Annals of Surgery

DOI: 10.1097/SLA.0000000000004683

Time to Cannulation after ICU Admission Increases Mortality for Patients Requiring Veno-Venous ECMO for COVID-19 Associated Acute Respiratory Distress Syndrome

Lauren A. Raff MD (lauren_raff@med.unc.edu**)**, University of North Carolina at Chapel Hill, Division of Acute Care Surgery, Department of Surgery, Chapel Hill, NC; **Jared R. Gallaher MD, MPH** (jared_gallaher@med.unc.edu), University of North Carolina at Chapel Hill, Division of Acute Care Surgery, Department of Surgery, Chapel Hill, NC; **Daniel Johnson BS** (Daniel_johnson@med.unc.edu), University of North Carolina at Chapel Hill School of Medicine; **Evan J. Raff MD** (evan_raff@med.unc.edu), University of North Carolina at Chapel Hill, Division of Hospital Medicine, Department of Medicine, Chapel Hill, NC; **Anthony G. Charles MD, MPH** (Anthony_charles@med.unc.edu), University of North Carolina at Chapel Hill, Division of Acute Care Surgery, Department of General Surgery, Chapel Hill, NC; **Trista S. Reid MD, MPH** (Trista_reid@med.unc.edu), University of North Carolina at Chapel Hill, Division of Acute Care Surgery, Department of Surgery, Chapel Hill, NC.

Corresponding author: Lauren A. Raff MD, 4009 Burnett Womack Building, CB# 9228, Chapel Hill, NC, 27599. Phone number: 919.966.4389. Fax number: 919.966.0369. Email: lauren_raff@med.unc.edu

Request for reprints to Lauren A. Raff MD

No sources of support were used for this study.

No funding was used for this study.

Running head: V-V ECMO for ARDS in COVID-19

Mini Abstract:

COVID-19 can cause an ARDS that is rapidly progressive, severe, and refractory to conventional therapies. ECMO can be used as a supportive therapy to improve patient survival, although the ideal candidate and optimal management strategy has not yet been defined. We present our experience with 25 patients placed on veno-venous ECMO for COVID-19 associated ARDS and identify factors that are associated with increased in-hospital mortality.

Structured Abstract

Objective: COVID-19 can cause acute respiratory distress syndrome (ARDS) that is rapidly progressive, severe, and refractory to conventional therapies. Extracorporeal membrane oxygenation (ECMO) can be used as a supportive therapy to improve outcomes but evidence-based guidelines have not been defined.

Summary Background Data: Initial mortality rates associated with ECMO for ARDS in COVID-19 were high, leading some to believe that there was no role for ECMO in this viral illness. With more experience, outcomes have improved. The ideal candidate, timing of cannulation, and best post-cannulation management strategy, however, has not yet been defined.

Methods: We conducted a retrospective review from April 1 to July 31 2020 of the first 25 patients with COVID-19 associated ARDS placed on V-V ECMO at our institution. We analyzed the differences between survivors to hospital discharge and those who died. Modified Poisson regression was used to model adjusted risk factors for mortality.

Results: 44% of patients (11/25) survived to hospital discharge. Survivors were significantly younger (40.5 years vs. 53.1 years; $p < 0.001$) with no differences between cohorts in mean body mass index, diabetes, or PaO2:FiO2 at cannulation. Survivors had shorter duration from symptom onset to cannulation (12.5 days vs. 19.9 days, $p = 0.028$) and shorter duration of intensive care unit (ICU) length of stay (LOS) prior to cannulation (5.6 days vs. 11.7 days, $p = 0.045$). Each day from ICU admission to cannulation increased the adjusted risk of death by 4% and each year increase in age increased the adjusted risk 6%.

Conclusions: ECMO has a role in severe, refractory ARDS associated with COVID-19. Increasing age and time from ICU admission were risk factors for mortality and should be considered in patient selection. Further studies are needed to define best practices for V-V ECMO use in COVID-19.

Introduction

The novel coronavirus, SARS-CoV-2, and the associated Coronavirus Disease 2019 (COVID-19), causes an acute respiratory distress syndrome (ARDS) that can rapidly progress. [1-2]. Reported mortality rates in critically ill COVID-19 patients with associated multi-organ failure are as high as 61.5% [1]. Consequently, when patients develop respiratory failure refractory to conventional mechanical ventilation and other adjunctive therapies (such as open lung and low tidal volume ventilation, inhaled vasodilators, prone positioning, and paralysis), extracorporeal membrane oxygenation (ECMO) is an appropriate supportive therapy to allow lung rest and diminution of ventilator induced lung injury. The indications for ECMO, as guided by the Extracorporeal Life Support Organization (ELSO), are well established. ECMO should be considered for patients with severe, refractory ARDS defined by the following parameters: PaO2/FiO2 < 60 mmHg for > 6 hours, PaO2/FiO2 < 50 mmHg for > 3 hours, or pH < 7.20 and PaCO2 > 80 mmHg for > 6 hours. Notable absolute contraindications include but are not limited to: mechanical ventilation > 10 days, significant underlying medical comorbidities, uncontrolled diabetes with chronic end-organ dysfunction, and severe multi-organ system failure. Relative contraindications include: age ≥ 65 years, body mass index (BMI) ≥ 40, immunocompromised status, and advanced chronic underlying systolic heart failure [3]. Given the paucity of knowledge regarding the natural history and mortality outcomes in patients with COVID -19, the indications for ECMO in the COVID population is no different from other infectious causes of acute hypoxic respiratory failure, although mortality outcomes may differ.

Initial data regarding the survival benefit of ECMO in COVID-19 were somewhat disappointing, particularly given the global experience with ECMO during the H1N1 flu pandemic, which was associated with reported hospital mortality rates as low as 21% [6-7]. Early reports from China demonstrated high mortality rates with ECMO for COVID-19 (up to 83%), though the relatively small number of cases limited the ability to draw definitive conclusions [1, 8-9]. Currently, the ELSO registry reports a 53% survival to hospital discharge in all COVID-19 patients treated with ECMO, with most placed on V-V ECMO (92%). [4]. The survival to hospital discharge rate of 53% is comparable to the 60% survival rate worldwide for all adult patients placed on ECMO for respiratory failure from any etiology, as reported in the ELSO International Summary Registry Report [5].

While there has been some improvement in the overall mortality for patients on ECMO for COVID-19, the ideal candidate for ECMO in this patient population is not well characterized. The best-reported outcomes have been for younger patients (< 50 years of age) with single organ failure (pulmonary). Factors associated with worse outcomes have included older age (>70 years of age), pre-ECMO renal failure, and prolonged duration of mechanical ventilation > seven days before ECMO cannulation [8, 10]. We therefore sought to describe our institutional experience with the first 25 patients placed on veno-venous (V-V) ECMO for COVID-19 associated severe, refractory hypoxic respiratory failure. Additionally, we compared the survivors in our cohort to the non-survivors and identified factors associated with in-hospital mortality.

Methods

University of North Carolina Medical Center (UNCMC) at Chapel Hill is a quaternary academic medical center with 905 inpatients beds, located in Chapel Hill, North Carolina. We have a robust ECMO program that cares for neonatal, pediatric, and adult patients with cardiac and respiratory failure. The hospital averages 60 adult cannulations per year. Starting in April 2020, hospitalizations for COVID-19 increased throughout our state and region. At UNCMC, critically ill patients with COVID-19 are admitted to the Medical Intensive Care Unit (MICU), staffed by pulmonologists/medical intensivists. The ECMO team consults on patients with evidence of refractory hypoxia or hypercarbia despite mechanical ventilation with high ventilatory pressures, use of paralytics, or application of prone positioning. If deemed a suitable candidate for ECMO, one of four ECMO attendings cannulates the patient in the MICU, and the ECMO team subsequently assumes care of the patient.

This was a retrospective review conducted from April 1 to July 31, 2020, of all patients >18 years of age with COVID-19 associated ARDS cannulated for V-V ECMO at UNCMC. All patients were cannulated with two cannulas, in either an internal jugular vein (IJ)/femoral vein or bi-femoral vein configuration. After cannulation, all patients were placed on rest ventilatory settings to decrease ventilator-associated lung injury (pressure control of 20 cm H_2O, rate of 10 breaths per minute, positive end-expiratory pressure of 10 cm H_2O, fraction of inspired oxygen of 40%). Tidal volumes were monitored to track improvement in pulmonary compliance over time. All patients except two received a weight-based heparin bolus at the time of cannulation, and all patients were therapeutically anticoagulated with a heparin drip during the entirety of ECMO therapy. All patients were cannulated at a single institution and, after cannulation, were managed by one of four surgical critical care ECMO providers. All COVID-19 patients admitted to the ICU at our institution are managed in the Medical ICU by medical intensivists. The ECMO team is consulted once the medical intensivist determines the patient is refractory to maximum ventilatory support. All patients cannulated were intubated and met ECMO criteria, with a P:F ratio < 100 at the time of cannulation.

We collected data via retrospective chart review and data variables included baseline patient demographics, medical comorbidities to calculate the Charlston Comorbidity Index (CCI), body mass index (BMI), date of first positive SARS-CoV-2 reverse transcription-polymerase chain reaction (RT-PCR) test, duration of COVID-19 symptoms prior to ECMO cannulation (days), duration of non-invasive positive pressure ventilation (NIPPV) prior to ECMO cannulation (days), duration of mechanical ventilation prior to ECMO cannulation (days), hospital and intensive care unit (ICU) lengths of stay (LOS) prior to ECMO cannulation (days), presence of barotrauma at the time of cannulation (defined as pneumothorax, pneumo-mediastinum, or subcutaneous emphysema on chest x-ray imaging), arterial blood gas values, PaO_2/ FIO_2 (P/F) ratio and ventilator settings at the time of ECMO cannulation, use of prone positioning and/or paralytics prior to ECMO cannulation, transfusion of blood products during ECMO course, use of COVID-19 specific therapies, and hospital disposition. The onset of symptoms was defined as the day symptoms began reported by the patient. The primary outcome was survival to hospital discharge. Secondary outcomes

included thrombotic and hemorrhagic complications, air emergencies in the circuit, presence of co-existing bacterial pneumonia requiring antibiotic use (separated by presumed and empirically treated versus culture-diagnosed), organ failure (liver, kidney, cardiac), and bacteremia. We defined thrombotic complications as deep venous thrombosis (DVT) or pulmonary embolism (PE) diagnosed by imaging or circuit thrombosis. We defined minor hemorrhagic complications as bleeding episodes managed at the bedside from mucosal surfaces, around the cannula or other lines, gastrointestinal bleeding that did not require intervention, or Foley catheter-associated bleeding. We defined major hemorrhagic complications as bleeding episodes requiring interventional radiology, endoscopy, operative exploration, or initiation of massive transfusion protocol.

We performed a bivariate analysis to compare patients who survived to those who died using Chi-squared tests for the categorical variables and 2-sample t-tests for continuous variables. For any non-normally distributed continuous variables, we used a Kruskal-Wallis test. Means are reported with standard deviations (SD) and medians with interquartile ranges (IQR).

We used modified Poisson regression modeling to identify risk factors for death after V-V ECMO cannulation. Modified Poisson regression offers the advantage of calculating risk ratios and has been validated for use with binary outcomes. [11, 12] An estimated adjusted risk ratio (RR) and 95% confidence interval (CI) are reported from the final model. We initially fit the model with variables that were identified as statistically significant in our bivariate analysis as well as any variables that were clinically significantly. Variables that were not significantly associated with mortality in the model were removed in a stepwise fashion.

We performed all statistical analysis with Stata/SE 16.1 (Stata- Corp LP, College Station, TX). The University of North Carolina Institutional Review Board approved this study and waived the need for informed consent.

Results

Twenty-five total patients were included in the analysis (Supplemental table 1, http://links.lww.com/SLA/C813). The mean age was 47 years (SD 10) with a male preponderance (n = 18; 72.0%). Most patients were obese with a mean BMI of 35.9 (SD 7.9). Sixteen patients (64.0%) were Latino, five (20.0%) were African American, and four were Caucasian (16.0%). Almost half of the study population had pre-existing diabetes (n = 12; 48%), but the median CCI was 1 (IQR 0-2). The mean time to cannulation from the onset of symptoms was 16.6 days (SD 8.5).

In total, 11 of 25 patients (44%) survived to hospital discharge (Supplemental table 1, http://links.lww.com/SLA/C813). Those who survived were significantly younger (40.5 years vs. 53.1 years; $p < 0.001$) and had a lower CCI (median 1 vs 2; $p = 0.039$) than those who did not survive. BMI ($p = 0.2$), sex ($p = 0.9$), race ($p = 0.1$), and incidence of diabetes ($p = 0.8$), were similar between the two cohorts. For patients less than 50 years old, survival was 71.4% (n = 10/14), but for patients 50 and older, survival was only 9.1% (n = 1/11). Among those patients who died, most (13/14) died from hypoxic respiratory failure after decannulation

following a prolonged course on ECMO with no improvement in their severe hypoxia or pulmonary compliance. One patient died after suffering brain death while on ECMO.

At the time of cannulation, patients who survived had a shorter interval between onset of symptoms and cannulation at 12.5 days (SD 8.4) compared to 19.9 days (SD 7.3; p = 0.028). Among the survivors, 72.1% (n = 8/11) used non-invasive ventilation prior to cannulation compared to 78.6% (n = 11/14) of those who died (p = 0.7), with similar mean durations of use (2.6 vs. 3.9 days, respectively; p = 0.5). A majority of patients were placed in the prone position prior to cannulation: 63.6% (n = 7/11) of patients who survived and 92.9% (n = 13/14) of those who died (p = 0.07). Patients who were not proned either decompensated too quickly for a trial or proning, did not tolerate it due to body habitus, or were hospitalized at another instutiton where proning was not available prior to cannulation. The number of days on mechanical ventilation before cannulation between the survivors (3.5 days, SD 5.5) and non-survivors (6.1 days, SD 4.2) was not significantly different (p = 0.15). When the number of days of non-invasive ventilation was added to the number of mechanical ventilation days, there was still no significant difference between the survivors and those who died (6.1 days, SD 8.5 vs. 10.0 days, SD 5.5, respectively; p = 0.2). On the other hand, time from ICU admission to cannulation was significantly shorter for survivors with a mean of 5.6 days (SD 8.7) compared to 11.7 days (SD 5.6; p = 0.045) for those who died. Organ failure (p = 0.3) and evidence of barotrauma (p = 0.8) at the time of cannulation were present in approximately one-third of both survivors and non-survivors. The P:F ratio at the time of cannulation was comparable between the survivors (66.7, SD 21.5) and those who died (73.9, SD 21.8; p = 0.6). Other laboratory values measured at the time of cannulation were similar between the two groups, including serum pH (p = 0.6), CRP (p = 0.2), fibrinogen (p = 0.3), and d-dimer (p = 0.15).

Most patients had a return cannula placed in their right internal jugular and a drainage cannula in their left or right femoral vein. (Supplemental table 2, http://links.lww.com/SLA/C814) The most common return cannula size was 21Fr and the most common drainage cannula size was 23Fr with no differences between those who survived and those died in cannula configuration. There were no differences in required circuit changes for oxygenator failure or thrombosis. (Supplemental table 2, http://links.lww.com/SLA/C814). Of those who survived, 3 (27.3%) developed organ failure while on the ECMO circuit compared to 8 non-survivors (57.1%; p = 0.1). In the survival group, 18.2% (n = 2/11) required continuous renal replacement therapy for renal failure compared to 35.7% (n = 5/14; p = 0.3) of those who died. There were zero air emergencies for survivors in contrast to four among the patients who died (28.6%; p = 0.053), but air emergencies did not contribute to death in these four patients. The diagnosis of DVT during hospitalization was common in both groups at 36.4% (n = 4/11) in survivors and 21.4% (n = 3/14; p = 0.4) in non-survivors. Conversely, there were significantly fewer minor bleeding complications among survivors at 36.4% (n = 4/11) versus 92.9% of non-survivors (n = 13/14; p = 0.003), with no major bleeding complications in either group. The mean number of days spent on the ECMO circuit was markedly shorter for survivors at 7.8 days (SD 2.5) compared to 15.0 days (SD 4.8; p <0.001).

The use of COVD-19 therapies was common among all patients. Overall, 92% of patients (n=23/25) received at least one of the following: remdesivir, dexamethasone, tocilizumab, or experimental convalescent plasma. Use of remdesivir was most common at 72.7% (n=8/11) among survivors and 71.4% (n=10/14) in non-survivors (p=0.9). (Supplemental table 2, http://links.lww.com/SLA/C814). There were also no differences in the use of dexamethasone (p=0.9), tocilizumab (p=0.4), or experimental convalescent plasma (p=0.1) between survivors and non-survivors. All patients in both groups were treated with antibiotics during their ECMO course for either culture-proven or suspected superimposed bacterial pneumonia.

Our modeling of risk factors of death while on V-V EMCO revealed two factors that were significantly associated with mortality. (Table 1). Each additional day spent in the ICU before ECMO cannulation conferred an adjusted risk ratio of death of 1.04 (95% CI 1.01-1.09; p = 0.027). Each additional year of age had an increased adjusted risk ratio of death of 1.06 (95% CI 1.03-1.09; p < 0.001). Notable factors that were not significant in our modeling included BMI, sex, race, diabetes, the presence of organ failure at the time of cannulation, and CCI. In addition, we also tested ventilation time prior to cannulation, which was not a significant predictor of mortality, likely due to prolonged use of non-invasive ventilation.

Discussion

To date, minimal data exist regarding ECMO use in critically ill COVID-19 patients. The initial experience published by providers in China reported high mortality rates in small groups of patients, leading some to believe that ECMO may not be appropriate for patients with severe ARDS in COVID-19 [1, 8-9]. However, over time, as provider experience has grown, overall reported outcomes have improved, and now ECMO is accepted as a viable modality for patients with COVID-19 associated severe ARDS refractory to conventional management strategies that meet ECMO criteria [3, 8]. The current global survival to hospital discharge rate of patients on ECMO for COVID-19 is 53% [4].

In our study of COVID-19 patients with ARDS managed with ECMO, the overall survival to hospital discharge rate is 44% but varied significantly based on age. For patients less than 50 years old, survival to hospital discharge is high at 71%, compared to 11% in those who are 50 years or older. Additionally, every year of age was associated with a 6% increase in the risk of death in the hospital. Our data also suggest that earlier cannulation after admission to the ICU may lead to lower mortality. Unfortunately, despite the existence of several clinical management guidelines for critically ill COVID-19 patients, the optimal candidate, ideal timing for cannulation, and best post-cannulation management strategies have not yet been definitively established [1, 3-4, 8, 13].

One potential reason for the poorer survival in our dataset compared to the reported ELSO rate of 53% may be our practice of not imposing strict absolute contraindications when selecting patients appropriate for ECMO. Patients were not immediately excluded based solely on older age, larger BMI, pre-existing organ failure, or longer duration of time on mechanical ventilation, all factors that have now been associated with worse outcomes [8, 10]. Jacobs et al. has reported a similar overall mortality rate in a comparable cohort of patients, suggesting that our mortality rate may be comparable to other single-institution

experiences [14]. Clearly, there is a reproducible and robust association between increasing age and medical comorbidities and worse outcomes in COVID-19, which persists despite aggressive critical care and even ECMO support.

Other factors identified in this study that were significantly associated with increased inpatient mortality included the duration of symptoms and duration of ICU LOS prior to ECMO cannulation. Patients who had a longer duration of symptoms prior to cannulation and longer duration of ICU LOS prior to cannulation were more likely to die in the hospital. We argue that ICU length of stay is a valuable surrogate for the duration of critical illness in COVID-19, especially considering that many patients with profound hypoxia are treated with NIPPV or other modes of high oxygen delivery for extended durations, often while self-proning, prior to intubation. Consequently, it is possible that the non-survivors simply had a longer duration of critical illness with a slower, more prolonged, decline than the survivors, and that this type of presentation is associated with worse outcomes in COVID-19.

While our study does not provide definitive evidence, we hypothesize that patients who decompensate earlier in their clinical course appear to have better clinical outcomes than those who acutely worsen later. This may signal that patients with later decompensation have already developed substantial fibrotic lung changes that are unlikely to improve on ECMO. This is further supported by our finding that survivors and non-survivors on ECMO were comparably sick at the time of cannulation and had equal access to commonly used treatment adjuncts. However, it remains unclear whether or not earlier initiation of ECMO in the non-survivors in our study would have led to decreased mortality [15]. In the largest case series to date in the United States, Mustafa et al demonstrated an overall high survival to hospital discharge rate (73%) in a group of 40 COVID-19 patients with ARDS on V-V ECMO with a focus on early cannulation (mean time from intubation to cannulation of 4 days). Their cannulation strategy was a bit different than many prior studies, however, and it is unclear whether early cannulation, cannulation strategy, or both are responsible for the high survival rate reported in this study [16]. Future studies should investigate the relationship between the duration of symptoms with clinical outcomes, including progression to ARDS or pulmonary fibrosis in COVID-19.

Critically ill patients with COVID-19 are known to be hypercoagulable, which makes balancing the risk of hemorrhage against the risk of thrombosis even more challenging for patients on ECMO [17-18]. ECMO alone is associated with an increased risk of thrombosis, and this risk seems to be even higher in COVID-19 patients. One study specifically evaluating the use of ECMO in COVID-19 reported that for 12 patients on V-V ECMO, four patients (33%) had thrombotic complications during their ECMO runs, two of which resulted in death (17%). Five patients (42%) also developed deep venous thrombosis (DVT) at a cannula site despite therapeutic anticoagulation. All patients had evidence of inflammatory and hypercoagulable state based on labs (elevated CRP, fibrinogen, D-dimer) [19]. Similarly, all patients in our cohort had evidence of a prothrombotic state based on labs, though there was no significant difference in the degree of elevation between the survivors and non-survivors. Approximately half of the patients in our study required ECMO circuit changes due to impending or acute oxygenator thrombosis or failure, with several patients requiring

multiple changes despite the escalation of anticoagulation goals. Specific guidelines for management of therapeutic anticoagulation for ECMO in COVID-19 do not exist, although ELSO recommends following existing anticoagulation guidelines and considering a higher target for anticoagulation goals [20].

Hemorrhagic complications were also frequent, although all were minor and none required operative intervention or embolization. Even with the well-documented prothrombotic state, COVID-19 patients on ECMO still have a significant risk of hemorrhage, potentially due to higher anticoagulation goals. The higher prevalence of bleeding complications among patients who died may suggest more severe derangement of the coagulation system. Future studies should evaluate COVID-19 associated coagulopathy and better define the specific anticoagulation parameters for patients on ECMO.

Our study was underpowered to identify some risk factors associated with mortality due to our relatively small sample size. However, our study does represent one of the more extensive single-institution case series currently published. Additionally, much of these patients' critical care was not standardized due to the involvement of outside hospitals and other providers before transfer to our center for management. Generalizability may be limited secondary to this being a single institution study. Although these factors limit our study's conclusions, we hope to provide a valuable starting place for continued future investigation.

Conclusion

ECMO has a role in severe, refractory ARDS associated with COVID-19. The ideal candidate, timing of cannulation, and management strategy after cannulation, particularly anticoagulation, has yet to be determined. In this study, we demonstrated that increasing age and time from ICU admission to cannulation were risk factors for mortality after V-V ECMO cannulation. Further studies are needed to define best practices for V-V ECMO use in COVID-19 to improve patient outcomes.

Funding: None.

Author contributions: LR, JG, ER, TR, AC collected data, analyzed data, wrote and edited the manuscript. DJ collected data.

Declaration of Competing Interest: None.

Acknowledgements: Thanks to all the ICU nurses and ECMO specialists who were devoted to caring for our patients.

References:

1. Yang X, Yu Y, Xu J, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-R pneumonia in Wuhan, China: a single centered, retrospective, observational study. Lancet Respir Med. 2020 May; 8(5): 475-481.
2. Jian C, Yang F, Zou H, et al. Chinese expert consensus on supportive treatment of extracorporeal membrane oxygenation novel coronavirus pneumonia. Chin K Emerg Med. 2020; 29(00): E009.
3. Shekar K, Badulak J, Peek G, et al. Extracorporeal Life Support Organization Coronavirus Disease 2019 Interim Guidelines: A Consensus Document from an International Group of Interdisciplinary Extracorporeal Membrane Oxygenation Providers. www.elso.org.
4. ELSO COVID-19 Patient Registry. www.elso.org.
5. ECLS Registry Report International Summary. www.elso.org
6. Australia and New Zealand Extracorporeal Membrane Oxygenation (ANZ ECMO) Influenza Investigators. Extracorporeal Membrane Oxygenation for 2009 Influenza (H1N1) Acute Respiratory Distress Syndrome. JAMA. 2009; 302(17): 1888-1895.
7. Zeng Y, Cai Z, Xianyu Y, et al. Prognosis when using extracorporeal membrane oxygenation (ECMO) for critically ill COVID-19 patients in China: a retrospective case series. Crit Care. 2020 Apr; 24: 148.
8. Rajagopal K, Keller S, Akkanti B, et al. Advanced Pulmonary and Cardiac of COVID-19 Patients: Emerging Recommendations from ASAIO – A "Living Working Document." ASAIO J. 2020 Jun; 66 (6): 588-598.
9. Li X, Guo Z, Li B, et al. Extracorporeal Membrane Oxygenation for Coronavirus Disease 2019 in Shanghai, China. ASAIO J. 2020 May; 66(5): 475-481.
10. Osho A, Philicia M, Hibbert K, et al. Veno-venous Extracorporeal Membrane Oxygenation for Respiratory Failure in COVID-19 Patients: Early Experience From a Major Academic Medical Center in North America. Annals of Surgery. 2020 Aug; 272(2): 75-78.
11. Zou G. A modified poisson regression approach to prospective studies with binary data. American journal of epidemiology. 2004 Apr 1;159(7):702-6.
12. Chen W, Qian L, Shi J, Franklin M. Comparing performance between log-binomial and robust Poisson regression models for estimating risk ratios under model misspecification. BMC medical research methodology. 2018 Dec 1;18(1):63.
13. World Health Organization: Clinical Management of Severe Acute Respiratory Infection (SARI) When COVID-19 Disease is Suspected. Interim Guidance. March 3, 2020. Available at: https://www.who.int/docs/default-source/coronaviruse/clinical-managemnet-of-novel-cov.pdf.
14. Jacobs J, Stammers A, St Louis J, et al. Extracorporeal Membrane Oxygenation in the Treatment of Severe Pulmonary and Cardiac Compromise in Coronavirus Disease 2019: Experience with 32 Patients. ASAIO J. 2020 May 11: 10.1097.
15. Le Breton C, Besset S, Freita-Ramos S, et al. Extracorporeal Membrane Oxygenation for Refractory COVID-19 Acute Respiratory Distress Syndrome. J Crit Care. 2020 Dec; 60: 10-12.

16. 14. Mustafa AK, Alexander PJ, Joshi DJ, et al. Extracorporeal Membrane Oxygenation for Patients with COVID-19 in Severe Respiratory Failure. JAMA Surg. 2020 Aug 11: e203950. Doi: 10.1001/jamasurg.2020.3950. Online ahead of print. PMID: 32780089.
17. Sinhania N, Bansal S, Nimmatoori D, et al. Current Overview on Hypercoagulability in COVID-19. Am J Cardiovasc Drugs. 2020 August 4: 1-11.
18. Helms J, Tacquard C, Severac F, et al. High Risk of Thrombosis in Patients in Severe SARS-CoV-2 Infection: A Multicenter Prospective Cohort Study. Intensive Care Med. 2020 May 4.
19. Beyls C, Huette P, Abou-Arab O, et al. Extracorporeal Membrane Oxygenation for COVID-19-Associated Severe Acute Respiratory Distress Syndrome and Risk of Thrombosis. Br J Anaesth. 2020 Aug; 125(2): e260-262.
20. Ogino, M. ELSO; 2020. ELSO COVID-19 Interim Guidelines. www.elso.org

Table 1. Risk factors for death after VV ECMO cannulation for ARDS secondary to COVID-19 infection.

	Adjusted Risk Ratio	95% CI	*p* Value
Risk factors for Death			
Each additional day from ICU admission to ECMO cannulation	1.04	1.01-1.09	0.027
Each additional year of age	1.06	1.03-1.09	<0.001