Extracorporeal Membrane Oxygenation for COVID-19 Respiratory Distress Syndrome: An Italian Society for Cardiac Surgery Report

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An increased need of extracorporeal membrane oxygenation (ECMO) support is going to become evident as treatment of SARS-CoV-2 respiratory distress syndrome. This is the first report of the Italian Society for Cardiac Surgery (SICCH) on preliminary experience with COVID-19 patients receiving ECMO support. Data from 12 Italian hospitals participating in SICCH were retrospectively analyzed. Between March 1 and September 15, 2020, a veno-venous (VV) ECMO system was installed in 67 patients (94%) and a veno-arterio-venous ECMO in four (6%). Five patients required VA ECMO after initial weaning from VV ECMO. Thirty (42.2%) patients were weaned from ECMO, while 39 (54.9%) died on ECMO, and six (8.5%) died after ECMO removal. Overall hospital survival was 36.6% (n = 26). Main causes of death were multiple organ failure (n = 14, 31.1%) and sepsis (n = 11, 24.4%). On multivariable analysis, predictors of death while on ECMO support were older age (p = 0.048), elevated pre-ECMO C-reactive protein level (p = 0.048), higher positive end-expiratory pressure on ventilator (p = 0.036) and lower lung compliance (p = 0.032). If the conservative treatment is not effective, ECMO support might be considered as life-saving rescue therapy for COVID-19 refractory respiratory failure. However warm caution and thoughtful approaches for timely detection and treatment should be taken for such a delicate patients population. *ASAIO Journal* 2021; 67;385–391

Key Words: COVID-19, pandemic, acute respiratory distress syndrome, extracorporeal membrane oxygenation, Italy

Due to SARS-CoV-2 rampant spread worldwide, on March 11, 2020, coronavirus disease 2019 (COVID-19) was labeled a pandemic by the World Health Organization (WHO).[1–11] Interim WHO guidelines recommend administering veno-venous (VV) extracorporeal membrane oxygenation (ECMO) to eligible patients with COVID-19 related severe respiratory distress syndrome at expert centers.[1,2] Italy was severely affected by the virus and went into official lockdown on March 9, 2020[1,10,11]. This article is the first report of the Italian Society for Cardiac Surgery (SICCH) on COVID-19 patients supported by ECMO across Italy.

Methods

Study Population

We conducted a retrospective cohort study of adult (≥18 years old) patients who underwent ECMO support for confirmed COVID-19 respiratory distress syndrome at 12 ECMO hub centers across Italy. All centers joined the SICCH task force for COVID-19 pandemic.[10,11]

Infection was confirmed by usage of real-time reverse transcription-polymerase chain reaction test of 2019-nCoV on serum and nasopharyngeal plus lower respiratory tract swab samples.

Consideration of ECMO was based on the presence of severe respiratory failure (Murray score >3.0 or pH <7.20 under protective ventilation[12–19]) associated with sustained clinical deterioration despite optimal conventional treatment and prone positioning, in accordance with Extracorporeal Life Support Organization (ELSO) guidelines.[12,13] Diffuse bilateral

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lung injury by SARS-CoV-2 was confirmed by chest X-ray or computed tomography (CT) scan (Figure 1) in the majority of patients (Tables 1 and 2).[20,21] Aggressive mechanical ventilation (peak or plateau airway pressure >30 cm H_2O or fraction of inspired oxygen [FiO_2] >0.8) for more than 7 days, uncontrolled active bleeding, severe comorbidity, advanced multiple organ failure (MOF), disseminated intravascular coagulation, age >75 years, and neurologic damage were considered contraindications to ECMO. Patients were considered for ECMO after a multidisciplinary team assessment conducted by experts from anesthesiology, cardiac surgery, cardiology, and infectious diseases. The study was approved by each single-center institutional review board and officially endorsed by SICCH task force for COVID-19.[10,11] Informed consent was not required, as ECMO was considered rescue therapy in all patients. Data were retrospectively entered into a dedicated electronic datasheet with prespecified variables by experienced clinicians, and underwent regular monitoring for completeness and quality. Data on baseline characteristics, ECMO therapy, and adverse events were retrieved from the electronic patient records. Follow-up ended September 30, 2020 and was complete for all patients.

Extracorporeal Membrane Oxygenation Support Setting and Management

The ultracompact Cardiohelp, RotaFlow, and CentriMag were adopted as ECMO systems. In all VV ECMO cases, the right femoral vein was cannulated percutaneously using the Seldinger technique with a 21-25 Fr heparin-coated cannula (inflow), while for reinfusion (outflow), a 15-17 Fr heparin-coated cannula was used, generally implanted into the right internal jugular vein.[22–28] In the case of hemodynamic instability and poor myocardial contractility, a 15-17 Fr heparin-coated cannula was added as second arterial return and inserted into the right femoral artery thus achieving the setting of a veno-arterio-venous (VAV) ECMO support.[22–28]

All the components of the ECMO system and tubings were heparin-coated (Bioline coating, Getinge; Maquet-Cardiopulmonary AG, Rastatt, Germany), and systemic anticoagulation was maintained using unfractionated heparin to a partial thromboplastin time of 1.5 normal.[22–28,30,31]

Pressures on the ECMO circuit, blood gas analysis, general laboratories, and complete blood coagulation study were also monitored daily. Echocardiography was not performed routinely.

After cannulation, patient management was optimized to minimize further ventilator-induced lung injury (VILI).[13–15,20–28] Regarding oxygenation, ECMO blood flow was maximized to reduce the FiO2 less than 0.6 and maintain hemoglobin saturation of more than 85%. Positive end-expiratory pressure (PEEP) was maintained above 8 cm H_2O. If severe hypoxemia (PaO2, <60 mm Hg) still subsisted, the threshold for red blood cell transfusion was elevated from 7.0 to 9.0 g/dl. The threshold for prophylactic platelet transfusion was 35,000/μl, whereas the targeted post-transfusion goal was 100,000/μl in the presence of active bleeding. Regarding CO_2 removal, sweep gas flow was maximized to allow a normal pH, small tidal volumes (<6 ml/kg per predicted body weight), and plateau pressures less than 25 cm H_2O. Paralysis and sedation were maintained.

Upon improvement in native lung function (FiO2 <0.5, PEEP <10 cm H_2O, peak inspiratory pressure in pressure-controlled ventilation <25 cm H_2O), ECMO flow was gradually reduced to 2.0 L/min. Sweep gas flow was then tapered and finally shut off within 40 minutes. If blood gases remained stable for more than 6 hours, the ECMO system was removed.[22–28]

Outcomes

The primary study outcome was mortality. Secondary outcomes were cerebral stroke, lung complications, severe acute kidney injury (AKI), new renal replacement therapy (RRT) need, MOF, bleeding events, superinfections, sepsis, confirmed pulmonary embolism (PE), mechanical ventilation duration, and length of intensive care unit (ICU) stay. Stroke was defined as any focal or global neurologic syndrome caused by ischemia or hemorrhage. The diagnosis was confirmed by brain CT or magnetic resonance imaging. Severe AKI was defined according to "Kidney Disease: Improving Global Outcomes classification criteria,"[29] that is, an increase in serum creatinine concentration to at least 3-fold the baseline level, a serum creatinine concentration increase of at least 4.0 mg/dl, or new RRT during the hospital stay. For all outcomes, survivors and non-survivors were compared.

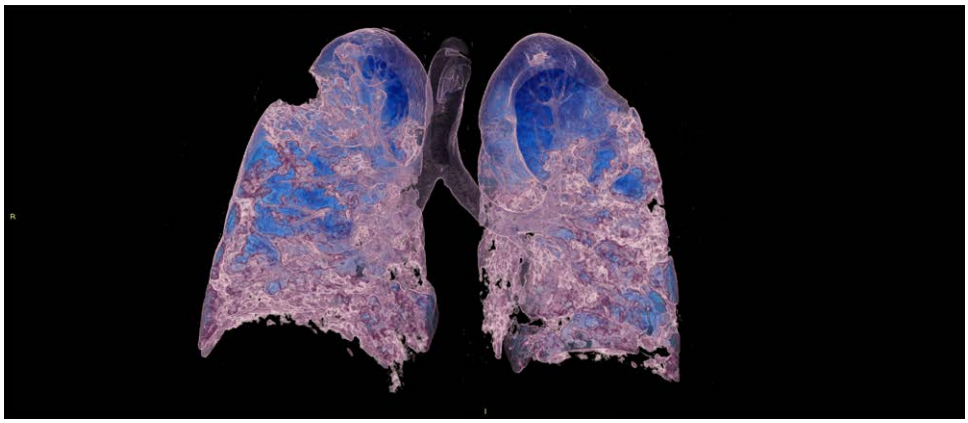

Figure 1. COVID-19 respiratory disease before ECMO installation. 3D-reconstructed computed tomography (CT) scan. ECMO, extracorporeal membrane oxygenation. full color online

Table 1. Characteristics of COVID-19 Patients Before ECMO Installation

Characteristics	Overall (n = 71)	Survivors (n = 26)	Non-survivors (n = 45)	*P*
Baseline				
Age (years)	55.4 ± 9.3	51.2 ± 11.1	57.3 ± 7.7	0.027
Female sex, n (%)	10 (14.1)	1 (3.8)	9 (20.0)	0.081
BMI (kg/m^2)	30.2 ± 6.1	29.9 ± 6.1	30.4 ± 6.2	0.849
Weight (kg)	92.2 ± 18.2	93.5 ± 21.3	91.5 ± 16.2	0.670
Race and ethnicity				0.724
White, n (%)	68 (95.8)	25 (96.2)	43 (95.6)	
Asian, n (%)	2 (2.8)	1(3.8)	1 (2.2)	
Black, n (%)	1 (1.4)	—	1 (2.2)	
Comorbidities, n (%)				
Diabetes	12 (16.9)	4 (15.4)	8 (17.8)	0.795
Hypertension	31 (43.7)	10 (38.5)	21 (46.7)	0.502
Coronary artery disease	6 (8.5)	2 (7.7)	4 (8.9)	1.000
Atrial fibrillation	5 (7.0)	2 (7.7)	3 (6.7)	1.000
Previous cardiac surgery	2 (2.8)	—	2 (4.4)	0.529
Concomitant heart disease	2 (2.8)	—	2 (4.4)	0.511
Asthma/COPD	5 (7.0)	1 (3.8)	4 (8.9)	0.646
Smoking	11 (15.5)	4 (15.4)	7 (15.6)	1.000
Previous bacterial pneumonia	4 (5.6)	3 (11.5)	1 (2.2)	0.136
Chronic kidney injury	3 (4.2)	—	3 (6.7)	0.294
Dialysis	2 (2.8)	—	2 (4.4)	0.529
Oral drug therapy, n (%)				
ACE-inhibitors	11 (15.5)	2 (7.7)	9 (20.0)	0.167
ARBs	6 (8.5)	3 (11.5)	3 (6.7)	0.662
Clinical manifestations, n (%)				
Fever*	62 (87.3)	25 (96.2)	37 (82.2)	0.089
Dry cough	39 (54.9)	14 (53.8)	25 (55.6)	0.889
Productive cough	4 (5.6)	1 (3.8)	3 (6.7)	0.619
Bacterial pneumonia	7 (9.8)	2 (7.7)	5 (11.1)	0.453
Bilateral lung involvement	66 (92.9)	24 (92.3)	42 (93.3)	0.871
Bloodstream infection	13(18.3)	2(7.7)	11(24.4)	0.079
Acute heart failure	3 (4.0)	1 (3.8)	2 (4.4)	1.000
Myocarditis	2 (3.0)	1 (3.8)	1 (2.2)	1.000

*Fever is defined as systemic body temperature ≥38.0°C.

ACE, angiotensin-converting enzyme inhibitors; ARBs, angiotensin II receptor blockers; BMI, body mass index; COPD, chronic obstructive pulmonary disease; ECMO, extracorporeal membrane oxygenation.

Statistical Analysis

Continuous variables were tested for normality with Shapiro–Wilk's test and reported as means with SD or as medians with interquartile range (IQR). To compare continuous variables between survivors and non-survivors, Student's t-test for unpaired data or Wilcoxon–Mann-Whitney *U* test were used. Categorical variables were reported as counts and percentages and compared by Pearson χ^2 analysis. All variables were compared between survivors and non-survivors by univariate analysis, and those with a $p < 0.2$ were entered into a multivariable model. Binary logistic regression was used to identify risk factors for mortality. As a final step, a parsimonious model was constructed. Bootstrapping in 1,000 samples was used to correct both estimators and 95% confidence limits. Model discrimination was evaluated using area under the receiver operating characteristic curves. R-studio version 1.1.463 (2009–2018) and SPSS 24.0 (SPSS, Inc, Chicago, IL) were used for all statistical analyses. All tests were two-tailed, and $p \leq 0.05$ was set as the criterion for statistical significance.

Results

Between March 1 and September 15, 2020, 71 adult patients who received ECMO for COVID-19 severe respiratory failure were enrolled into the study, in Italy. The number of patients treated with ECMO at each center varied from 1 to 23. All participating centers were tertiary-care hospitals with dedicated ECMO activity and officially designated COVID-19 centers by the Italian Ministry of Health. Tables 1 and 2 summarize the sample's demographic, morphometric, baseline clinical characteristics, and drug treatments administered.

Before ECMO, all patients were on invasive mechanical ventilation with rapid in-hospital deterioration early after ICU admission for advanced respiratory support. Mean lactate levels were 3.6 ± 5.4 (range: 1.6–20) while mean PaO2/FiO2 ratio was 78.7 ± 39.3 (range: 39–143). Other ventilation parameters are summarized in Tables 1 and 2. D-dimer levels before ECMO support averaged 8844.3 ± 4109.8 (range: 235–75,196) μg/ml. VV ECMO support was installed in 67 patients (94%) and VAV ECMO in four (6%) (Table 3). A femoro-jugular configuration was used for all VV ECMO patients while a femoro-femoro-jugular setting was adopted in the VAV ECMO cases.[22–28] Intra-aortic balloon pump support was used in three cases (5%) (Table 3). Five VV ECMO-weaned patients required a second course of ECMO with a VA ECMO femoro-femoral configuration, due to refractory hemodynamic instability and recurrent respiratory failure.[22–28]

Time between patients' ICU admission and ECMO insertion averaged 11.6 ± 8.9 (range: 0–41) days while pre-ECMO intubation meantime was 6.5 ± 5.3 (1–10.1) days.

No pump failure occurred during mechanical circulatory support while ECMO circuit change was performed in 10 cases (14.1%), at the time of documented oxygenator low performance (Table 3). Moderate dosage of intravenous vasoactive drug infusion (norepinephrine drip of 0.05–0.08 μg/Kg/min,

Table 2. Characteristics of COVID-19 Patients Before ECMO Installation

Characteristics	Overall (n = 71)	Survivors (n = 26)	Non-survivors (n = 45)	*P*
Baseline				
Arterial blood analysis*				
PaO2	68 ± 39	79 ± 49	61 ± 13	0.025
$PaCO_2$	63 ± 20	62 ± 19	65 ± 20	0.521
Lactates (mmol/L)	3.0 (1.3–4.1)	3.1 (1.4–4.5)	3.0 (1.3–4.3)	0.347
Prior noninvasive ventilation				
CPAP, n (%)	53 (74.6)	19 (73.1)	34 (75.6)	0.817
BiPAP, n (%)	18 (25.3)	7 (26.9)	11 (24.4)	0.711
Invasive mechanical ventilation, n (%)	71 (100)	26 (100)	45 (100)	—
Ventilator setting†				
PEEP (cmH_2O)	13.3 ± 4.1	12.1 ± 4.6	14.5 ± 3.7	0.031
Tidal volume (mL/kg)	469.6 ± 114.4	427.7 ± 80.2	494.5 ± 129.1	0.030
FiO2	92.4 ± 14.5	90. ± 16.1	93.9 ± 15.6	0.482
Compliance (mL/cmH_2O)	34.4 ± 18.1	41.8 ± 24.5	30.1 ± 11.4	0.024
PaO2/FiO2	78.7 ± 39.3	92.6 ± 51.9	71.2 ± 27.8	0.042
Pre-ECMO mechanical ventilation time (days)	5.5 (1.6–7.1)	6.1 (2.0–7.1)	4.8 (1.6–6.4)	0.075
Inflammatory parameters				
CRP (mg/dL)	21.4 (11–36)	15.1 (7–32)	25.2 (15–36)	0.028
Leukocytes ($\times 10^9$/L)	15.2 ± 8.5	13.9 ± 8.5	15.7 ± 8.4	0.488
Antiretroviral therapy, n (%)	50 (70.4)	16 (61.5)	34 (75.6)	0.212
Remdesivir	16 (22.5)	5 (19.2)	11 (24.4)	0.771
Lopinavir	38 (53.5)	12 (46.2)	26 (57.8)	0.344
Ritonavir	36 (50.7)	11 (42.3)	25 (55.6)	0.282
Rescue therapy, n (%)				
Tocilizumab	21 (29.6)	7 (26.9)	14 (31.1)	0.710
Chloroquine	59 (83.1)	19 (73.1)	40 (88.9)	0.087
Antibiotics, n (%)				
Azithromycin	32 (45.1)	10 (38.5)	22 (48.9)	0.395
Other antibiotics	68 (95.8)	25 (96.2)	43 (95.6)	0.904
Pre-ECMO support, n (%)				
Prone positioning	60 (85)	23 (89)	37 (82)	0.735
Neuromuscular blockade	60 (85)	23 (89)	37 (82)	0.735
Epinephrine	14 (19.7)	6 (23.1)	8 (17.8)	0.589
Norepinephrine	55 (77.5)	21 (80.8)	34 (75.6)	0.612
Inhaled pulmonary vasodilators	13 (18.3)	4 (15.4)	9 (20.0)	0.756

*Arterial blood analysis. The PaO2 and $PaCO_2$ are measured within 6 h before ECMO initiation and are the measure nearest to ECMO initiation while still remaining pre-ECMO initiation.

†Mode of mechanical ventilation. The Compliance, FiO2, PaO2:FiO2, PEEP, Tidal Volume are measured within 6 hours before ECMO initiation and are the measure nearest to ECMO initiation while still remaining pre-ECMO initiation.

BiPAP, bilevel positive airway pressure; CPAP, continuous positive airway pressure; CRP, C-reactive protein; ECMO, extracorporeal membrane oxygenation; ECPR, extracorporeal cardiopulmonary resuscitation; FiO_2, fraction of inspired oxygen; $PaCO_2$, partial pressure of arterial carbon dioxide; PaO2:FiO2, ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen; PEEP, positive end-expiratory pressure.

mostly) and consecutive positive fluid balance was frequently needed during ECMO support.[22–28]

The mean overall duration of ECMO was 15.4 ± 10.1 days (range: 1–41) (Table 3). Extracorporeal membrane oxygenation flow averaged 4.9 ± 0.8 L/min (range: 2.24–6.30). Thirty (42.2%) patients were weaned from ECMO. In these patients, CT scan (Figure 1) and chest X-ray imaging revealed typical ground-glass features and reduced consolidations. CytoSorb (Aferetica, BO, Italy) hemoadsorption[13–15] was arbitrarily adopted in 14 (19.7%) patients by five institutions without significant beneficial results. In all weaned patients, lung-protective ventilation was sustained during ECMO support and maintained for 48–72 hours after ECMO cessation.[13–15,20,21] A percutaneous tracheostomy was performed in 32 (45.1%) patients after a median time of 8.0 (5–16) days since the beginning of ECMO support.[22,32] Thirty-nine (54.9%) patients died on ECMO, including the secondary VA ECMO run cases (Table 3). Six (8.5%) patients died after ECMO removal. Overall, 26 patients (36.6%) survived in hospital and were successfully discharged home with societal isolation. The most common causes of hospital death were MOF (31.1%) and sepsis (24.4%) (Table 3). All discharged patients have been followed by official COVID-19 outpatients care units of all participating hospitals.

Baseline characteristics were similar in survivors and non-survivors, except for age (Tables 1 and 2), as survivors were younger (51.2 ± 11.1 *vs.* 57.3 ± 7.7, $p = 0.027$). Clinical presentation was similar in the two cohorts, except for PaO2 which was lower among non-survivors (61 ± 13 *vs.*79 ± 49, $p = 0.025$). Mechanical ventilation settings differed, as non-survivors required a higher mean level of PEEP (14.5 ± 3.7 *vs.* 12.1 ± 4.6, $p = 0.031$), exhibited higher tidal volumes (494.5 ± 129.1 *vs.* 427.7 ± 80.2, $p = 0.030$) and had less lung compliance (30.1 ± 11.4 *vs.* 41.8 ± 24.5, $p = 0.024$). Non-survivors were less likely to have received a tracheostomy (n = 15, 33.3% *vs.* n = 17, 65.4%, $p = 0.009$) (Table 3). Among inflammatory markers, only the C-reactive protein (CRP) level was higher in non-survivors (25.2, 15–36 *vs.* 15.1, 7–32, $p = 0.028$) (Tables 1 and 2). Extracorporeal membrane oxygenation flow was higher in non-survivors than survivors (5.3 ± 0.7 *vs.* 4.5 ± 0.9, $p = 0.009$) (Table 3).

On multivariable analysis, predictors of death were older age ($p = 0.048$), elevated pre-ECMO CPR level ($p = 0.048$), higher PEEP ($p = 0.036$), and less lung compliance ($p =$

Table 3. ECMO Support Settings and Outcomes of COVID-19 ECMO Patients

	Overall (n = 71)	Survivors (n = 26)	Non-survivors (n = 45)	*p*
Primary ECMO configuration				0.619
VV ECMO, n (%)	67 (94.4)	25 (96.2)	42 (93.3)	
VAV ECMO, n (%)	4 (5.6)	1 (3.8)	3 (6.7)	
Second run ECMO configuration				
VA ECMO, n (%)	5 (7.0)	1 (3.8)	4 (8.9)	0.424
Distal leg perfusion, n (%)	5 (7.0)	0	5 (11.1)	0.078
IABP, n (%)	3 (5)	1 (3.8)	2 (4.4)	0.800
Anticoagulation management				0.165
Heparin, n (%)	69 (93.0)	24 (92.3)	45 (100)	
Bivaluridin, n (%)	2 (7.0)	2 (7.7)	0	
ECMO flow (L/min)	4.9 ± 0.8	4.5 ± 0.9	5.3 ± 0.7	0.009
ECMO-related adverse events, n (%)	56 (78.9)	16 (61.5)	40 (88.9)	0.007
Cerebral stroke	6 (8.5)	0	6 (13.3)	0.079
Pulmonary embolism	4 (5.6)	2 (7.7)	2 (4.4)	0.620
Deep vein thrombosis	2 (2.8)	2 (7.7)	0	0.131
Bleeding (not requiring surgery)	6 (8.5)	2 (7.7)	4 (8.8)	1.000
Bleeding requiring surgery	3 (4.2)	1 (3.8)	2 (4.4)	1.000
Bacterial superinfection pneumonia	39 (54.9)	13 (50.0)	26 (57.8)	0.526
Sepsis	14 (19.7)	0	14 (31.1)	0.002
AKI (requiring dialysis)	3 (4.2)	0	3 (6.7)	0.179
Multiple organ failure (MOF)	14 (19.7)	0	14(31.1)	0.002
Pump failure	—	—	—	—
Circuit change	10 (14.1)	3 (11.5)	7 (15.5)	0.212
ECMO duration (days)	15 (8–23)	14 (5–24)	15 (10–22)	0.319
ECMO weaning/removal, n (%)	30 (42.3)	24 (92.3)	6 (13.3)	<0.001
Death on ECMO, n (%)	39 (54.9)	—	39 (86.7)	N/A
Death in ICU, n (%)	6 (8.5)	—	6 (13.3)	N/A
Post-ECMO ICU LOS (days)	24 (14–37)	21 (12–35)	33 (23–45)	0.001
Tracheostomy, n (%)	32 (45.1)	17 (65.4)	15 (33.3)	0.009
Global mechanical ventilation (pre-, in-, and post-ECMO) time (days)	25.5 (1.6–37)	27.2 (1.8–34)	36.4 (1.5–43)	0.065
Hospital LOS (days)	30 (18–45)	25 (16–40)	44 (34–61)	<0.001
Cause of death, n (%)				
MOF	14 (19.7)	—	14 (31.1)	
Sepsis	11 (15.4)	—	11 (24.4)	
Bleeding	6 (8.4)	—	6 (13.3)	
Bacterial pneumonia	5 (7.1)	—	5 (11.1)	
Cerebral stroke (hemorrhagic)	4 (5.6)	—	4 (8.8)	
Acute heart failure	2 (2.8)	—	2 (4.4)	
Pulmonary embolism	2 (2.8)	—	2 (4.4)	
Cerebral stroke (ischemic)	1 (1.4)	—	1 (2.2)	

Data are median (interquartile range [IQR]) or numbers (n) and percentage (%).

ACE, angiotensin-converting enzyme inhibitors; AKI, acute kidney injury; ARBs, angiotensin II receptor blockers; BiPAP, bilevel positive airway pressure; BMI, body mass index; CPAP, continuous positive airway pressure; CRP, C-reactive protein; COPD, chronic obstructive pulmonary disease; ECMO, extracorporeal membrane oxygenation; ECPR, extracorporeal cardiopulmonary resuscitation; FiO2, fraction of inspired oxygen; IABP, intra-aortic balloon pump; ICU, intensive care unit; LOS, length of stay; MOF, multiple organ failure; $PaCO_2$, partial pressure of arterial carbon dioxide; PaO2:FiO2, ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen; PEEP, positive end-expiratory pressure; VA, veno-arterial; VAV, veno-arterio-venous; VV, veno-venous.

0.032) (Table 4), while having a tracheostomy was protective ($p = 0.007$).

Discussion

SARS-CoV-2 causes respiratory failure due to alveolar damage.[5–9,20,21] The rate of severe respiratory distress syndrome ranges from 15% to 30%.[5–9] Currently, no specific therapy exists. The ELSO registry counts more than 2,611 respiratory ECMO having been implanted worldwide, showing an overall in-hospital mortality rate of 45% and patients discharge alive to home or acute rehabilitation of 23%.[12,13] Contrary to preliminary literature results that indicated dismal outcomes with 84%–100% mortality of patients with COVID-19 given ECMO,[12,13,22–28] the estimated 31% probability of day 60 mortality for ECMO-treated patients was similar in the EOLIA trial[22] or the prospective LIFEGARD registry[21] or the recent Paris-Sorbonne University Hospital Network analysis.[28]

In COVID-19 patients, the initial pulmonary pattern is dissimilar to the conventional acute respiratory distress syndrome, as hypoxia and hypoxic vasoconstriction are prevalent and pulmonary compliance is generally higher in the former.[20,21]

Clinical characteristics of our ECMO-treated patients (Tables 1 and 2) showed a mean PaO2/FiO2 of 78 (SD 39) mm Hg which was similar to that of patients in the EOLIA22 (73 [SD 30] mm Hg) or LIFEGARD21 (71 [SD 34] mm Hg) trials but lower than for patients of Paris-Sorbonne University Hospital Network[28] (62 [SD 18] mm Hg). The mean respiratory system compliance of our overall population was 34 (SD 18) ml/cmH_2O and the mean PaO2/FiO2 of non-survivors cohort was 71 (SD 27) mm Hg, thus indicating a distress respiratory severity before ECMO support was initiated.

While on mechanical ventilation, in COVID-19 patients, high PEEP levels may compromise right cardiac filling and increase the need for fluid resuscitation or norepinephrine.[20,21] The "lung-protective ventilation" is the recommended strategy.[13–18,20,21] If the conventional mechanical ventilation proves

Table 4. Multivariable Analysis to Identify Predictors of Death in COVID-19 ECMO Patients

	OR	95% CI	*p*
Age (years)	1.085	1.001–1.192	0.048
Pre-ECMO CRP	1.017	1.001–1.145	0.048
Pre-ECMO PEEP	1.174	1.013–1.456	0.036
Pre-ECMO lung compliance	1.954	1.617–1.997	0.032
Tracheostomy	0.200	0.062–0.646	0.007

CRP, C-reactive protein; ECMO, extracorporeal membrane oxygenation; OR, odds ratio; PEEP, positive end-expiratory pressure.

ineffective, ECMO support should be considered.[13–21] In our study, high preoperative PEEP (>15) on ventilator and low respiratory system compliance (<30) were independent predictors of mortality (Table 4), thus indicating a late ECMO establishment as reported in other studies published in the last 7 months.[20–28] Schmidt *et al*.[28] showed COVID-19 patients with poor prognosis having significantly low respiratory system compliance and high driving pressure confirming, in such a clinical scenario, a extensive SARS-CoV-2-induced alveolar damage.

Moreover, 94% of French patients[28] benefited from prone positioning before ECMO (compared with 56% in EOLIA22 and 26% in LIFEGARD21). However, in our series, only 32% of patients benefited from prone positioning and survived (Tables 1 and 2).

Not having a tracheostomy was an additional risk factor for death (Table 4), thereby supporting the need for a radical ventilatory treatment, to enable a early spontaneous breathing but not in the case of unstable or bleeding patients who might be at high risk associated with the procedure.[30,31] Moreover, there has been a higher number of tracheostomies in patients doing better, in our study (Table 3). However, virus aerosolization and the risk of infection transmission might be greater in patients with a tracheostomy.[30]

Challenging clinical COVID-19 scenarios are MOF, respiratory superinfections,[31] and sepsis.[4–10] In our study, MOF (31.1%) and sepsis (24.4%) were the most common causes of death (Table 3). Thus, aggressive antibiotic therapy to prevent or treat ongoing superinfection and a early timing for ECMO insertion, which avoid multiple organ deterioration, result crucial.[22–28]

It has been reported a highly activated coagulation cascade in COVID-19 syndrome associated with micro- and macrothromboses in all organ systems.[4–10] Schmidt *et al*.[28] observed an extremely high on ECMO rate of PE (19%), even if compared with the EOLIA trial[22] results. In our analysis, PE occurred only in 5.6% of our ECMO patients and did not impact the outcomes (Table 3). Nonetheless, PE remains a frequent finding on autopsy.[32,33]

The higher anticoagulation regimen while on ECMO support, and specific SARS-CoV-2 associated vasculitis may provide diffuse associated microbleeds.[22–28] In our series, bleeding complications and hemorrhagic stroke were frequent and resulted to be the cause of death in 22.2% of our ECMO non-survivors (Table 3).

The interplay between coagulation and inflammation while on ECMO may play a significant role.[34,35] In our studied population a high pre-ECMO CRP (>25) resulted to be a risk factor for mortality (Table 4), probably due to a severe inflammatory preoperative status. This may be supported by an ECMO flow need which was higher in non-survivors than survivors (Table 3).

In COVID-19 syndrome, myocardial injury, low cardiac output, and arrhythmias may result from direct, viral-induced damage to cardiomyocytes.[4–11,13–15] Thus, VA ECMO might need to be considered. In our study, five patients (7%) had to be switched from VV to VA ECMO due to concurrent heart failure (Table 3). Unfortunately, four of these five patients did not survive due to MOF, suggesting that myocardial tissue involvement may negatively impact on outcomes.

Compared with the EOLIA trial[22] of patients with severe respiratory distress syndrome treated with ECMO, in our study of patients with COVID-19, ECMO support (median 15 [IQR 8–23] days *vs*. 11 [7–18] days) and ICU stay (24 [14–37] days *vs*. 23 [13–34] days) lasted similarly, confirming the severity of SARS-CoV-2 associated pulmonary damage and organ failure (Table 3). However median durations were less when compared with the Paris-Sorbonne University Network COVID-19 analysis[28] which showed clinically worst patients (ECMO support 20 [IQR 10–40] days and ICU stay 36 [23–60] days).

The COVID-19 pandemic has disproportionately claimed the lives of older patients. However, mortality also has been observed in younger patients without severe comorbidities,[4–11] and, rarely, in children and adolescents, who generally exhibit a systemic inflammatory syndrome which may be similar to Kawasaki disease.[36,37]

In our population, non-survivors had a mean age of 57.3 years, which was significantly higher than among survivors (Tables 1 and 2).

We acknowledge several limitations to our study, including the retrospective nature of data collection, the limited size of our cohort of patients, and the absence of non-ECMO treated patients, as control. The current preliminary findings provide an additional contribution to the global scientific community discussion on selection and management of COVID-19 patients with severe hypoxemia and hemodynamic instability. We believe ECMO should be considered early for patients with COVID-19-related profound respiratory failure, despite optimized conventional care.

However, warm caution and thoughtful approaches for detection and treatment should be taken for COVID-19 patients to preserve life. Enhancing referral logistics, diverting resources to experienced ECMO centers, and avoiding VILI may provide better results. However, long-term follow-up of patients is needed to evaluate COVID-19's potential pulmonary and physical sequelae.

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