

# Outcomes and risk factors for the survival of COVID-19 related ARDS patients treated with extracorporeal membrane oxygenation

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## Research

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# Abstract

**Background:** In current pandemic of COVID-19, approximately 15% to 30% of critically ill COVID-19 patients developed acute respiratory distress syndrome (ARDS) with a high mortality. Extracorporeal membrane of oxygenation (ECMO) provides direct support for both lung and heart in ARDS. However, the role of ECMO in COVID-19 related ARDS was still controversial. The aim of this study was to provide insights into the mortality, intensive care unit (ICU) management, risk factors for mortality, 180-day short term prognosis of the COVID-19 related severe ARDS patients receiving ECMO treatment.

**Methods:** From Feb 2<sup>nd</sup>, 2020 to April 27<sup>th</sup>, 2020, we included adult COVID-19 related ARDS patients admitted to intensive care unit in Tongji Hospital. Totally, 53 patients were retrospectively analyzed. They were divided into ECMO (mechanical ventilation with ECMO, n=16) and non-ECMO group (mechanical ventilation, n=37). The primary outcome was all-cause 60-day mortality. The secondary outcomes were complications on ECMO, successful weaning from ECMO, and all-cause 180-day mortality.

**Results:** The all-cause 60-day mortality was 37.5% (6/16) in ECMO group and 86.5% (32/37) in non-ECMO group (HR, 0.196; 95% CI, 0.053-0.721; p=0.014). 10 (62.5%) patients were successfully weaned from ECMO. The all-cause 180-day mortality was 56.3% (9/16) in ECMO group and 33 (89.2%, 33/37) in non-ECMO group (HR, 0.298; 95% CI, 0.130-0.680; p=0.004). All the patients in ECMO group suffered from at least one device-related complication with coagulopathy (81.3%) being most frequently seen. Up to 180-day follow up after disease onset, the ECMO-treated survivors maintained good quality of life without severe complications or disabilities. Hypercapnia, thrombopenia, myocardial injury and elevation of IL-8 and IL-10 during ECMO treatment were strongly associated with death.

**Conclusion:** This study showed the COVID-19 patients significantly benefited from ECMO treatment during severe ARDS, which supported the application of ECMO as an indicated strategy in the management of COVID-19 related ARDS.

## Introduction

COVID-19, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has been demonstrated to manifest as fever, cough, and dyspnea, with radiological evidence of viral pneumonia[1]. Approximately 15–30% of these patients developed acute respiratory distress syndrome (ARDS)[2]. ARDS is an acute inflammatory lung injury that results in increased vascular permeability and pulmonary gas exchange obstacle[3]. The pathological findings of COVID-19 showed bilateral diffuse alveolar damage with cellular fibromyxoid exudates, desquamation of pneumocytes and hyaline membrane formation, indicating ARDS, which greatly resemble those seen in severe acute respiratory syndrome (SARS) and Middle Eastern respiratory syndrome (MERS) coronavirus infections[4]. Management of ARDS remains largely supportive, with mechanical ventilation forming the cornerstone of therapy[3]. Despite the application of lung protective ventilation strategy, recruitment maneuvers and the prone positioning, associated mortality of ARDS is still high up to exceeding 60%[5]. In these situations, extracorporeal

membrane of oxygenation (ECMO), as a form of modified cardiopulmonary bypass, brings up systemic oxygen delivery and mitigates ventilator induced lung injury. It provides direct support for both lung and heart during ARDS[6]. ECMO has been applied in the salvage of ARDS during H1N1 pandemic in 2009, and the patients who received ECMO therapy appeared to benefit[7, 8]. However, the Rescue Lung Injury in Severe ARDS (EOLIA) trial, a randomized clinical trial in ECMO-treated patients with severe ARDS, didn't show significant decrease in mortality. But Bayesian post hoc analysis of this trial and a subsequent meta-analysis together suggested ECMO was beneficial for patients with severe ARDS[6, 9].

In current pandemic of COVID-19, published data showed a high mortality of mechanically ventilated patients with COVID-19 related ARDS, varying from 46–88% [10–14]. The role of ECMO in the management of these ARDS patients is still unclear at this point. Current knowledge on ECMO utilization in COVID-19 related ARDS patients remains limited to registry data from extracorporeal life support organization (ELSO) and small cohorts, there is no consensus on the indication. Present reports from the ELSO, America, Italy and China on the mortality of ECMO-treated patients varied, ranging from 42–83%, and a lot of patients were still on ECMO or mechanical ventilation at the time of data publication[10, 15–18]. There is no clear view on the prognosis of ECMO application. In the present study, we retrospectively described the baseline characteristics, intensive care unit (ICU) management, and variables associated with mortality in COVID-19 induced ARDS treated with or without ECMO. The risk factors that impact on the prognosis of ECMO were analyzed. With 180-day follow up, we provided an insight into the short-term prognosis of the COVID-19 related severe ARDS patients on ECMO treatment.

## Methods

### Patient Selection

From Feb 2nd, 2020 to April 27th, 2020, a total of 3203 patients with COVID-19 were admitted to Tongji Hospital in Wuhan, China. Positive rapid SARS-CoV-2 diagnostic test results were confirmed using quantitative real-time polymerase chain reaction (PCR) assays on nasal swabs. The protocol was approved by the local research ethics committee.

ECMO therapy was indicated if patients presented parameters for severe ARDS:  $\text{PaO}_2/\text{FiO}_2 < 50$  mmHg for  $> 3$  hours, or  $< 80$  mmHg for  $> 6$  hours, or an arterial blood pH of  $< 7.25$  with a partial pressure of arterial carbon dioxide ( $\text{PaCO}_2$ )  $\geq 60$  mmHg for  $> 6$  hours, with the respiratory rate increased to 35 breaths per minute and mechanical-ventilation settings adjusted to keep a plateau pressure (Pplat) of  $\leq 32$  cmH<sub>2</sub>O[19].

We used the following criteria to include or exclude cases for the application of ECMO. Inclusion Criteria: 1. Diagnosed COVID-19 related severe ARDS. 2. Patient hospitalized in ICU with informed consent granted. Exclusion Criteria: 1. Patients younger than 18, or older than 70 years old. 2. Existed irreversible cerebral vascular disease or tumor. 3. Poor venous vascular condition and impracticable for central venous catheter placement. 4. Patients with inadequate or missing data for statistical analysis.

Retrospectively collected data included demographic data, major co-morbidities, respiratory and hemodynamic parameters at admission, before ventilator/ECMO initiation and throughout ARDS evolution. Technical characteristics of ECMO therapy, complications and outcomes from the electronic medical records system were summarized. The severity of illness was assessed using the Murray Lung Injury Score, the Acute Physiology and Chronic Health Evaluation (APACHE) II and the Sequential Organ Failure Assessment (SOFA) score at each time point. Patients were followed up for 180-day after disease onset.

### **ECMO-based Management Protocol**

Before consideration for ECMO, patients were sedated and ventilator optimized (defined as the inspired oxygen fraction ( $\text{FiO}_2$ )  $\geq 0.80$ , a tidal volume of 6 ml per kilogram of predicted body weight, and PEEP  $\geq 10\text{cmH}_2\text{O}$ ). [5] Neuromuscular blocking agents, recruitment maneuvers, and prolonged periods of prone positioning were used according to the condition.

We have chosen to place 18–20 F cannulas in the right internal jugular vein and 22 F cannula in the femoral vein for veno-venous cannulation. We used centrifugal pumps (Maquet-Getinge, Germany) with flow of 3–5 L/min and 18–20 F cannulae (Edwards Lifesciences, Irvine, CA, USA) in all patients. Circuits were heparin-coated and composed of Quadrox D with Bioline Coating oxygenators (Maquet-Getinge, BE-PLS 2050, Germany). Ventilator settings after ECMO initiation: Pplat 20–30  $\text{cmH}_2\text{O}$ , PEEP 10–12  $\text{cmH}_2\text{O}$ , respiratory rate 10–20 per min and  $\text{FiO}_2$  adjusted to obtain arterial  $\text{O}_2$  saturation of 90–95% while  $\text{FiO}_2$  was set at 100% on the oxygenator. Anticoagulation was achieved with unfractionated heparin and was adjusted to a target activated partial-thromboplastin time (APTT) of 40 to 55 seconds. Threshold for transfusion were  $50 \times 10^9/\text{L}$  for platelets or 9 g/dL for hemoglobin. ECMO was continued until lung recovery or until irreversible multiorgan failure. Patients were weaned from veno-venous ECMO when the following criteria were met: during trialing off ECMO (sweep gas at 0 L/min), increase ventilator support as needed to settings that are acceptable to facilitate weaning off ECMO ( $\text{VT} \leq 6\text{--}8\text{ mL/kg}$ ,  $\text{Pplat} \leq 30\text{ cmH}_2\text{O}$ ,  $\text{PEEP} \leq 16\text{ cmH}_2\text{O}$ ,  $\text{FiO}_2 \leq 0.5$ ,  $\text{pH} > 7.3$ ,  $\text{SaO}_2 > 88\%$ ). If gas exchange is adequate for a 2–4 h period, the patient can be decannulated[20].

### **Study Outcomes**

The primary outcome was all-cause 60-day mortality. The secondary outcomes were ECMO related complications, successful weaning from ECMO, and all-cause 180-day mortality. In-hospital complications were recorded for ECMO-treated patients including occurrence of pneumothorax, stroke, infection at the site of ECMO cannula insertion, cannula thrombosis, severe hemorrhagic complications, and blood transfusions. Follow-up was performed up to 180 days after disease onset by telephone contact with the patients and their family.

### **Statistical Analysis**

Quantitative variables were presented as median (interquartile range, IQR) and compared using Wilcoxon rank-sum test. Categorical variables are presented as number (percentage) with 95% confidence interval (CI) and were compared using chi-square test. The association of ECMO application with all-cause mortality was evaluated using Kaplan-Meier analysis and log-rank test. Hazard ratios (HRs) and 95% CIs were estimated using Cox proportional hazards models. The HRs were calculated and adjusted for age, gender, medical histories (hypertension, coronary heart disease, and diabetes), treatments (intravenous immunoglobulin, continuous renal replacement treatment, blood transfusion, external nutrition, recruitment maneuvers, prone positioning). Statistical analysis was performed using the SPSS statistical software 21.0 or R software version 3.6.0. (R Core Team (2019)). A two-sided  $p < 0.05$  was considered statistically significant.

## Results

### Patient characteristics

From Feb 2nd, 2020 to April 27th, 2020, we included 3203 COVID-19 patients admitted to ICU. After exclusion, 53 patients who were diagnosed as COVID-19 related severe ARDS and required mechanical ventilation were retrospectively analyzed (Fig. 1). Among these patients, 16 patients were implanted ECMO and received mechanical ventilation (ECMO group), 37 patients were on conventional mechanical ventilation (Non-ECMO group). The average age of all 53 patients was 58 years old and 77.4% were males. All the patients had at least one comorbidity, mostly hypertension (43.4%), followed by diabetes (28.3%). The medians of Acute lung injury score, SOFA and Acute Physiology and APACHEII were 3.80 (3.30, 3.80), 11 (10.25, 12.75) and 17 (15.00, 19.75) respectively. The median length from symptom onset to endotracheal intubation was 19.00 (14.00, 25.00) days. The median length of mechanical ventilation was 11.00 (5.00, 19.00) days. The characteristics of patients at baseline, including age, gender, existing comorbidities, critical illness scores and multiple organ function indicated by laboratory tests were comparable between the two groups (**Table 1 and Table 1s**).

### ICU Management And ECMO Settings

Before initiation of ECMO, all patients had similarly high ventilation parameters including high respiratory supportive pressure control (PC), PEEP, Pplat and  $\text{FiO}_2$ . They remained similar  $\text{PaO}_2/\text{FiO}_2$  ratio and  $\text{PaCO}_2$ , which indicated similar severity of hypoxemia and hypercapnia in both groups. Rescue therapies were more needed in ECMO group, with 100% recruitment maneuvers and prone positioning, while 32.4% and 27% in non-ECMO group ( $p < 0.001$ ). 100% of the patients received neuromuscular blocking agents in ECMO group, while 54.1% in non-ECMO group. 34 patients (91.9%) in non-ECMO and 14 patients (87.5%) in ECMO groups received steroids before ECMO initiation. 100% (16/16) of the patients in ECMO group received intravenous immunoglobulin (IVIG), while 56.8% (21/37) in non-ECMO group ( $p < 0.001$ ). As to continuous renal replacement treatment (CRRT), 81.2% (13/16) of the patients in ECMO group received CRRT treatment, but only 37.8% (14/37) in non-ECMO group ( $p = 0.004$ , **Table 2**).

After ECMO started, physicians reduced PC pressure support and PEEP level. Arterial blood gas improved in  $\text{PaO}_2/\text{FiO}_2$  and decreased in  $\text{PaCO}_2$  from the first 24 hour after ECMO initiation as well (Supplementary excel). ECMO was initiated on a median of 3.50 (1.00, 5.50) days after mechanical ventilation, and the patients in ECMO group has longer mechanical ventilation days than non-ECMO group (19.0 vs. 9.0 days,  $p = 0.002$ , **Table 1**). Among all ECMO-treated patients, 13 patients received veno-venous ECMO and 3 received veno-arterial fashion. Vascular cannulas were inserted through jugular/femoral veins or arteries.

The median duration of ECMO support lasted for 16.00 (7.00, 20.00) days (Table 4). The median ECMO flow was 3.32 (2.88, 3.55) L /min at ECMO initial, 3.25 (3.05, 3.55) L /min in the first 24 hours and 3.53 (3.23, 3.75) L /min in the 72 hours. The activated clotting time (ACT) of whole blood was maintained at 169–202 by heparin infusion during ECMO therapy. ECMO associated protective ventilation rapidly decreased  $\text{PaCO}_2$  in all patients, especially in the patients in non-survivor group (from 70.6 to 33.4 mmHg), despite similar ventilator parameters and ECMO settings with pump flow at 3.38 (2.92, 3.50) L/min in survivors versus 3.30 (2.82, 3.71) in non-survivors ( $p = 0.817$ ) and  $\text{FiO}_2$  at 65% (47%, 100%) versus 90% (75%, 100%) ( $p = 0.358$ ) in the first 24 hours (**Table 2s and Supplementary excel sheet**) .

## Complications

The characteristics, complications and outcomes according to survival status are detailed in **Table 3** and **Table 4**. There was no patient died from complications related to ECMO cannulation, but bleeding was the most frequently happened complication (81.3%), followed by thrombocytopenia (75%). Patients in non-survivor group had significantly higher rates of heart rhythm disturbances (75% vs 12.5%,  $p = 0.012$ ) and thrombocytopenia (100.0% vs 50.0%,  $p = 0.021$ ) (**Table 4**). Incidences of complications such as pneumothorax, hemorrhagic stroke, embolism in the pipe, bleeding, stroke and hypothermia were similar in two groups.

## ECMO treatment significantly improved outcomes of COVID-19 related ARDS patients

At 30 days after the disease onset, 6.6% (2/16) of the patients in ECMO group and 56.8% (21/37) in non-ECMO group died (HR, 0.114; 95% CI, 0.011–1.205;  $P = 0.071$ . Figure 1s). At 60 days, 37.5% (6/16) of the patients in ECMO group and 86.5% (32/37) in non-ECMO group died (HR, 0.196; 95% CI, 0.053–0.721;  $p = 0.014$ ) (Fig. 2 **and Table 1**). 66.7% of deaths in ECMO group occurred within 60 days, the all-cause 60-day mortality was significantly lower in ECMO-treated patients. On day 90, 7 patients (43.8%, 7/16) in ECMO group and 33 (89.2%, 33/37) in non-ECMO group died (HR, 0.27; 95% CI, 0.081–0.94;  $p = 0.034$ . Figure 1s). 10 (62.5%) patients were successfully weaned from ECMO, but one of them died of pulmonary secondary bacterial infection on day 96 and another one died of cerebral hemorrhage on day 134 after the disease onset. On day 180, 9 patients (56.3%, 9/16) in ECMO group and 33 (89.2%, 33/37) in non-ECMO group died (HR, 0.298; 95% CI, 0.130–0.680;  $p = 0.004$ . Figure 2). The all-cause 180-day mortality remained lower in the ECMO group. Adjustment for important prognostic factors, including age, gender, hypertension, coronary heart disease, diabetes and treatments, did not change the significance. Up to 180-day follow up after the disease onset, these ECMO-treated survivors lived without disabilities.

## Risk factors for the COVID-19 related ARDS patients treated with ECMO

To uncover the predictive risk factors for the outcomes of the COVID-19 related ARDS patients treated with ECMO, 16 ECMO-treated patients were divided into survivor (n = 8) and non-survivor (n = 8) groups. We compared the characteristics, treatments and laboratory tests with time. After intubation, the mechanical ventilation supportive conditions and laboratory results were similar between survivors and non-survivors. Before the initiation of ECMO, we identified three statistically significant risk factors associated with death. Non-survivors had more severe hypercapnia (PaCO<sub>2</sub> 70.6 vs. 57.0 mmHg, p = 0.049), lower platelet (83.0 vs. 172.5 × 10<sup>9</sup>/L p = 0.036) and higher myoglobin (294.2 vs. 96.1 ng/mL p = 0.02) than survivors. Besides, compared with survivors, the serum levels of hs-cTnI, CK-MB, NT-proBNP, IL-6, IL-8, and IL-10 of non-survivors notably increased after the initiation of ECMO. By the point they were weaned from ECMO, the counts of lymphocyte and platelet dramatically decreased, while the levels of hs-cTnI, CK-MB, NT-proBNP, IL-8, and IL-10 increased in non-survivor group. These differences echoed the severity of patients evaluated by critical evaluation scores in both groups (Fig. 3, **Table 4 and supplementary excel sheet**).

## Discussion

We reported the experiences of treating COVID-19 related severe ARDS patients treated with ECMO in our tertiary care center. Our findings showed a significant improvement in survival of severe COVID-19 related ARDS patients receiving ECMO treatment compared with conventional ventilation. Up to 180-day follow up after disease onset, these survived patients maintained good quality of life without severe complications or disabilities. Hypercapnia, thrombopenia, myocardial injury and elevation of IL-8 and IL-10 during the treatment of ECMO were strongly associated with survival prediction.

Dyspnea accompanied by hypoxemia is the most common symptom of critically ill patients with COVID-19[21]. As they consistently meet the criteria for ARDS, the majority of severe patients required mechanical ventilation. Moreover, most of the patients underwent prolonged prone positioning and received neuromuscular blocking agents, but their hypoxemia persisted in our cohort. The mortality of our COVID-19 related severe ARDS patients who required mechanical ventilation was 89.2% (33/37), which was extremely discouraging. Consistently, high mortality rates were reported in ventilated patients of New York City Area in U.S. (88.1%, 282/320)[11] and another medical center in Wuhan (81%, 30/37) [10]. These data suggested a poor prognosis of COVID-19 related ARDS than the ARDS caused by traditional etiology we previously treated[5].

Over the past few decades, application of ECMO for ARDS has increased substantially, but its use remains controversial[5]. During the pandemic of H1N1 in 2009, the patients who received ECMO therapy appeared to benefit[7, 8]. In Conventional Ventilatory Support versus ECMO for Severe Adult Respiratory Failure (CESAR) trial, it was established that transferring adult patients with severe but potentially reversible respiratory failure to a center with an ECMO-based management protocol significantly improved survival without severe disabilities[22]. With the reported data during the pandemic of COVID-

19, the overall pooled prevalence of mortality in ECMO patients ranged at 42–83%, and a lot of patients were still on ECMO or mechanically ventilated at the time of publication[10, 15–18], the efficiency of ECMO treatment seems obscure. In our cohort, the all-cause 60-day mortality of patients who received ECMO was 37.5% (6/16), while 89.2% (33/37) in non-ECMO group. Up to 180-day, mortality of patients who received ECMO was 56.2% (9/16), which was still much lower than non-ECMO group. The Patients who received ECMO therapy appeared to be significantly benefited, which further supported the application of ECMO as an indicated strategy in COVID-19 related ARDS patients rather than only a salvage procedure.

As to device-related complication, coagulopathy was most frequently seen in our patients receiving ECMO treatment (**Table 4**). Especially, the rate of intracranial bleeding (12.5%) in our ECMO-treated patients was higher than the 2% rate recorded in the EOLIA Trial [5] and an ECMO-treated cohort during H1N1[23], which may result from COVID-19 related coagulopathy[24]. Furthermore, severe COVID-19 is frequently accompanied by thrombopenia which has been identified as a predictive risk factor for poor outcome not only for our ECMO-treated patients but those critically ill patients[1, 25]. ECMO related anemia and coagulopathy led to 100% blood transfusion in our ECMO group to maintain hemoglobin levels above 70 g/L and relatively normal coagulation parameters. We noticed that red cell concentrates were the most frequently transfused component in COVID-19 patients on ECMO, which was also reported by other teams[26, 27]. Fresh frozen plasma, cryoprecipitate and platelet transfusions were used to balance the coagulation system. Furthermore, the anticoagulation regimen has been precisely managed by centrifugal pumps speed at 3–5 L/min and APTT maintained between 40 to 55 seconds (ACT 180–200 s) with unfractionated heparin. Collectively, highly experienced teams were needed to carefully manage the anticoagulation regimen.

Myocardial injury is defined as the release of structural proteins and cardiac troponin from myocardium to serum caused by various pathological conditions including shock, respiratory failure, severe anemia, heart failure and sepsis, etc.[28]. Myocardial injury has been identified as a risk factor to increase mortality in our ECMO-treated recipients. The causes could be ischemic heart disease, or viral myocarditis directly caused by SARS-CoV-2, which had been proved by endomyocardial biopsy[29–31]. COVID-19 related fulminant myocarditis and myocardial infarction may evolve into circulatory failure. According to the death attribution analysis in our center, among the 236 deceased COVID-19 cases, 102 patients (43.22%) died of concurrent respiratory and circulatory failure, 84 patients (35.59%) died of circulatory failure, 27 patients (11.44%) died of respiratory failure (Data not published). In these conditions, veno-arterial ECMO may be the primary choice for circulatory support. However, 8 patients experienced myocardial injury and 16 patients needed vasoactive drugs to maintain blood pressure in ECMO group, only 3 patients received veno-arterial ECMO because of echocardiography verified cardiac dysfunction in our cohort. More attempts and observations are needed in the future to clarify the role of veno-arterial ECMO support in improving the survival of patients treated with ECMO.

## Limitations



There are several limitations that deserve to be underlined. Firstly, the present data mainly stem from three branches of our institution with a relatively small sample size, which may have variability in reported outcomes. Secondly, it is a retrospective study, the baseline of general characteristics could not be strictly controlled. Under this situation, a randomized controlled trial to study the benefit of ECMO for severe ARDS caused by COVID-19 is needed desperately. Thirdly, we had a follow-up of 180 days after disease onset, which is still a relative short-term outcome. Long-term follow-up is needed to comment on the outcome of our patients, particularly in relation to the degree of pulmonary dysfunction and quality of life.

## **Conclusion**

This article retrospectively describes a significant improvement in survival of COVID-19 related ARDS patients receiving ECMO treatment compared with conventional ventilation up to 180 days. These ECMO-survived patients maintained good quality of life without severe complications or disabilities. Hypercapnia, thrombopenia, myocardial injury and elevation of IL-8 and IL-10 during the treatment of ECMO were closely associated with survival prediction. Our findings suggest that ECMO appears to be a stand-alone treatment strategy in ventilated critically ill COVID-19 patients with refractory respiratory failure. This knowledge also may help to identify potential candidates for ECMO support according to their mortality risk and provides guidance to solve crucial economic and ethical issues.

## **Declarations**

### **Ethics approval and consent to participate**

This study was approved by the Institutional Review Board of the Tongji Hospital (TJ20200427-8).

### **Consent for publication**

Not applicable.

### **Availability of data and material**

The data used and/or analyzed in the present study are available from the corresponding author on reasonable request.

### **Competing interests**

No competing interests need to be declared

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## Authors' contributions

LYW, JGJ, and DWW conceived the study; PC and KQC collected the data; LYW, PC, and LN conducted the analysis; LYW wrote the manuscript; LYW, JGJ, and DWW redacted the manuscript.

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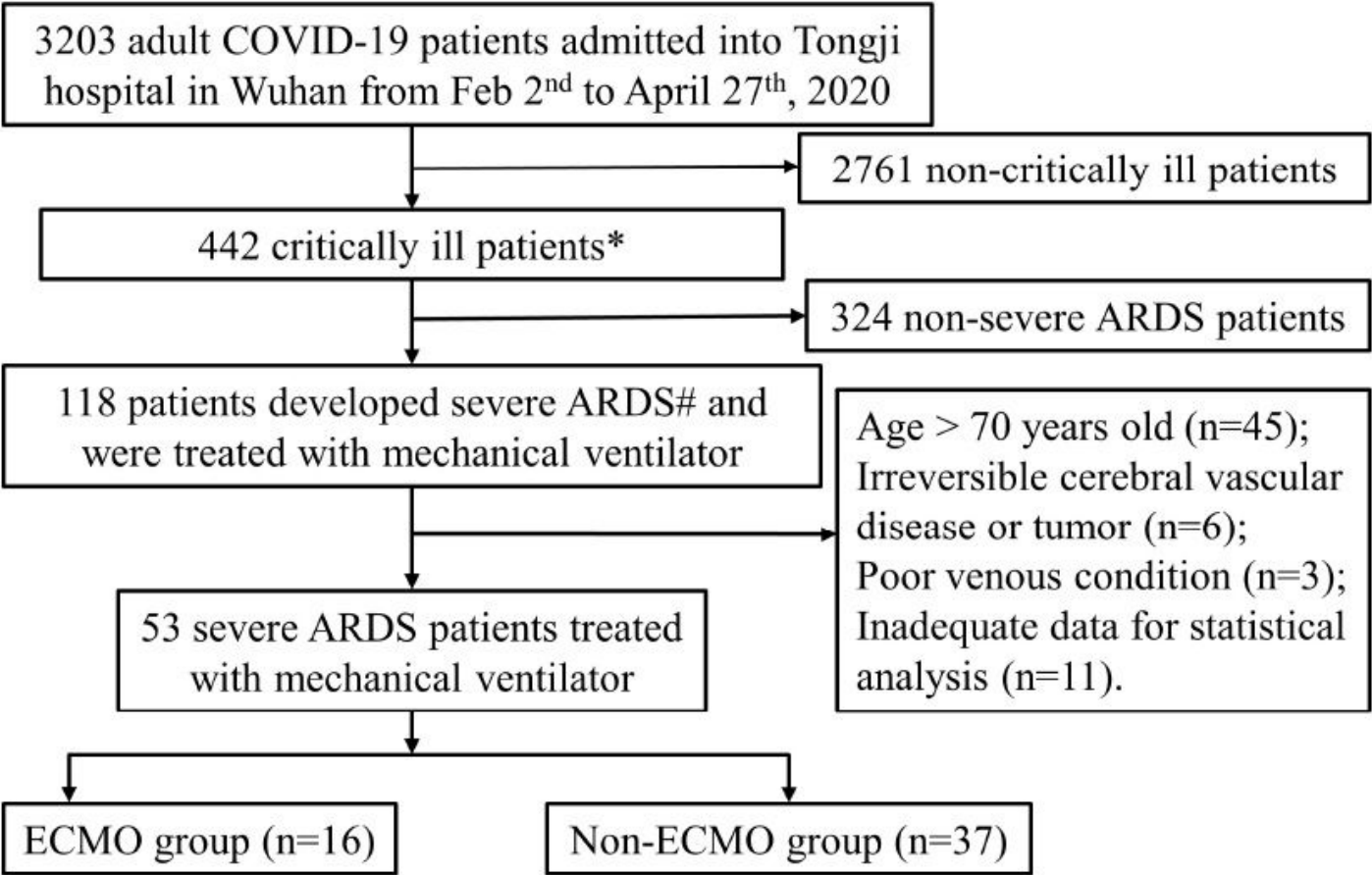
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## Tables

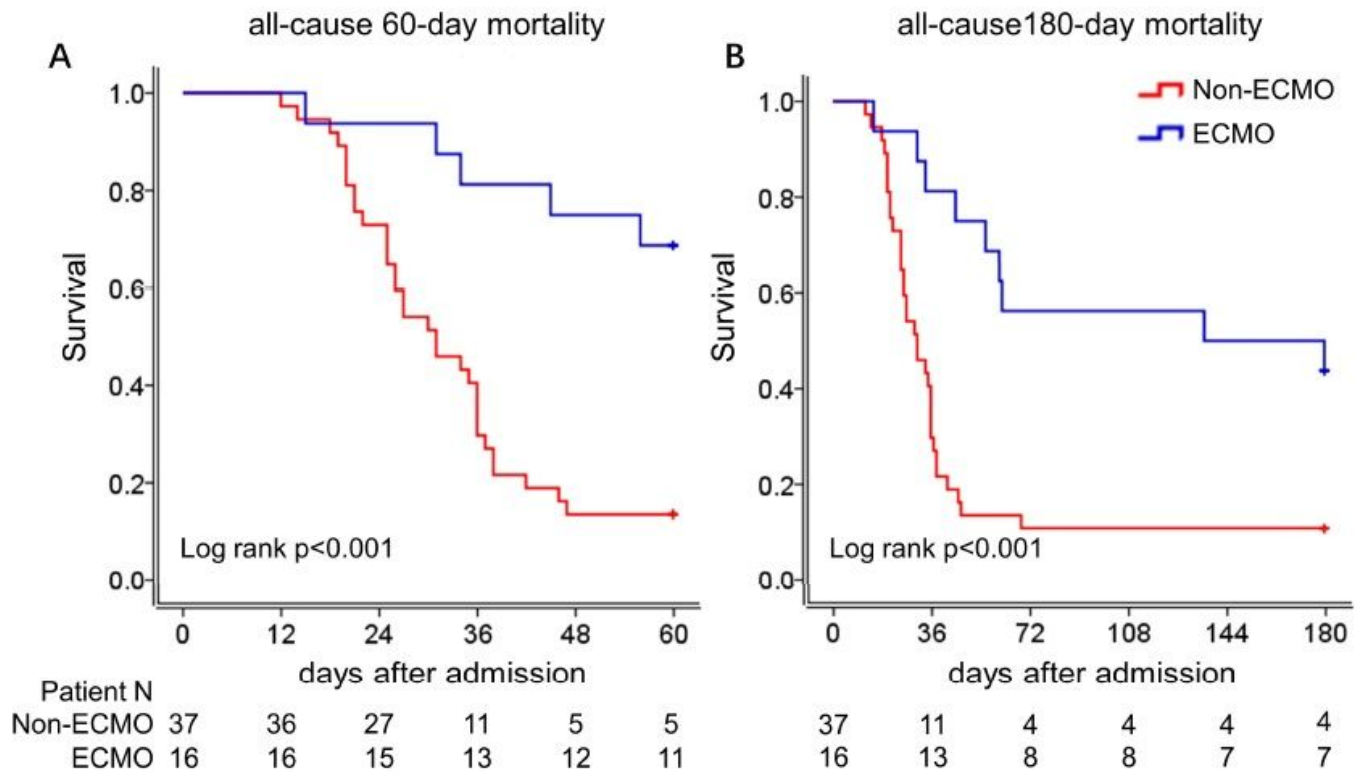
Due to technical limitations the Tables are available as a download in the Supplementary Files.

## Figures



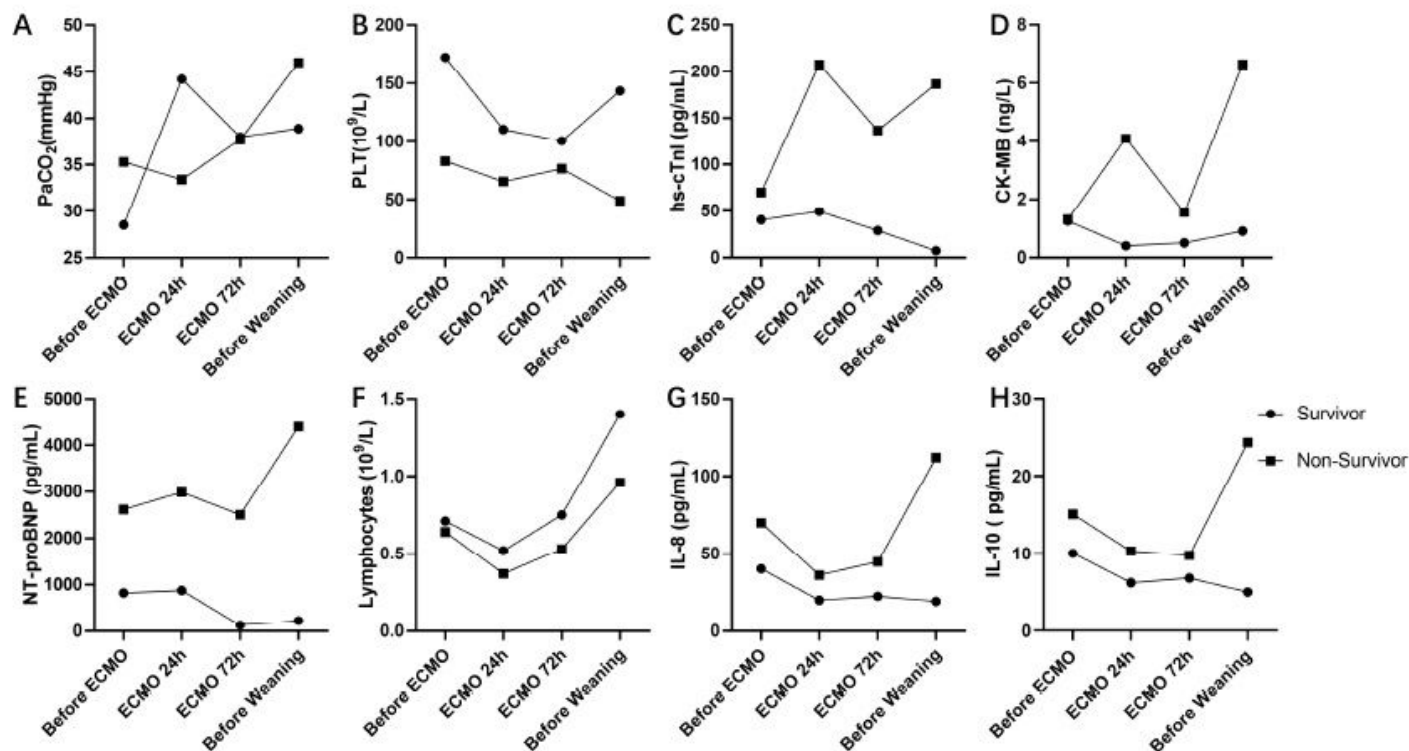
**Figure 1**

Flow chart of patients included in the COVID-19 related severe acute respiratory distress syndrome (ARDS) and extracorporeal membrane oxygenation (ECMO)/non-ECMO cohorts. \*Critically ill COVID-19 patients have one or more the following situations: 1) shock, 2) respiratory failure requiring mechanical ventilation, and 3) any other organ failure in need of management in ICU. #Severe ARDS was defined by  $\text{PaO}_2/\text{FiO}_2 < 50$  mmHg for  $>3$  hours, or  $< 80$  mmHg for  $> 6$  hours, or an arterial blood pH of  $< 7.25$  with a partial pressure of arterial carbon dioxide ( $\text{PaCO}_2$ )  $\geq 60$  mmHg for  $> 6$  hours, with the respiratory rate increased to 35 breaths per minute and mechanical-ventilation settings adjusted to keep a plateau pressure ( $\text{Pplat}$ ) of  $\leq 32$  cmH<sub>2</sub>O.



**Figure 2**

All-cause 60-day and 180-day mortalities. (A) All-cause 60-day mortality was 37.5% (6/16) in ECMO group and 86.5% (32/37) in non-ECMO group (HR, 0.196; 95% CI, 0.053-0.721;  $p=0.014$ ). (B) All-cause 180-day mortality was 56.3% (9/16) in ECMO group and 89.1% (33/37) in non-ECMO group (HR, 0.298; 95% CI, 0.130-0.680;  $p=0.004$ ).



**Figure 3**

Laboratory test results in ECMO survivor and non-survivor groups. (A) PaCO<sub>2</sub>, (B) PLT, (C) hs-cTnI, (D) CK-MB, (E) NT-proBNP, (F) Lymphocytes, (G) IL-8, (H) IL-10.

## Supplementary Files

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