	33.2 (29.5-38.3)	31.3 (29.0-37.5)	0.32
< 30	60 (33.5)	35 (29.7)	25 (41.0)	
30–40	86 (48.0)	62 (52.5)	24 (39.3)	0.22
> 40	33 (18.4)	21 (17.8)	12 (19.7)	
Healthcare worker – no. (%)	7 (3.7)	5 (3.9)	2 (3.2)	0.89
Coexisting Conditions – no. (%)				
Presence of any chronic condition	119 (62.6)	77 (60.6)	42 (66.7)	0.42
Presence of multiple chronic conditions	60 (31.6)	34 (26.8)	26 (41.3)	0.04
Chronic lung disease	13 (6.8)	6 (4.7)	7 (11.1)	0.13
Chronic obstructive pulmonary disease	7 (3.7)	3 (2.4)	4 (6.4)	0.22
Other pulmonary disease	7 (3.7)	3 (2.4)	4 (6.4)	0.22
Coronary artery disease	7 (3.7)	4 (3.2)	3 (4.8)	0.69
Congestive heart failure	2 (1.1)	1 (0.8)	1 (1.6)	0.61
Chronic liver disease	4 (2.1)	1 (0.8)	3 (4.8)	0.11
Chronic kidney disease	3 (1.6)	1 (0.8)	2 (3.2)	0.26
End stage renal disease	2 (1.1)	1 (0.8)	1 (1.6)	0.61
Active malignancy	3 (1.6)	1 (0.8)	2 (3.2)	0.26
Diabetes mellitus	60 (31.6)	38 (29.9)	22 (34.9)	0.49
Hypertension	83 (43.7)	56 (44.1)	27 (42.9)	0.87
Alcohol abuse disorder	6 (3.2)	4 (3.2)	2 (3.2)	1.00
Current or former smoker	26 (13.7)	18 (14.2)	8 (12.7)	0.78
Pregnancy or postpartum	5 (2.6)	4 (3.2)	1 (1.6)	0.53
Characteristics Prior to Hospital Admission				
Home medications – no. (%)				
Immunosuppressive medication	16 (8.4)	9 (7.1)	7 (11.1)	0.35
ACE-I	27 (14.2)	19 (15.0)	8 (12.7)	0.67
ARB	17 (9.0)	9 (7.1)	8 (12.7)	0.20
Beta-blocker	22 (11.6	15 (11.8)	7 (11.1)	0.89
Other antihypertensive	30 (15.8)	19 (15.0)	11 (17.5)	0.66
Statin	39 (20.5)	23 (18.1)	16 (25.4)	0.24
NSAID	13 (6.8)	8 (6.3)	5 (7.9)	0.76
Aspirin	20 (10.5)	7 (5.5)	13 (20.6)	0.001
Anticoagulation	6 (3.2)	6 (4.7)	0 (0.0)	0.18
Characteristics at ICU Admission				
Source of admission to ICU – no. (%)				0.42
Emergency department	69 (36.3)	47 (37.0)	22 (34.9)	
Hospital ward	31 (16.3)	17 (13.4)	14 (22.2)	
Transfer from another hospital	88 (46.3)	62 (48.8)	26 (41.3)	
Other	2 (1.1)	1 (0.8)	1 (1.6)	
Laboratory Values – median (IQR)				
White-cell count, per mm^3	10.9 (7.0-16.4)	10.4 (7.1-14.7)	11.7 (6.0-19.9)	0.30
Lymphocyte count, per mm^3	8 (4-12)	9 (5-12)	6 (3-12)	0.15
Hemoglobin, g/dl	12.9 (11.1-14.2)	12.7 (10.9-14.5)	13.0 (11.6-14.0)	0.92
Platelet count, per mm^3	232 (165-287)	234 (169-281)	209 (140-298)	0.42
Creatinine, mg/dl	1.0 (0.8-1.4)	0.9 (0.8-1.3)	1.0 (0.9-1.5)	0.08
Albumin, g/dl	3.0 (2.5-3.4)	3.0 (2.5-3.5)	2.9 (2.5-3.3)	0.29
Aspartate aminotransferase, U/L	55 (38-95)	54 (40-95)	55 (35-96)	0.70
Alanine aminotransferase, U/L	42 (24-73)	41 (24-78)	42 (26-66)	0.91
Total bilirubin, mg/dl	0.6 (0.4-0.90)	0.6 (0.4-0.8)	0.7 (0.4-1.0)	0.37
Lactate, mmol/L	1.6 (1.2-2.4)	1.6 (1.2-2.3)	1.5 (1.3-2.5)	0.79
Arterial pH	7.35 (7.29-7.43)	7.35 (7.29-7.44)	7.34 (7.28-7.42)	0.44
D-dimer, ng/mL	1593 (563-4147)	1375 (565-4154)	1898 (548-4000)	0.74

Fibrinogen, mg/dL	612 (422-740)	604 (438-711)	655 (378-812)	0.74
C-reactive protein, mg/L	156 (82-282)	161 (96-288)	144 (55-275)	0.34
Interleukin-6, pg/mL	163 (31-400)	252 (21-400)	84 (37-236)	0.25
Procalcitonin, ng/ml	0.6 (0.2-2.0)	0.6 (0.2-2.0)	0.4 (0.1-2.0)	0.24
Ferritin, ng/ml	1246 (701-2637)	1083 (523-2545)	1764 (1040-2752)	0.04
Creatine phosphokinase, U/L	305 (121-760)	306 (133-767)	292 (109-760)	0.72
Severity of Illness Indicators				
Invasive Mechanical Ventilation – no. (%)	149 (78.4)	7.5	50 (79.4)	0.82
PEEP, cmH_2O – median (IQR)	15 (12-18)	15 (12-18)	15 (13-16)	0.68
PaO_2/FiO_2 ratio*, mm Hg – median (IQR)	85 (66-120)	82 (66-111)	87 (65-126)	0.86
Acute kidney injury requiring RRT – no. (%)	11 (5.9)	8 (6.4)	3 (4.8)	0.68
Shock – no. (%)	108 (56.8)	68 (53.5)	40 (63.5)	0.19
ICU Therapies Prior to ECMO Cannulation				
Rescue therapies for hypoxemia – no. (%)				
Prone positioning	135 (71.1)	87 (68.5)	48 (76.2)	0.27
Neuromuscular blockade	149 (78.4)	96 (75.6)	53 (84.1)	0.18
Inhaled nitric oxide	30 (15.8)	23 (18.1)	7 (11.1)	0.21
Inhaled epoprostenol	36 (19.0)	24 (18.9)	12 (19.1)	0.98
Therapeutic anticoagulation – no. (%)	136 (71.6)	88 (69.3)	48 (76.2)	0.32
Investigational therapeutics – no. (%)				
Remdesivir	25 (13.2)	16 (12.6)	9 (14.3)	0.75
Hydroxychloroquine	87 (45.8)	60 (47.2)	27 (42.9)	0.57
Azithromycin	98 (51.6)	70 (55.1)	28 (44.4)	0.17
Convalescent plasma	26 (13.7)	17 (13.4)	9 (14.3)	0.87
Tocilizumab	61 (32.1)	47 (37.0)	14 (22.2)	0.04
Corticosteroids	63 (33.2)	40 (31.5)	23 (36.5)	0.49
Acute Organ Injury and Secondary Infection within 24 Hours Prior to ECMO Cannulation†				
Acute kidney injury requiring RRT – no. (%)	33 (17.6)	18 (14.3)	15 (24.2)	0.09
Shock – no. (%)	157 (82.6)	100 (78.7)	57 (90.5)	0.04
Acute liver injury – no. (%)	4 (2.1)	0 (0.0)	4 (6.4)	0.01
Secondary infection – no. (%)	11 (5.8)	5 (3.9)	6 (9.5)	0.18
Characteristics within 24 Hours Prior to ECMO Cannulation†				
RESP Score – median (IQR)	3 (1-5)	4 (2-5)	2 (-1-4)	0.0002
PaO_2/FiO_2 ratio*, mm Hg – median (IQR)	72 (61-90)	74 (63-93)	69 (58-79)	0.02
< 80	118 (62.8)	72 (57.6)	46 (73.0)	
80-99	39 (20.7)	28 (22.4)	11 (17.5)	0.14
100-149	28 (14.9)	23 (18.4)	5 (7.9)	
150-200	3 (1.6)	2 (1.6)	1 (1.6)	
PEEP, cmH_2O – median (IQR)	15 (14-18)	16 (14-18)	15 (14-18)	0.66
FiO_2 – median (IQR)	100 (80-100)	100 (80-100)	100 (80-100)	0.82
P_aCO_2, mmHg – median (IQR)	55 (46-66)	55 (47-65)	55 (45-68)	0.73
Tidal volume, mL/kg IBW – median (IQR)	6.0 (5.3-7.1)	6.0 (5.3-7.1)	6.2 (5.2-7.1)	0.64
Respiratory rate, min^{-1} – median (IQR)	27 (22-30)	26 (21-30)	28 (22-32)	0.26
Plateau pressure, cmH_2O – median (IQR)	30 (28-35)	30 (28-35)	31 (28-34)	0.73
Driving pressure, cmH_2O – median (IQR)	15 (11-18)	15 (12-18)	15 (11-17)	0.99
Compliance, cmH_2O^{-1} – median (IQR)	28 (21-36)	27 (19-38)	30 (22-36)	0.41
Mode of mechanical ventilation – no. (%)				0.43
Volume Control	120 (64.5)	75 (60.5)	45 (72.6)	
Pressure Control	49 (26.3)	35 (28.2)	14 (22.6)	
SIMV	6 (3.2)	5 (4.0)	1 (1.6)	
APRV	11 (5.9)	9 (7.3)	2 (3.2)	
Laboratory Values within 24 Hours Prior to ECMO Cannulation†				
White-cell count, per mm^3	13.5 (9.2-18.8)	12.9 (9.0-16.7)	14.5 (9.6-21.9)	0.15
Lymphocyte count, per mm^3	5 (3-8)	6 (3-8)	4 (3-7)	0.29
Hemoglobin, g/dl	10.8 (9.5-12.0)	11.1 (9.9-12.4)	10.2 (9.0-11.5)	0.01
Platelet count, per mm^3	239 (172-302)	247 (191-313)	188 (133-274)	0.001
Albumin, g/dl	2.4 (2.1-2.8)	2.5 (2.2-3.0)	2.3 (2.0-2.6)	0.01
Arterial pH – median (IQR)	7.30 (7.23-7.36)	7.31 (7.26-7.36)	7.29 (7.21-7.36)	0.08
Lactate, mmol/L	1.9 (1.4-2.9)	1.9 (1.5-2.9)	2.2 (1.4-3.1)	0.20
D-dimer, ng/mL	3483 (1758-6860)	3502 (1758-7429)	3340 (1780-5744)	0.59
Fibrinogen, mg/dL	618 (394-807)	594 (385-740)	700 (454-865)	0.17
C-reactive protein, mg/L	191 (77-326)	176 (47-320)	214 (116-345)	0.15
Interleukin-6, pg/mL	228 (34-526)	315 (18-1147)	114 (40-251)	0.22
Ferritin, ng/ml	1412 (865- 2561)	1399 (798-2507)	1662 (1010-2597)	0.56
Timing Characteristics – median (IQR)				
Days from symptom onset to cannulation	13 (10-17)	12 (10-16)	13 (9-18)	0.41
Days from hospital admission to cannulation	6 (4-9)	5 (3-7)	6 (4-11)	0.01
Days from ICU admission to cannulation	3 (1-6)	3 (0-5)	4 (1-6)	0.10
Days from mechanical ventilation to cannulation	2 (0-5)	2 (0-5)	3 (1-6)	0.07
Hospital Characteristics				
ICU bed size				0.10
<50	44 (23.2)	25 (19.7)	19 (30.2)	
50-99	38 (20.0)	23 (18.1)	15 (23.8)	
≥100	108 (56.8)	79 (62.2)	29 (46.0)	

Table E3 Legend. Variable definitions are presented in Table E2**.** *Abbreviations: ACE-I, angiotensin converting enzyme inhibitors; APRV, airway pressure release ventilation; ARB, angiotensin-receptor blocker; ECMO, extracorporeal membrane oxygenation; FiO2, fraction of inspired oxygen; ICU, intensive care unit; IBW, ideal body weight; IQR, interquartile range; NSAID, nonsteroidal anti-inflammatory drug; PaO_2, partial pressure of arterial oxygen; P_aCO_2, partial pressure of carbon dioxide; PEEP, positive end expiratory pressure; RESP, respiratory extracorporeal membrane oxygenation survival prediction; RRT, renal replacement therapy; SIMV, synchronized intermittent mandatory ventilation.*

*PaO_2/FiO_2 refers to the ratio of the partial pressure of arterial oxygen (PaO_2) over the fraction of inspired oxygen (FiO_2) and was only assessed in patients receiving invasive mechanical ventilation. Values are recorded prior to ECMO initiation.
†Includes values from the day prior to cannulation and the day of ECMO cannulation

Data regarding BMI was missing in 11 (5.8%) patients.
Data regarding white blood cell count at ICU admission was missing in 7 (3.7%) patients.
Data regarding lymphocyte count at ICU admission was missing in 33 (17.4%) patients.
Data regarding hemoglobin at ICU admission was missing in 7 (3.7%) patients.
Data regarding platelet count at ICU admission was missing in 8 (4.2%) patients.
Data regarding creatinine at ICU admission was missing in 5 (2.6%) patients.
Data regarding albumin at ICU admission was missing in 18 (9.5%) patients.
Data regarding AST at ICU admission was missing in 17 (8.9%) patients.
Data regarding ALT at ICU admission was missing in 18 (9.5%) patients.
Data regarding bilirubin at ICU admission was missing in 18 (9.5%) patients.
Data regarding lactate at ICU admission was missing in 42 (22.1%) patients.
Data regarding arterial pH at ICU admission was missing in 34 (17.9%) patients.
Data regarding d-dimer at ICU admission was missing in 54 (28.4%) patients.
Data regarding fibrinogen at ICU admission was missing in 118 (62.1%) patients.
Data regarding CRP at ICU admission was missing in 51 (26.8%) patients.
Data regarding IL-6 at ICU admission was missing in 150 (78.9%) patients.
Data regarding procalcitonin at ICU admission was missing in 60 (31.6%) patients.
Data regarding ferritin at ICU admission was missing in 66 (34.7%) patients.
Data regarding CPK at ICU admission was missing in 81 (42.6%) patients.
Data regarding PEEP at ICU admission was missing in 53 (27.9%) patients.
Data regarding PaO_2/FiO_2 at ICU admission was missing in 52 (27.4%) patients.
Data regarding pre-cannulation PaO2/FiO2 was missing in 4 (2.1%) patients.
Data regarding pre-cannulation PEEP was missing in 2 (1.1%) patients.
Data regarding pre-cannulation PaCO2 was missing in 15 (7.9%) patients.
Data regarding pre-cannulation tidal volume was missing in 17 (8.9%) patients.
Data regarding pre-cannulation respiratory rate was missing in 8 (4.2%) patients.
Data regarding pre-cannulation plateau pressure was missing in 74 (38.9%) patients.
Data regarding pre-cannulation driving pressure was missing in 75 (39.5%) patients.
Data regarding pre-cannulation compliance was missing in 76 (40.0%) patients.
Data regarding pre-cannulation white blood cell count was missing in 1 (0.5%) patients.
Data regarding pre-cannulation lymphocyte count was missing in 30 (15.8%) patients.
Data regarding pre-cannulation hemoglobin was missing in 1 (0.5%) patients.
Data regarding pre-cannulation platelet count was missing in 2 (1.1%) patients.
Data regarding pre-cannulation albumin was missing in 11 (5.8%) patients.
Data regarding pre-cannulation pH was missing in 4 (2.1%) patients.
Data regarding pre-cannulation lactate was missing in 33 (17.4%) patients.
Data regarding pre-cannulation d-dimer was missing in 48 (25.3%) patients.
Data regarding pre-cannulation fibrinogen was missing in 80 (42.1%) patients.
Data regarding pre-cannulation CRP was missing in 35 (18.4%) patients.
Data regarding pre-cannulation IL-6 was missing in 158 (83.2%) patients.
Data regarding pre-cannulation ferritin was missing in 48 (25.3%) patients.
Data regarding pre-cannulation ventilation mode was missing in 2 (1.1%) patients.
Data regarding alcohol use is missing for 1 (0.5%) patient.

Table E4. Characteristics Post-ECMO Cannulation

Characteristic	All ECMO Patients (N=190)	ECMO 60-Day Survivors (N=127)	ECMO 60-Day Non-Survivors (N=63)	P-Value
Respiratory Characteristics Within 24 Hours Post-ECMO Cannulation				
PaO_2/FiO_2 ratio, mm Hg – median (IQR)	157 (105-206)	170 (118-208)	129 (83-197)	0.02
PEEP, cmH_2O – median (IQR)	12 (10-15)	13 (10-15)	12 (10-14)	0.21
FiO_2 – median (IQR)	50 (40-70)	50 (40-60)	50 (40-90)	0.046
P_aCO_2, mm Hg – median (IQR)	43 (37-48)	43 (37-48)	43 (37-48)	0.73
Tidal volume, mL/kg IBW – median (IQR)	4.9 (3.4-5.9)	4.9 (3.3-6.0)	5.0 (3.9-5.5)	0.67
Respiratory rate, min^{-1} – median (IQR)	14 (11-20)	15 (12-21)	14 (10-18)	0.01
Plateau pressure, cm H_2O – median (IQR)	26 (23-30)	26 (23-29)	27 (23-31)	0.20
Driving pressure, cm H_2O – median (IQR)	14 (11-18)	13 (10-17)	15 (11-20)	0.11
Compliance, ml. cm H_2O^{-1} – median (IQR)	21 (14-30)	23 (15-30)	17 (12-27)	0.18
Mode of mechanical ventilation – no. (%)				0.51
Volume Control	66 34.92	42 (33.3)	24 (38.1)	
Pressure Control	112 59.26	76 (60.3)	36 (57.1)	
SIMV	7 3.70	6 (4.8)	1 (1.6)	
APRV	3 1.59	1 (0.8)	2 (3.2)	
HFOV	1 0.53	1 (0.8)	0 (0.0)	
ECMO Flow Rate, LPM	4.5 (4.0-5.0)	4.5 (4.0-5.0)	4.6 (3.9-5.0)	0.58
Laboratory Values Within 24 Hours Post-ECMO Cannulation				
Arterial pH – median (IQR)	7.39 (7.34-7.44)	7.40 (7.35-7.44)	7.38 (7.32-7.42)	0.04
Lactate, mmol/L	1.7 (1.3-2.2)	1.6 (1.4-2.1)	2.0 (1.2-2.3)	0.36

Table E4 Legend. Values were evaluated on the ICU day following ECMO cannulation. *Abbreviations: APRV airway pressure release ventilation, ECMO extracorporeal membrane oxygenation, FiO_2 fraction of inspired oxygen, HFOV high frequency oscillatory ventilation, IBW ideal body weight, IQR interquartile range, LPM liters per minute, PaO_2 pressure of arterial oxygen, P_aCO_2 partial pressure of carbon dioxide, PEEP positive end expiratory pressure, SIMV synchronized intermittent mandatory ventilation.*

Data regarding post-cannulation PaO2/FiO2 was missing in 10 (5.3%) patients.
Data regarding post-cannulation PEEP was missing in 12 (6.3%) patients.
Data regarding post-cannulation FiO2 was missing in 9 (4.7%) patients.
Data regarding post-cannulation PaCO2 was missing in 2 (1.1%) patients.
Data regarding post-cannulation tidal volume was missing in 10 (5.3%) patients.
Data regarding post-cannulation respiratory rate was missing in 1 (0.5%) patients.
Data regarding post-cannulation plateau pressure was missing in 65 (34.2%) patients.
Data regarding post-cannulation driving pressure was missing in 69 (36.3%) patients.
Data regarding post-cannulation compliance was missing in 70 (36.8%) patients.
Data regarding ECMO flow rate was missing in 6 (3.2%) patients.
Data regarding post-cannulation pH was missing in 13 (6.8%) patients.
Data regarding post-cannulation lactate was missing in 44 (23.2%) patients.
Data regarding post-cannulation ventilation mode was missing in 1 (0.5%) patients.

Table E5. Outcomes of Patients who Received ECMO through last follow-up

Outcome Measure	All ECMO Patients (N=190)
Outcomes – no. (%)	
Mortality Status	
Still hospitalized	9 (4.7)
Death	67 (35.3)
Survival to hospital discharge	114 (60.0)
Transfer to another hospital	3 (2.6)
Long-term acute care facility	18 (15.8)
Sub-acute rehabilitation facility or skilled nursing facility	29 (25.4)
Acute rehabilitation facility	6 (5.3)
Home	57 (50.0)
Unknown*	1 (0.9)
Length of stay	
Days in the ICU – median (IQR)	31 (20-43)
Days in the hospital – median (IQR)	39 (28-53)

Table E5 Legend. Outcome definitions are defined in Supplementary Table E2. Long-term acute care facilities are vent-capable facilities. Sub-acute rehabilitation facility or skilled nursing facility refers to patients who are deemed temporarily unsafe for discharge to their homes and require assistance with activities of daily living. Acute rehabilitation facilities are generally reserved for patients who are able to participate in a minimum number of hours of physical and/or occupational therapy per day; these patients require physical strengthening before they can return home. Abbreviations: ECMO, extracorporeal membrane oxygenation; ICU, intensive care unit; IQR, interquartile range.

**Discharge disposition is missing for 1 of 114 patients (0.9%) who were discharged alive.*

Table E6. Characteristics of Patients who Received Early ECMO Cannulation vs. Late Cannulation

Characteristic	All ECMO Patients (N=190)	ECMO Cannulation on ICU Days 1-7 (N=158)	ECMO Cannulation on ICU Days 8-14 (N=32)	P-Value
Baseline Demographics				
Age (yr) – median (IQR)	49 (41-58)	49 (41-58)	48 (38-56)	0.58
Male sex – no. (%)	137 (72.1)	115 (72.8)	22 (68.8)	0.64
Race – no. (%)				0.99
White	77 40.74	63 (40.1)	14 (43.8)	
Black	42 22.22	34 (21.7)	8 (25.0)	
Asian	15 7.94	13 (8.3)	2 (6.3)	
Hispanic – no. (%)	62 (32.6)	51 (32.3)	11 (34.4)	0.97
Body mass index (kg/m^2) – median (IQR)	32.7 (29.1-38.0)	32.8 (29.4-38.0)	31.4 (28.6-38.2)	0.32
Coexisting Conditions – no. (%)				
Presence of any chronic condition	119 (62.6)	96 (60.8)	23 (71.9)	0.24
Presence of multiple chronic conditions	60 (31.6)	50 (31.7)	10 (31.3)	0.97
Current or former smoker	26 (13.7)	21 (13.3)	5 (15.6)	0.78
Characteristics at ICU Admission				
Invasive Mechanical Ventilation – no. (%)	149 (78.4)	129 (81.7)	20 (62.5)	0.02
PEEP, cmH_2O – median (IQR)	15 (12-18)	15 (12-18)	14 (14-16)	0.42
PaO_2/FiO_2 ratio*, mm Hg – median (IQR)	85 (66-120)	84 (66-113)	89 (65-170)	0.36
Acute kidney injury requiring RRT – no. (%)	11 (5.9)	11 (7.0)	0 (0.0)	0.22
Shock – no. (%)	108 (56.8)	97 (61.4)	11 (34.4)	0.01
ICU Therapies Prior to ECMO Cannulation – no. (%)				
Prone positioning	135 (71.1)	109 (69.0)	26 (81.3)	0.16
Neuromuscular blockade	149 (78.4)	122 (77.2)	27 (84.4)	0.37
Inhaled nitric oxide or epoprostenol	64 (33.7)	54 (34.2)	10 (31.3)	0.75
Therapeutic anticoagulation	136 (71.6)	112 (70.9)	24 (75.0)	0.64
Remdesivir	25 (13.2)	19 (12.0)	6 (18.8)	0.39
Tocilizumab	61 (32.1)	51 (32.3)	10 (31.3)	0.91
Corticosteroids	63 (33.2)	48 (30.4)	15 (46.9)	0.07
Acute Organ Injury and Secondary Infection within 24 Hours Prior to ECMO Cannulation†				
Acute kidney injury requiring RRT – no. (%)	33 (17.6)	28 (17.8)	5 (16.1)	0.82
Shock – no. (%)	157 (82.6)	131 (82.9)	26 (81.3)	0.82
Acute liver injury – no. (%)	4 (2.1)	4 (2.5)	0 (0.0)	0.36
Secondary infection – no. (%)	11 (5.8)	4 (2.5)	7 (21.9)	<0.001
Characteristics within 24 Hours Prior to ECMO Cannulation†				
RESP Score – median (IQR)	3 (1-5)	3 (2-5)	2 (-2-4)	0.02
PaO_2/FiO_2 ratio*, mm Hg – median (IQR)	72 (61-90)	72 (61-89)	69 (54.5-100)	0.60
PEEP, cmH_2O – median (IQR)	15 (14-18)	15 (14-18)	15 (14-18)	0.79
FiO_2 – median (IQR)	100 (80-100)	100 (80-100)	100 (78-100)	0.23
P_aCO_2, mmHg – median (IQR)	55 (46-66)	53 (46-66)	61 (50-66)	0.19
Tidal volume, mL/kg IBW – median (IQR)	6.0 (5.3-7.1)	6.0 (5.3-6.9)	6.0 (5.4-7.3)	0.48
Respiratory rate, min^{-1} – median (IQR)	27 (22-30)	26 (20-30)	29 (24-32)	0.13
Plateau pressure, cmH_2O – median (IQR)	30 (28-35)	30 (28-34)	31 (26-36)	0.84
Driving pressure, cmH_2O – median (IQR)	15 (11-18)	15 (12-18)	16 (11-18)	0.74
Compliance, ml. cmH_2O^{-1} – median (IQR)	28 (21-36)	28 (21-36)	27 (17-38)	0.67
Hospital Characteristics				
ICU bed size				0.46
<50	44 (23.2)	34 (21.5)	10 (31.3)	
50-99	38 (20.0)	33 (20.9)	5 (15.6)	
≥100	108 (56.8)	91 (57.6)	17 (53.1)	
Outcomes – no. (%)				
Mortality Status				0.26
Still hospitalized	9 (4.7)	9 (5.7)	0 (0.0)	
Death	67 (35.3)	53 (33.5)	14 (43.8)	
Survival to hospital discharge	114 (60.0)	96 (60.8)	18 (56.3)	
Length of stay				
Days in the ICU – median (IQR)	31 (20, 43)	29 (19, 43)	34 (28, 44)	0.09
Days in the hospital – median (IQR)	39 (28, 53)	39 (26, 53)	45 (33, 51)	0.25

Table E6 Legend. Variable definitions are presented in Table E2**.** *Abbreviations: ECMO, extracorporeal membrane oxygenation; FiO2, fraction of inspired oxygen; ICU, intensive care unit; IBW, ideal body weight; IQR, interquartile range; PaO_2, partial pressure of arterial oxygen; P_aCO_2, partial pressure of carbon dioxide; PEEP, positive end expiratory pressure; RESP, respiratory extracorporeal membrane oxygenation survival prediction; RRT, renal replacement therapy; SNF, skilled nursing facility*

*PaO_2/FiO_2 refers to the ratio of the partial pressure of arterial oxygen (PaO_2) over the fraction of inspired oxygen (FiO_2) and was only assessed in patients receiving invasive mechanical ventilation. Values are recorded prior to ECMO initiation.
†Includes values from the day prior to cannulation and the day of ECMO cannulation

Table E7. Multivariable Cox model for death among patients included in the target trial emulation of ECMO versus no ECMO

Covariate	Hazard Ratio (95%CI) for Death
Demographics and co-existing conditions	
Age (years)	
18-49 (REF)	1
50-59	1.17 (0.90-1.53)
60-70	1.45 (1.13-1.87)
Male sex	1.14 (0.93-1.40)
Body mass index (kg/m^2)	
<40 (REF)	1
≥40	0.97 (0.76-1.23)
Unknown	0.86 (0.55-1.34)
Hypertension	0.95 (0.77-1.17)
Diabetes mellitus	1.05 (0.86-1.27)
Coronary artery disease	1.64 (1.25-2.16)
Congestive heart failure	1.06 (0.78-1.43)
Chronic obstructive pulmonary disease	1.40 (1.02-1.93)
Severity of illness*	
PaO_2/FiO_2, mm Hg	
80-99 (REF)	1
<80	1.29 (1.13-1.47)
Shock	1.14 (0.98-1.33)
Secondary infection	1.26 (1.02-1.56)
Renal SOFA score	
0 (Cr <1.2 mg/dl) (REF)	1
1 (Cr 1.2-1.9 mg/dl)	1.34 (1.12-1.60)
2-4 (Cr >2mg/dL, UOP <500mL, RRT)	1.88 (1.57-2.26)
Liver SOFA score	
0 (Bilirubin <1.2 mg/dl) (REF)	1
1 (Bilirubin 1.2-1.9 mg/dl)	1.23 (1.01-1.51)
2-4 (Bilirubin ≥2 mg/dl)	1.27 (0.95-1.69)
Coagulation SOFA score	
0 (Platelet count ≥ 150 K/mm^3) (REF)	1
1 (Platelet count 100-149 K/mm^3)	1.35 (1.11-1.65)
2-4 (Platelet count <100 K/mm^3)	1.64 (1.20-2.23)
Rescue therapies for hypoxemia†	
Prone position ventilation	1.03 (0.87-1.23)
Neuromuscular blockade	0.92 (0.77-1.10)
Inhaled vasodilators	1.12 (0.86-1.47)
ECMO receipt	**0.55 (0.41-0.74)**

Table E7 Legend.
*Severity of illness data were assessed on the day of ECMO initiation or non-initiation.
†Rescue therapies for hypoxemia were assessed up to and including the day of ECMO initiation or non-initiation.

Abbreviations: PaO_2, partial pressure of arterial oxygen over the fraction of inspired oxygen; REF, reference group; RRT, renal replacement therapy; SOFA, Sequential Organ Failure Assessment; UOP, urine output.

Table E8. Sensitivity analysis with 1-to-2 matching of ECMO-treated to ECMO-non-treated patients. For every patient who initiated ECMO on day 1, we randomly selected two eligible control patients (mechanically ventilated and PaO_2/FiO_2<100 on day 1) who did not initiate ECMO. We repeated the process on days 2 through 7, with ECMO non-treated patients only being included once.

	ECMO (N=130)	No ECMO (N=260)
Demographic characteristics		
Age (yrs)		
Median (IQR)	49 (41–58)	57 (48–64)
18–49	66 (50.8)	77 (29.6)
50–59	41 (31.5)	79 (30.4)
60–70	23 (17.7)	104 (40.0)
Male sex – no. (%)	95 (73.1)	176 (67.7)
White Race – no. (%)	51 (39.2)	86 (33.1)
Body mass index (kg/m^2)		
Median (IQR)	32.5 (29.5–37.9)	33.0 (28.9–38.4)
<40	98 (75.4)	199 (76.5)
≥40	21 (16.2)	51 (19.6)
Unknown	11 (8.5)	10 (3.8)
Co-existing conditions		
Hypertension	62 (47.7)	153 (58.8)
Diabetes mellitus	38 (29.2)	108 (41.5)
Coronary artery disease	4 (3.1)	22 (8.5)
Congestive heart failure	2 (1.5)	19 (7.3)
Chronic obstructive pulmonary disease	4 (3.1)	16 (6.2)
Severity of illness[†]		
PaO_2/FiO_2, mm Hg – median (IQR)	69 (60–80)	77 (66–85)
PEEP – median (IQR)	15 (12–18)	14 (12–17)
Shock[‡] - no. (%)	104 (80.0)	167 (64.2)
Lactate, mmol/L – median (IQR)	2.0 (1.4–3.1)	1.6 (1.1–2.2)
Arterial pH – median (IQR)	7.33 (7.28–7.39)	7.34 (7.27–7.39)
Secondary infection	26 (20.0)	39 (15.0)
Renal SOFA score[§]		
0 (Cr <1.2 mg/dl)	67 (51.5)	124 (47.7)
1 (Cr 1.2-1.9 mg/dl)	34 (26.2)	49 (18.8)
2-4 (Cr >2mg/dL, UOP <500mL, RRT[‖])	29 (22.3)	87 (33.5)
Liver SOFA score[§]		
0 (Bilirubin <1.2 mg/dl)	109 (83.8)	229 (88.1)
1 (Bilirubin 1.2-1.9 mg/dl)	13 (10.0)	17 (6.5)
2-4 (Bilirubin ≥2 mg/dl)	8 (6.2)	14 (5.4)
Coagulation SOFA score[§]		
0 (Platelet count ≥ 150 K/mm^3)	108 (83.1)	235 (90.4)
1 (Platelet count 100-149 K/mm^3)	17 (13.1)	19 (7.3)
2-4 (Platelet count <100 K/mm^3)	5 (3.8)	6 (2.3)
Rescue therapies for hypoxemia**		
Prone position ventilation	92 (70.8)	117 (45.0)
Neuromuscular blockade	100 (76.9)	130 (50.0)
Inhaled vasodilators	47 (36.2)	33 (12.7)

Abbreviations: PaO_2, partial pressure of arterial oxygen over the fraction of inspired oxygen; PEEP, positive end expiratory pressure; RRT, renal replacement therapy; SOFA, Sequential Organ Failure Assessment; UOP, urine output.

[†]Severity of illness data are shown on the day of ECMO initiation or non-initiation.
[‡]Shock is defined as the requirement for at least one vasopressor.
[§]Categories 2, 3, and 4 of the renal, liver, and coagulation components of the SOFA score were binned due to low frequency of events.
[‖]Includes both acute RRT as well as end stage renal disease requiring RRT.
**Rescue therapies for hypoxemia were assessed up to and including the day of ECMO initiation or non-initiation.

Table E9. Sensitivity analysis limited to a more homogeneous group of ECMO-treated and ECMO-non-treated patients. This analysis is limited to patients with the following characteristics: <65 years old; absence of coronary artery disease, congestive heart failure, and COPD; mechanically ventilated and with a PaO_2/FiO_2 ratio <80 mm Hg; and receipt of at least one rescue therapy for hypoxemia (prone position ventilation, neuromuscular blockade, or inhaled vasodilators) prior to ECMO initiation or non-initiation.

	Unique Patients		Final Cohort*	
	ECMO (N=77)	No ECMO (N=370)	ECMO (N=77)	No ECMO (N=1032)
Demographic characteristics				
Age (yrs)				
Median (IQR)	50 (41–58)	52 (45–58)	50 (41–58)	53 (45–59)
18–49	38 (49.4)	146 (39.5)	38 (49.4)	412 (39.9)
50–59	25 (32.5)	149 (40.3)	25 (32.5)	389 (37.7)
60–70	14 (18.2)	75 (20.3)	14 (18.2)	231 (22.4)
Male sex – no. (%)	53 (68.8)	263 (71.1)	53 (68.8)	745 (72.2)
White Race – no. (%)	32 (41.6)	119 (32.2)	32 (41.6)	341 (33.0)
Body mass index (kg/m^2)				
Median (IQR)	32.7 (29.9–37.9)	33.4 (28.8–39.7)	32.7 (29.9–37.9)	33.5 (29.3–39.7)
<40	62 (80.5)	272 (73.5)	62 (80.5)	762 (73.8)
≥40	13 (16.9)	87 (23.5)	13 (16.9)	247 (23.9)
Unknown	2 (2.6)	11 (3.0)	2 (2.6)	23 (2.2)
Co-existing conditions				
Hypertension	39 (50.6)	177 (47.8)	39 (50.6)	492 (47.7)
Diabetes mellitus	23 (29.9)	133 (35.9)	23 (29.9)	368 (35.7)
Severity of illness†				
PaO_2/FiO_2, mm Hg – median (IQR)	70 (60–90)	76 (65–107)	65 (60–70)	67 (59–74)
PEEP – median (IQR)	16 (14–18)	15 (11–18)	16 (14–18)	16 (12–18)
Shock‡ - no. (%)	48 (62.3)	201 (54.3)	65 (84.4)	683 (66.2)
Lactate, mmol/L – median (IQR)	1.8 (1.3–2.6)	1.7 (1.2–2.3)	2.0 (1.4–2.8)	1.6 (1.1–2.3)
Arterial pH – median (IQR)	7.36 (7.29–7.42)	7.34 (7.27–7.42)	7.33 (7.28–7.39)	7.32 (7.25–7.39)
Secondary infection	5 (6.5)	28 (7.6)	13 (16.9)	168 (16.3)
Renal SOFA score§				
0 (Cr <1.2 mg/dl)	51 (66.2)	227 (61.4)	42 (54.5)	470 (45.5)
1 (Cr 1.2-1.9 mg/dl)	18 (23.4)	80 (21.6)	21 (27.3)	224 (21.7)
2-4 (Cr >2mg/dL, UOP <500mL, RRT‖)	8 (10.4)	63 (17.0)	14 (18.2)	338 (32.8)
Liver SOFA score§				
0 (Bilirubin <1.2 mg/dl)	67 (87.0)	330 (89.2)	64 (83.1)	865 (83.8)
1 (Bilirubin 1.2-1.9 mg/dl)	6 (7.8)	30 (8.1)	9 (11.7)	109 (10.6)
2-4 (Bilirubin ≥2 mg/dl)	4 (5.2)	10 (2.7)	4 (5.2)	58 (5.6)
Coagulation SOFA score§				
0 (Platelet count ≥ 150 K/mm^3)	62 (80.5)	328 (88.6)	65 (84.4)	913 (88.5)
1 (Platelet count 100-149 K/mm^3)	12 (15.6)	35 (9.5)	12 (15.6)	88 (8.5)
2-4 (Platelet count <100 K/mm^3)	3 (3.9)	7 (1.9)	0 (0)	31 (3.0)
Rescue therapies for hypoxemia**				
Prone position ventilation	35 (45.5)	97 (26.2)	56 (72.7)	576 (55.8)
Neuromuscular blockade	39 (50.6)	116 (31.4)	64 (83.1)	640 (62.0)
Inhaled vasodilators	17 (22.1)	24 (6.5)	36 (46.8)	197 (19.1)

Abbreviations: PaO_2, partial pressure of arterial oxygen over the fraction of inspired oxygen; PEEP, positive end expiratory pressure; RRT, renal replacement therapy; SOFA, Sequential Organ Failure Assessment; UOP, urine output.

*The number of observations in the final cohort differs from the number of unique patients because more than one observation per patient was used, thereby creating a pseudo-cohort. This approach (described further in the supplemental methods) was used to eliminate the potential for immortal time bias.

†Severity of illness data are shown on the day of ICU admission for the unique patients and on the day of ECMO initiation or non-initiation for the final cohort.

‡Shock is defined as the requirement for at least one vasopressor.

§Categories 2, 3, and 4 of the renal, liver, and coagulation components of the SOFA score were binned due to low frequency of events.

‖Includes both acute RRT as well as end stage renal disease requiring RRT.

**Rescue therapies for hypoxemia were assessed on the day of ICU admission for the unique patients and up to and including the day of ECMO initiation or non-initiation for the final cohort.

Table E10. Sensitivity analysis limited to patients with a PaO_2/FiO_2 ratio <80 mm Hg

	Unique Patients		Final Cohort*	
	ECMO (N=130)	No ECMO (N=1167)	ECMO (N=95)	No ECMO (N=1922)
Demographic characteristics				
Age (yrs)				
Median (IQR)	50 (43–59)	58 (49–64)	50 (43–59)	58 (49–64)
18–49	45 (47.4)	193 (26.3)	45 (47.4)	539 (28.0)
50–59	29 (30.5)	221 (30.1)	29 (30.5)	572 (29.8)
60–70	21 (22.1)	320 (43.6)	21 (22.1)	811 (42.2)
Male sex – no. (%)	68 (71.6)	479 (65.3)	68 (71.6)	1272 (66.2)
White Race – no. (%)	36 (37.9)	254 (34.6)	36 (37.9)	678 (35.3)
Body mass index (kg/m^2)				
Median (IQR)	32.7 (29.7–37.9)	32.7 (28.2–38.8)	32.7 (29.7–37.9)	33.1 (28.7–39.7)
<40	76 (80.0)	544 (74.1)	76 (80.0)	1398 (72.7)
≥40	17 (17.9)	161 (21.9)	17 (17.9)	459 (23.9)
Unknown	2 (2.1)	29 (4.0)	2 (2.1)	65 (3.4)
Co-existing conditions				
Hypertension	48 (50.5)	444 (60.5)	48 (50.5)	1142 (59.4)
Diabetes mellitus	30 (31.6)	322 (43.9)	30 (31.6)	819 (42.6)
Coronary artery disease	3 (3.2)	78 (10.6)	3 (3.2)	206 (10.7)
Congestive heart failure	2 (2.1)	75 (10.2)	2 (2.1)	208 (10.8)
Chronic obstructive pulmonary disease	3 (3.2)	58 (7.9)	3 (3.2)	159 (8.3)
Severity of illness†				
PaO_2/FiO_2, mm Hg – median (IQR)	70 (60–91)	76 (63–113)	65 (58–71)	67 (58–73)
PEEP – median (IQR)	15 (14–18)	14 (10–16)	15 (12–18)	15 (12–18)
Shock‡ - no. (%)	60 (63.2)	397 (54.1)	79 (83.2)	1294 (67.3)
Lactate, mmol/L – median (IQR)	1.7 (1.3–2.6)	1.6 (1.1–2.3)	2.1 (1.4–3.1)	1.5 (1.2–2.2)
Arterial pH – median (IQR)	7.35 (7.29–7.43)	7.35 (7.28–7.42)	7.33 (7.27–7.39)	7.32 (7.26–7.39)
Secondary infection	10 (10.5)	62 (8.4)	20 (21.1)	348 (18.1)
Renal SOFA score§				
0 (Cr <1.2 mg/dl)	61 (64.2)	395 (53.8)	47 (49.5)	802 (41.7)
1 (Cr 1.2-1.9 mg/dl)	24 (25.3)	166 (22.6)	29 (30.5)	439 (22.8)
2-4 (Cr >2mg/dL, UOP <500mL, RRT‖)	10 (10.5)	173 (23.6)	19 (20.0)	681 (35.4)
Liver SOFA score§				
0 (Bilirubin <1.2 mg/dl)	83 (87.4)	663 (90.3)	78 (82.1)	1649 (85.8)
1 (Bilirubin 1.2-1.9 mg/dl)	7 (7.4)	49 (6.7)	11 (11.6)	167 (8.7)
2-4 (Bilirubin ≥2 mg/dl)	5 (5.3)	22 (3.0)	6 (6.3)	106 (5.5)
Coagulation SOFA score§				
0 (Platelet count ≥ 150 K/mm^3)	79 (83.2)	629 (85.7)	78 (82.1)	1669 (86.8)
1 (Platelet count 100-149 K/mm^3)	12 (12.6)	82 (11.2)	14 (14.7)	187 (9.7)
2-4 (Platelet count <100 K/mm^3)	4 (4.2)	23 (3.1)	3 (3.2)	66 (3.4)
Rescue therapies for hypoxemia**				
Prone position ventilation	41 (43.2)	158 (21.5)	62 (65.3)	863 (44.9)
Neuromuscular blockade	44 (46.3)	159 (21.7)	73 (76.8)	923 (48.0)
Inhaled vasodilators	19 (20.0)	39 (5.3)	40 (42.1)	294 (15.3)

Abbreviations: PaO_2, partial pressure of arterial oxygen over the fraction of inspired oxygen; PEEP, positive end expiratory pressure; RRT, renal replacement therapy; SOFA, Sequential Organ Failure Assessment; UOP, urine output.

*The number of observations in the final cohort differs from the number of unique patients because more than one observation per patient was used, thereby creating a pseudo-cohort. This approach (described further in the supplemental methods) was used to eliminate the potential for immortal time bias.

†Severity of illness data are shown on the day of ICU admission for the unique patients and on the day of ECMO initiation or non-initiation for the final cohort.

‡Shock is defined as the requirement for at least one vasopressor.

§Categories 2, 3, and 4 of the renal, liver, and coagulation components of the SOFA score were binned due to low frequency of events.

‖Includes both acute RRT as well as end stage renal disease requiring RRT.

**Rescue therapies for hypoxemia were assessed on the day of ICU admission for the unique patients and up to and including the day of ECMO initiation or non-initiation for the final cohort.

Table E11. Sensitivity analysis limited to patients with PaO_2/FiO_2 ratio <150 mm Hg

	Unique Patients		Final Cohort*	
	ECMO (N=149)	No ECMO (N=1792)	ECMO (N=149)	No ECMO (N=7502)
Demographic characteristics				
Age (yrs)				
Median (IQR)	49 (41–57)	58 (49–64)	49 (41–57)	58 (48–64)
18–49	79 (53.0)	482 (26.9)	79 (53.0)	2088 (27.8)
50–59	44 (29.5)	545 (30.4)	44 (29.5)	2271 (30.3)
60–70	26 (17.4)	765 (42.7)	26 (17.4)	3143 (41.9)
Male sex – no. (%)	110 (73.8)	1180 (65.8)	110 (73.8)	4956 (66.1)
White Race – no. (%)	59 (39.6)	635 (35.4)	59 (39.6)	2653 (35.4)
Body mass index (kg/m^2)				
Median (IQR)	32.7 (29.4–38.0)	32.0 (27.6–37.9)	32.7 (29.4–38.0)	32.2 (27.8–38.3)
<40	113 (75.8)	1382 (77.1)	113 (75.8)	5726 (76.3)
≥40	25 (16.8)	351 (19.6)	25 (16.8)	1536 (20.5)
Unknown	11 (7.4)	59 (3.3)	11 (7.4)	240 (3.2)
Co-existing conditions				
Hypertension	67 (45.0)	1021 (57.0)	67 (45.0)	4211 (56.1)
Diabetes mellitus	43 (28.9)	760 (42.4)	43 (28.9)	3120 (41.6)
Coronary artery disease	5 (3.4)	173 (9.7)	5 (3.4)	706 (9.4)
Congestive heart failure	2 (1.3)	146 (8.1)	2 (1.3)	580 (7.7)
Chronic obstructive pulmonary disease	4 (2.7)	128 (7.1)	4 (2.7)	522 (7.0)
Severity of illness[†]				
PaO_2/FiO_2, mm Hg – median (IQR)	82 (66–108)	111 (80–158)	72 (61–87)	102 (79–124)
PEEP – median (IQR)	15 (12–18)	14 (10–16)	15 (12–18)	14 (10–16)
Shock[‡] - no. (%)	91 (61.1)	936 (52.2)	116 (77.9)	4757 (63.4)
Lactate, mmol/L – median (IQR)	1.7 (1.2–2.6)	1.5 (1.1–2.1)	1.9 (1.4–3.0)	1.4 (1.1–2.0)
Arterial pH – median (IQR)	7.35 (7.29–7.44)	7.36 (7.29–7.42)	7.33 (7.28–7.39)	7.36 (7.29–7.41)
Secondary infection	12 (8.1)	138 (7.7)	29 (19.5)	1267 (16.9)
Renal SOFA score[§]				
0 (Cr <1.2 mg/dl)	98 (65.8)	1058 (59.0)	76 (51.0)	3629 (48.4)
1 (Cr 1.2-1.9 mg/dl)	31 (20.8)	379 (21.1)	39 (26.2)	1534 (20.4)
2-4 (Cr >2mg/dL, UOP <500mL, RRT[‖])	20 (13.4)	355 (19.8)	34 (22.8)	2339 (31.2)
Liver SOFA score[§]				
0 (Bilirubin <1.2 mg/dl)	130 (87.2)	1621 (90.5)	123 (82.6)	6474 (86.3)
1 (Bilirubin 1.2-1.9 mg/dl)	13 (8.7)	120 (6.7)	15 (10.1)	614 (8.2)
2-4 (Bilirubin ≥2 mg/dl)	6 (4.0)	51 (2.8)	11 (7.4)	414 (5.5)
Coagulation SOFA score[§]				
0 (Platelet count ≥ 150 K/mm^3)	124 (83.2)	1509 (84.2)	125 (83.9)	6585 (87.8)
1 (Platelet count 100-149 K/mm^3)	18 (12.1)	225 (12.6)	19 (12.8)	674 (9.0)
2-4 (Platelet count <100 K/mm^3)	7 (4.7)	58 (3.2)	5 (3.4)	243 (3.2)
Rescue therapies for hypoxemia**				
Prone position ventilation	59 (39.6)	337 (18.8)	100 (67.1)	3320 (44.3)
Neuromuscular blockade	61 (40.9)	313 (17.5)	116 (77.9)	3269 (43.6)
Inhaled vasodilators	24 (16.1)	58 (3.2)	53 (35.6)	757 (10.1)

Abbreviations: PaO_2, partial pressure of arterial oxygen over the fraction of inspired oxygen; PEEP, positive end expiratory pressure; RRT, renal replacement therapy; SOFA, Sequential Organ Failure Assessment; UOP, urine output.

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[†]Severity of illness data are shown on the day of ICU admission for the unique patients and on the day of ECMO initiation or non-initiation for the final cohort.

[‡]Shock is defined as the requirement for at least one vasopressor.

[§]Categories 2, 3, and 4 of the renal, liver, and coagulation components of the SOFA score were binned due to low frequency of events.

[‖]Includes both acute RRT as well as end stage renal disease requiring RRT.

**Rescue therapies for hypoxemia were assessed on the day of ICU admission for the unique patients and up to and including the day of ECMO initiation or non-initiation for the final cohort.

SUPPLEMENTAL FIGURES

Figure E1. Number of ECMO Patients by City Among Contributing Sites

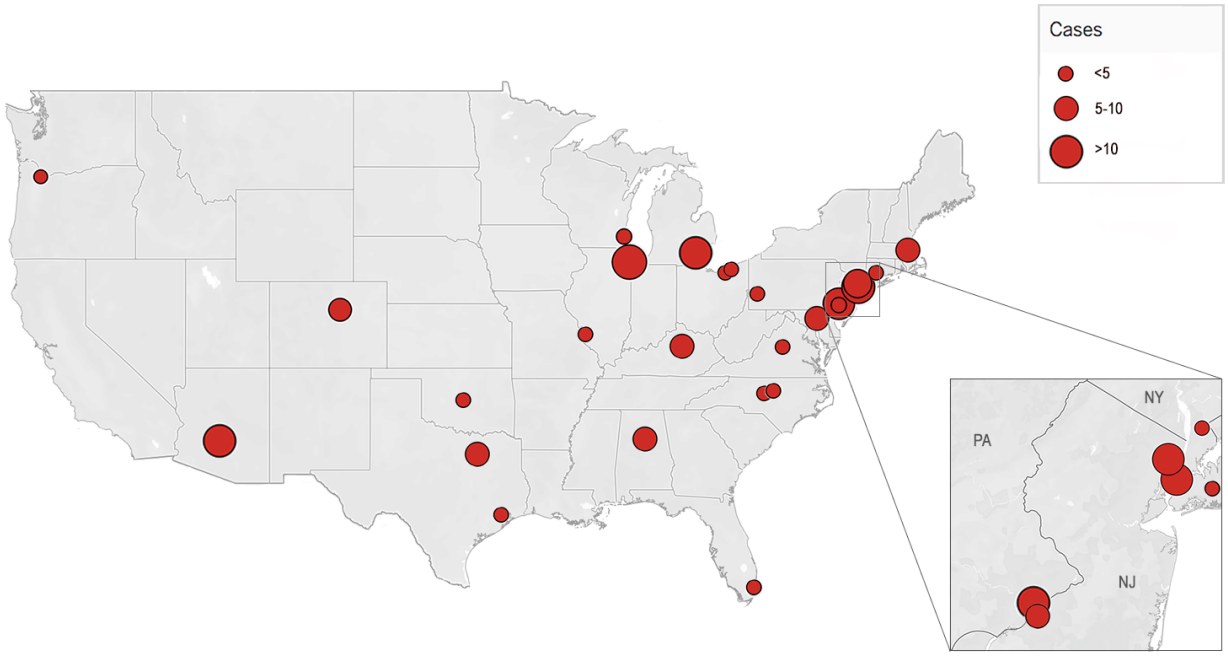


Figure E2. ECMO Cannulation by ICU Day

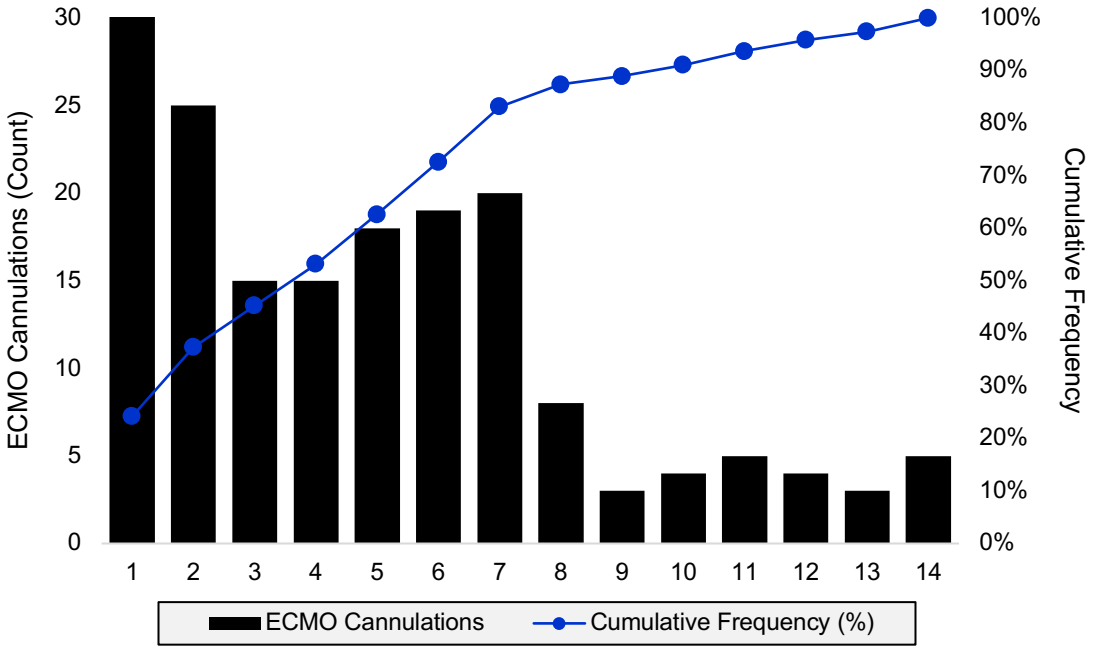
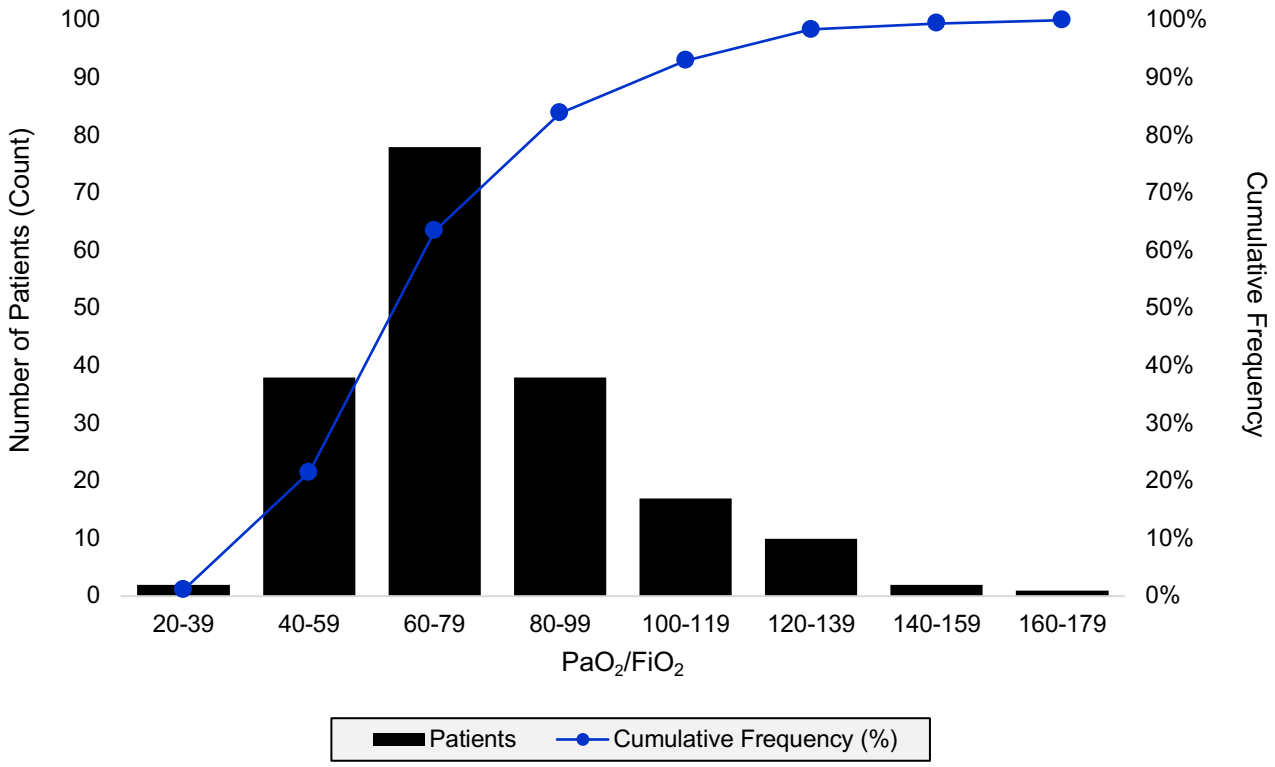


Figure E3. Distribution of Pre-Cannulation PaO_2/FiO_2 Ratio



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