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ASAIO Journal Publish Ahead of Print

DOI: 10.1097/MAT.0000000000001399

Extracorporeal Membrane Oxygenation for COVID-19 respiratory distress syndrome: an Italian Society for Cardiac Surgery Report

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Running Head: ECMO for COVID-19 in Italy

Key Words: COVID-19; Pandemic; ARDS; Extracorporeal Membrane Oxygenation; Italy.

Word Count: 2694.

Disclosures: None.

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Abstract

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 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 1st and September 15th, 2020, a veno-venous (VV) ECMO system was installed in 67 patients (94%) and a veno-arterio-venous (VAV) 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.

Introduction

Due to SARS-CoV-2 rampant spread worldwide, on March 11st, 2020, COVID-19 (COrona VIrus Disease-19) was labelled 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 9th, 2020[1,10,11]. This paper 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-year-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 (RT-PCR) 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 and/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 lung injury by SARS-CoV-2 was confirmed by chest X-ray and/or computed tomography (CT) scan (Figure 1) in the majority of patients (Table 1 and Table 2) [20,21]. Aggressive mechanical ventilation (peak or plateau airway pressure >30 cmH_2O or fraction of inspired oxygen [FiO2] >0.8) for more than seven days, uncontrolled active bleeding,

severe comorbidity, advanced multiple organ failure (MOF), disseminated intravascular coagulation, age >75 years, and neurological 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 (IRB) 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 pre-specified 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 30th, 2020 and was complete for all patients.

ECMO 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[13-15,20,21,22-28]. Regarding oxygenation, ECMO blood flow was maximized to reduce the fraction of inspired oxigen (FiO2) less than 0.6 and maintain hemoglobin saturation more than 85%. Positive end-expiratory pressure (PEEP) was maintained above 8 cmH2O. If severe hypoxemia (PaO2, <60 mmHg) 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 CO2 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 cmH2O. Paralysis and sedation were mantained.

Upon improvement in native lung function (FiO2 <0.5, PEEP <10 cmH_2O, peak inspiratory pressure in pressure controlled ventilation [PIP] <25 cmH2O), 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 over six 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, multiple organ failure (MOF), bleeding events, superinfections, sepsis, confirmed pulmonary embolism, mechanical ventilation duration, and length of intensive care unit (ICU) stay. Stroke was defined as any focal or global neurological syndrome caused by ischemia and/or hemorrhage. The diagnosis was confirmed by brain computed tomography (CT) and/or magnetic resonance imaging (MRI). Severe acute kidney injury (AKI) was defined according

to 'Kidney Disease: Improving Global Outcomes classification criteria'[29]; i.e., an increase in serum creatinine concentration to at least 3-fold the baseline level, a serum creatinine concentration increase of at least 4.0mg/dL, or new RRT during the hospital stay. For all outcomes, survivors and non-survivors were compared.

Statistical analysis

Continuous variables were tested for normality with Shapiro–Wilk's test and reported as means with standard deviation (SD) or as medians with interquartile range. To compare continuous variables between survivors and non-survivors, Student's *t* test for unpaired data or Wilcoxon–Mann–Whitney test were used. Categorical variables were reported as counts and percentages and compared by Pearson $\chi 2$ 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 1000 samples was used to correct both estimators and 95% confidence limits. Model discrimination was evaluated using area under the receiver operating characteristic (ROC) curves. R-studio version 1.1.463 (2009-2018) and SPSS 24.0 (SPSS, Inc, Chicago, Ill) 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 1st and September 15th, 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. Table 1 and Table 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 PaO_2/FiO_2 ratio was 78.7±39.3 (range: 39-143). Other ventilation parameters are summarized in Table 1 and Table 2. D-dimer levels before ECMO support averaged 8844.3±4109.8 (range: 235-75196) 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 (IABP) support was used in 3 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 mean time 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, 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). ECMO flow averaged 4.9±0.8 L/min (range: 2.24-6.30). Thirty (42.2%) patients were weaned from ECMO. In these patients, computed tomography (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 5 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, twenty-six patients (36.6%) survived in hospital and were successfully discharged home with societal isolation. The most common causes of hospital death were multiple organ failure (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 (Table 1 and Table 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 PaO_2 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) (Table 1 and Table 2). ECMO 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=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 Extracorporeal Life Support Organization (ELSO) registry counts more than 2611 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 (ARDS), 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 (Table 1 and Table 2) showed a mean PaO2/FiO2 of 78 [Standard Deviation (SD) 39] mmHg which was similar to that of patients in the EOLIA[22] (73 [SD 30] mmHg) or LIFEGARD[21] (71 [SD 34] mmHg) 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/cmH2O and the mean PaO2/FiO2 of non-survivors cohort was 71 [SD 27] mmHg 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 and/or norepinephrine[20,21]. The 'lung protective ventilation' is the recommended strategy[13-18,20,21]. If the conventional mechanical ventilation proves 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 EOLIA[22] and 26% in LIFEGARD[21]). However, in our series, only 32% of patients benefited from prone-positioning and survived (Table 1 and Table 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 multiple organ failure (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 macro-thromboses in all organ systems[4-10]. Schmidt et al. [28] observed an extremely high on-ECMO rate of pulmonary embolism (19%), even if compared with the EOLIA trial[22] results. In our analysis, pulmonary embolism (PE) occurred only in 5.6% of our ECMO patients and did not impact on 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 (Table 1 and Table 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 present 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 optimised 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 ventilator induced lung injury (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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Figure Legend

Figure 1. COVID-19 respiratory disease before ECMO installation. 3D-reconstructed computed tomography (CT) scan.

Figure 1