

# Extracorporeal Membrane Oxygenation Therapy for Critically Ill Coronavirus Disease 2019 Patients in Wuhan, China: A Retrospective Multicenter Cohort Study\*

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**Summary:** Currently, little in-depth evidence is known about the application of extracorporeal membrane oxygenation (ECMO) therapy in coronavirus disease 2019 (COVID-19) patients. This

retrospective multicenter cohort study included patients with COVID-19 at 7 designated hospitals in Wuhan, China. The patients were followed up until June 30, 2020. Univariate and multivariate logistic regression analyses were performed to identify the risk factors associated with unsuccessful ECMO weaning. Propensity score matching was used to match patients who received veno-venous ECMO with those who received invasive mechanical ventilation (IMV)-only therapy. Of 88 patients receiving ECMO therapy, 27 and 61 patients were and were not successfully weaned from ECMO, respectively. Additionally, 15, 15, and 65 patients were further weaned from IMV, discharged from hospital, or died during hospitalization, respectively. In the multivariate logistic regression analysis, a lymphocyte count  $\leq 0.5 \times 10^9/L$  and D-dimer concentration  $>4 \times$  the upper limit of normal level at ICU admission, a peak PaCO<sub>2</sub>  $>60$  mmHg at 24 h before ECMO initiation, and no tracheotomy performed during the ICU stay were independently associated with lower odds of ECMO weaning. In the propensity score-matched analysis, a mixed-effect Cox model detected a lower hazard ratio for 120-day all-cause mortality after ICU

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admission during hospitalization in the ECMO group. The presence of lymphocytopenia, higher D-dimer concentrations at ICU admission and hypercapnia before ECMO initiation could help to identify patients with a poor prognosis. Tracheotomy could facilitate weaning from ECMO. ECMO relative to IMV-only therapy was associated with improved outcomes in critically ill COVID-19 patients.

**Key words:** coronavirus disease 2019; extracorporeal membrane oxygenation; mechanical ventilation; acute respiratory distress syndrome; viral pneumonia

On April 26, 2020, the number of hospitalized coronavirus disease 2019 (COVID-19) cases decreased to zero in Wuhan, the Chinese city most severely affected by the COVID-19 pandemic. However, the global pandemic situation remains critical, as the number of new severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection cases continues to increase without signs of alleviation. Recent studies have revealed that up to 12.2% of hospitalized COVID-19 patients in the USA were refractory to oxygen therapy and required advanced forms of respiratory support, such as invasive mechanical ventilation (IMV)<sup>[1]</sup>. COVID-19-induced acute respiratory distress syndrome (ARDS) is characterized by a decrease in lung compliance, which necessitates a high IMV driving pressure to maintain oxygenation and may consequently cause ventilator-induced lung injury. This led to disappointing outcomes of IMV in critically ill COVID-19 patients and mortality rates as high as 88.1%<sup>[1]</sup>. Extracorporeal membrane oxygenation (ECMO) therapy can support not only ventilation but also gas exchange. Such a complete lung replacement therapy would guarantee both oxygen intake and CO<sub>2</sub> removal. This aspect is particularly important because a deficiency in gas exchange has been identified as the dominant cause of hypoxemia in COVID-19 patients who develop ARDS. Moreover, the use of ECMO may protect the lungs, in contrast to IMV, and this could better enable viral depletion and lung recovery.

ECMO has been widely used as a life-saving therapy in critically ill patients with viral pneumonia since the demonstration of its superiority over IMV during the 2009 H1N1 influenza pandemic<sup>[2-3]</sup>. Although sporadic studies have reported the use of ECMO in COVID-19 patients, the results were generally disappointing<sup>[4-5]</sup>. This study aimed to systematically and comprehensively elaborate the efficacy, therapeutic considerations, and outcomes of ECMO application in COVID-19 patients in Wuhan, the largest cohort in China. We sought to identify the risk factors that accounted for unsuccessful ECMO weaning, so as to facilitate decision making regarding eligibility for ECMO implementation. Using propensity score matching, we matched ECMO and IMV patients to compare the effectiveness and outcomes of the two approaches, using 120-day in-hospital mortality after ICU admission as the primary end point. We

hypothesized that in critically ill COVID-19 patients, ECMO use would be associated with an improved outcome when compared to IMV-only therapy.

## 1 PATIENTS AND METHODS

### 1.1 Study Design and Patient Enrollment

This retrospective, multicenter study included patients who had been diagnosed with COVID-19 according to the Guidelines on Diagnosis and Treatment for New Coronavirus Pneumonia (5th edition), published by the National Health Commission of the People's Republic of China. Seven designated local hospitals in Wuhan that were temporarily transformed for treating COVID-19 and providing ECMO therapy for more than 5 patients with COVID-19 were included in the present study: Tongji Hospital and Union Hospital of Huazhong University of Science and Technology, Zhongnan Hospital and Renmin Hospital of Wuhan University, Wuhan Jinyintan Hospital, Wuhan Pulmonary Hospital, and Leishenshan Hospital. In total, 94 patients received ECMO therapy and 536 received IMV-only therapy. The institutional ethical committee of each participating hospital approved the study protocol and waived the requirement for informed patient consent. The patients' clinical outcomes during hospitalization were monitored until June 30, 2020. For patients who were transferred between hospitals, the courses were merged and considered as a single course. Patients without a definite outcome (e.g., weaned from ECMO, discharged, or deceased) because of incomplete medical records were excluded.

### 1.2 Initiation, Management, and Weaning of ECMO

The indications and contradictions of ECMO therapy were determined by the local ECMO team in accordance with the Guidelines on the Diagnosis and Treatment for New Coronavirus Pneumonia of Severely and Critically Ill Patients (2nd edition) released by the National Health Commission of the People's Republic of China. The multidisciplinary ECMO team comprised intensive care specialists, cardiac surgeons, perfusionists, and nursing personnels. ECMO was considered when protective ventilation and prone-position ventilation were ineffective and one or more of the following criteria were met, despite the application of an optimal ventilatory strategy [fraction of inspired oxygen (FiO<sub>2</sub>) ≥ 0.8, tidal volume of 6 mL/

kg of predicted body weight, positive end-expiratory pressure (PEEP)  $\geq 10$  cmH<sub>2</sub>O]: (1) partial pressure of oxygen (PaO<sub>2</sub>): FiO<sub>2</sub> <50 mmHg >3 h; (2) PaO<sub>2</sub>:FiO<sub>2</sub> <80 mmHg >6 h; (3) PaO<sub>2</sub>:FiO<sub>2</sub> <100 mmHg at a FiO<sub>2</sub>=1.0; (4) arterial pH <7.25 and PaCO<sub>2</sub> >60 mmHg >6 h with a respiratory rate >35 breaths/min; (5) arterial pH <7.20 with a respiratory rate >35 breaths/min and plateau pressure >30 cmH<sub>2</sub>O; (6) cardiogenic shock or cardiac arrest. Relative contradictions included (1) a combination of irreversible diseases; (2) contradictions to anticoagulation; (3) mechanical ventilation >7 days under high ventilatory settings (FiO<sub>2</sub> >0.9 and plateau pressure >30 cmH<sub>2</sub>O); (4) immunocompromised status; or (5) lack of vascular access for ECMO because of vascular deformity. Veno-venous (V-V) ECMO was preferred for patients with normal cardiac function. Veno-arterial (V-A) ECMO was applied when cardiogenic shock was diagnosed. ECMO management and weaning were performed at the multidisciplinary team's discretion when the lung function was improved and lung abnormalities were resolved. The details and weaning course were as previously described<sup>[6]</sup>.

### 1.3 Data Collection

We obtained the electronic medical records from hospitals and extracted data concerning the patients' demographic information, comorbidities, medical histories, laboratory and imageological findings, inpatient medications, medical orders, treatments, daily progress notes, nursing records, and final outcomes (i.e., ICU discharge, hospital discharge, and mortality). The patients' names and IDs were anonymized to protect privacy before data extraction. All data were reviewed by experienced clinicians, entered into a computerized database, and double-checked. If essential data were missing in the electronic records, we contacted the corresponding physicians-in-charge directly.

### 1.4 Definitions

The onset of COVID-19 was defined as the first date when the symptoms were noticed. Patients who were successfully weaned from ECMO and remained alive for at least 48 h were classified as the weaned group. Patients who died despite receiving ECMO therapy or remained on ECMO until June 30, 2020, were classified as the non-weaned group. Acute kidney injury was identified as an increase of  $\geq 26.5$   $\mu\text{mol/L}$  in the serum creatinine concentration within 48 h<sup>[7]</sup>. Acute cardiac injury was identified as a serum cardiac troponin I (cTnI) concentration above the upper limit of normal (ULN). Acute hepatic injury was defined as an increase in the serum aspartate aminotransferase or alanine aminotransferase (ALT) concentration to more than three times the ULN<sup>[8]</sup>. Disseminated intravascular coagulation (DIC) was defined according to the criteria set by the International Society on Thrombosis and Hemostasis<sup>[9]</sup>. The following criteria for discharge were applied as recommended by the guidelines: (1) throat

swab or sputum specimens collected at an interval of at least 24 h yielded negative SARS-CoV-2 test results; (2) body temperature was normal for 3 consecutive days; (3) symptoms of COVID-19 were resolved; and (4) chest computed tomography manifestations of COVID-19 were significantly improved. Nosocomial infection was diagnosed in patients who exhibited signs of bacteremia or pneumonia and a positive pathogen culture from lower respiratory tract specimens (e.g., qualified sputum, endotracheal aspirate, or bronchoalveolar lavage fluid) or blood samples at 48 h after hospital admission.

### 1.5 Propensity Score-matched Analysis

Propensity score-matched cohorts of patients who received ECMO therapy or IMV-only therapy were created based on variables expected to be confounders associated with the outcomes of ECMO or IMV-only treatment. These variables included age, sex, comorbidities (hypertension, diabetes), and laboratory examination findings at ICU admission [lymphocyte count, C-reactive protein, creatinine, total bilirubin, ALT, lactate dehydrogenase (LDH), N-terminal pro-hormone brain natriuretic peptide (NT-proBNP) or BNP, and D-dimer]. Only patients who received V-V ECMO treatment were included in the ECMO group for this cohort analysis (fig. 1). We used non-parametric missing value imputation based on the missForest procedure on the R platform to account for missing laboratory variable data<sup>[10]</sup>. A random forest model that included the remaining variables in the data set was performed to predict the missing values for those variables. Internally cross-validated errors were also estimated. Patients who were died within 24 h after ECMO or IMV initiation were excluded. ECMO and IMV-only patients were paired at a 1:1 ratio according to the propensity scores, using exact matching with a caliper size of 0.05. The balance between covariates was evaluated by estimating the standardized differences before and after matching. Only standardized differences with absolute values of <0.1 were considered to indicate qualified balancing. A mixed-effect Cox model was used to compare the two treatment groups in terms of the primary endpoint, which was 120-day all-cause mortality after ICU admission during hospitalization.

### 1.6 Statistical Analysis

Continuous variables are presented as medians and interquartile ranges (IQRs), and categorical variables are expressed as number (*n*) and corresponding percentages. Continuous variables and ordered categorical variables were analyzed using the Mann-Whitney *U* test, whereas proportions of unordered categorical variables were compared using the  $\chi^2$  test or Fisher's exact test when the sample sizes were small. Univariate logistic regression models were initially applied to analyze the association between each

single variable and the final weaning of ECMO, and indices with  $P$  values  $<0.1$  were included in a further multivariate logistic regression. The odds ratios (ORs) and 95% confidence intervals (CIs) were reported.

The risk of reaching the primary endpoint and the corresponding hazard ratio (HR) were calculated using the mixed-effect Cox model and compared between the ECMO and IMV-only groups. We adjusted multiple variables considered relevant to the endpoint, including age, sex, comorbidities (hypertension, chronic lung disease), laboratory examination findings at ICU admission (platelet, total bilirubin, LDH, NT-proBNP or BNP, creatinine, D-dimer), and treatments during the ICU stay (prone position ventilation, convalescent plasma). We modeled the site as a random effect in the mixed-effect Cox model. The proportional hazard assumptions were verified using correlation testing based on Schoenfeld residuals. The cumulative death rates were compared using the Kaplan–Meier method. A two-sided  $P$  value of  $<0.05$  was considered statistically significant. The data were analyzed using the R platform version 3.6.3 with the “tableone” and “stats” packages (R Foundation for Statistical Computing, Vienna, Austria), STATA software version 15.0 (Stata Corp., College Station, USA) and SPSS Statistics version 23.0 (IBM, Armonk, USA).

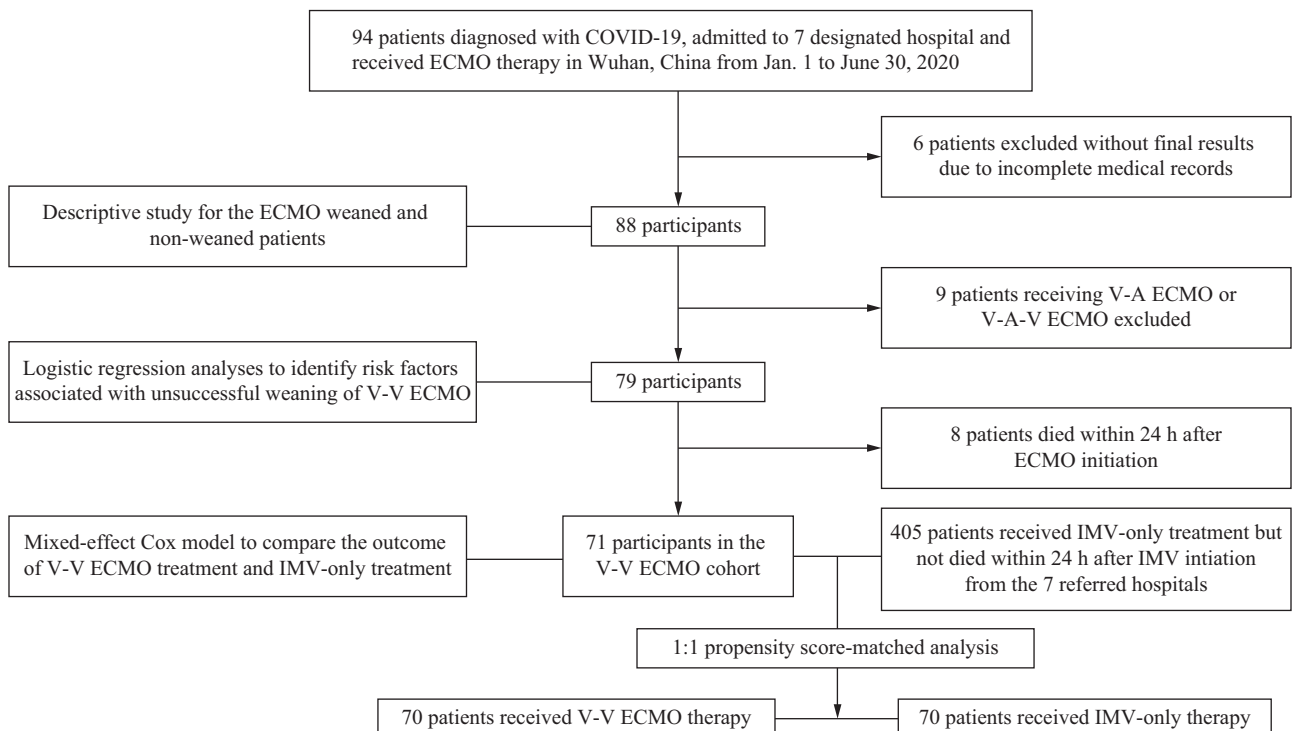
## 2 RESULTS

### 2.1 Clinical Characteristics of COVID-19 Patients Who Received ECMO Therapy in Wuhan

Ninety-four critically ill COVID-19 patients

received ECMO therapy at 7 designated hospitals in Wuhan before June 30, 2020. Six patients without final results due to incomplete medical records were excluded. Of the remaining 88 patients, 27 were successfully weaned (weaned group) and 61 were unsuccessfully weaned (non-weaned group) from ECMO (fig. 1). Figure 2 presents the number of patients concurrently treated with ECMO in Wuhan between January 1 and June 30. ECMO was first implemented on January 2, and concurrent ECMO cases peaked on March 7 ( $n=36$ ; fig. 2). The first patient in the weaned group received ECMO support on January 28 (fig. 2). Patients in the non-weaned group had a median (IQR) age of 62.00 (52.00–68.00) years and were significantly older than those in the weaned group [median: 50.00 (42.00–64.00) years; table 1]. The male sex was predominant in both groups (table 1). The median (IQR) duration from symptom onset to first admission was 12.00 (7.00–20.25) days (table 1). Approximately half of the patients had comorbidities, of which hypertension and diabetes mellitus were the most frequent (table 1).

The majority of patients presented with lymphocytopenia at the time of ICU admission, which was more severe in the non-weaned group (table 1). Similarly, small proportions of patients in both groups demonstrated thrombocytopenia and elevated total bilirubin, ALT, and creatinine concentrations (table 1). Similarly, large proportions of patients in both groups exhibited substantially elevated serum C-reactive protein, LDH, D-dimer, and IL-6 concentrations (table 1). Nearly half of the patients exhibited elevated NT-



**Fig. 1** Flow diagram of patient enrollment and propensity score matching in this study



**Table 1 Demographic and clinical characteristics of patients with COVID-19**

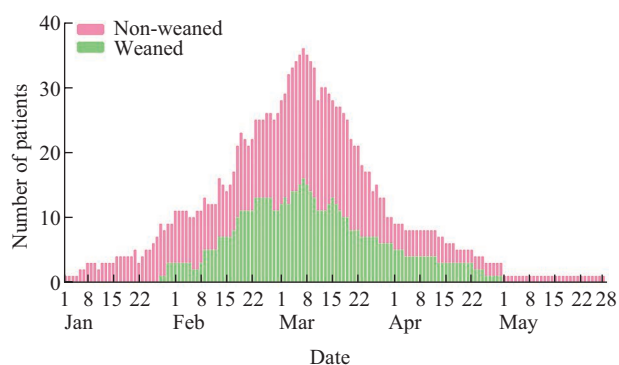
Parameters	All patients (n=88)	Weaned (n=27)	Non-weaned (n=61)	P value
Clinical characteristics on hospital admission				
Age, years	58.50 (47.00–66.50)	50.00 (42.00–64.00)	62.00 (52.00–68.00)	0.038
18–40	8/88 (9.1%)	4/27 (14.8%)	4/61 (6.6%)	0.055
41–60	38/88 (43.2%)	14/27 (51.9%)	24/61 (39.3%)	
61–70	31/88 (35.2%)	7/27 (25.9%)	24/61 (39.3%)	
>70	11/88 (12.5%)	2/27 (7.4%)	9/61 (14.8%)	
Female	32/88 (36.4%)	8/27 (29.6%)	24/61 (39.3%)	0.382
Symptom onset to first admission, days	12.00 (7.00–20.25)	14.00 (8.50–20.00)	11.00 (7.00–21.00)	0.710
Any comorbidity	45/88 (51.1%)	15/27 (55.6%)	30/61 (49.2%)	0.581
Major comorbidities				
Hypertension	35/88 (39.8%)	11/27 (40.7%)	24/61 (39.3%)	0.902
Diabetes Mellitus	18/88 (20.5%)	7/27 (25.9%)	11/61 (18.0%)	0.397
Chronic lung disease	1/88 (1.1%)	0/27 (0.0%)	1/61 (1.6%)	1.000
Cardiovascular disease (excluding hypertension)	8/88 (9.1%)	3/27 (11.1%)	5/61 (8.2%)	0.971
Neurological disease	3/88 (3.4%)	3/27 (11.1%)	0/61 (0.0%)	0.027
Chronic liver disease	4/88 (4.5%)	0/27 (0.0%)	4/61 (6.6%)	0.308
Chronic renal disease	0/88 (0.0%)	0/27 (0.0%)	0/61 (0.0%)	
Malignancy	1/88 (1.1%)	0/27 (0.0%)	1/61 (1.6%)	1.000
Laboratory examinations on ICU admission				
Leukocyte count, $\times 10^9/L$	12.68 (8.10–17.19)	12.72 (8.19–19.06)	12.63 (8.11–16.40)	0.790
$>10 \times 10^9/L$	57/88 (64.8%)	16/27 (59.3%)	41/61 (67.2%)	0.471
Lymphocyte count, $\times 10^9/L$	0.65 (0.39–0.86)	0.75 (0.50–0.96)	0.54 (0.32–0.84)	0.065
$\leq 0.5 \times 10^9/L$	36/88 (40.9%)	7/27 (25.9%)	29/61 (47.5%)	0.057
Platelet, $\times 10^9/L$	164.50 (104.75–225.75)	165.00 (142.00–212.50)	164.00 (100.00–234.00)	0.825
<LLN	27/88 (30.7%)	5/27 (18.5%)	22/61 (36.1%)	0.100
C-reactive protein, mg/L	95.40 (56.80–160.00)	86.40 (29.43–138.10)	96.70 (64.50–160.00)	0.095
>100	39/85 (45.9%)	12/26 (46.2%)	27/59 (45.8%)	0.973
Total bilirubin, $\mu\text{mol/L}$	13.90 (9.35–21.58)	11.60 (9.19–17.20)	14.60 (10.21–25.30)	0.080
>ULN	21/88 (23.9%)	3/27 (11.1%)	18/61 (29.5%)	0.062
ALT, U/L	37.00 (21.00–61.25)	39.00 (25.00–80.50)	36.00 (21.00–54.00)	0.326
>ULN	33/88 (37.5%)	12/27 (44.4%)	21/61 (34.4%)	0.371
LDH, U/L	547.00 (432.00–700.00)	531.00 (436.00–647.75)	571.00 (432.00–736.00)	0.562
>1.5 $\times$ ULN	69/80 (86.25%)	21/24 (87.5%)	48/56 (85.7%)	1.000
NT-proBNP, pg/mL	225.20 (73.40–968.00)	195.00 (84.60–1218.50)	227.10 (73.10–869.30)	0.727
>ULN	40/87 (46.0%)	14/27 (51.9%)	26/60 (43.3%)	0.461
cTnI, pg/mL	33.00 (12.90–239.40)	30.00 (12.20–225.30)	37.00 (16.70–235.75)	0.696
>ULN	40/85 (47.1%)	11/26 (42.3%)	29/59 (49.2%)	0.560
Creatinine, $\mu\text{mol/L}$	66.20 (51.25–97.40)	65.00 (46.30–85.30)	69.00 (54.60–101.00)	0.260
>ULN	24/88 (27.3%)	5/27 (18.5%)	19/61 (31.1%)	0.220
D-dimer, mg/L	4.51 (1.63–16.87)	2.96 (1.31–11.32)	7.28 (2.28–19.04)	0.152
>4 $\times$ ULN	60/87 (69.0%)	14/27 (51.9%)	46/60 (76.7%)	0.021
Serum IL-6, pg/mL	44.30 (12.51–196.20)	74.86 (15.88–199.20)	40.26 (11.80–188.00)	0.339
>10 $\times$ ULN	31/70 (44.3%)	11/23 (47.8%)	20/47 (42.6%)	0.677
Scores on ICU admission				
Murray score	3.00 (2.70–3.30)	3.00 (2.67–3.15)	3.00 (2.70–3.33)	0.146
Missing data	0/88 (0.0%)	0/27 (0.0%)	0/61 (0.0%)	
SOFA score	8.00 (6.00–10.00)	7.50 (6.00–9.00)	8.00 (7.00–11.00)	0.207
Missing data	11/88 (12.5%)	3/27 (11.1%)	8/61 (13.1%)	
24-h before ECMO initiation				
Highest respiratory rate, breaths/min	24.00 (20.00–28.00)	22.00 (18.00–24.00)	25.00 (22.00–28.00)	0.008
Highest PEEP, $\text{cmH}_2\text{O}$	10.00 (8.00–11.00)	10.00 (7.50–10.00)	10.00 (8.00–12.00)	0.123
Lowest $\text{PaO}_2/\text{FiO}_2$ , mmHg	88.75 (65.79–128.27)	128.85 (81.50–168.73)	81.41 (61.50–104.81)	0.015
>200	3/60 (5.0%)	2/16 (12.5%)	1/44 (2.3%)	0.067
80–200	32/60 (53.3%)	10/16 (62.5%)	22/44 (50.0%)	
<80	25/60 (41.7%)	4/16 (25.0%)	21/44 (47.7%)	

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Parameters	All patients (n=88)	Weaned (n=27)	Non-weaned (n=61)	P value
Highest PaCO <sub>2</sub> , mmHg	58.65 (42.85–71.83)	47.00 (33.80–54.20)	64.00 (45.00–74.30)	0.003
>60	31/66 (47.0%)	2/17 (11.8%)	29/49 (59.2%)	0.001
35–60	25/66 (37.9%)	10/17 (58.8%)	15/49 (30.6%)	
<35	10/66 (15.2%)	5/17 (29.4%)	5/49 (10.2%)	
Lowest arterial pH	7.38 (7.27–7.43)	7.41 (7.36–7.47)	7.36 (7.26–7.42)	0.045
>7.45	13/65 (20.0%)	5/17 (29.4%)	8/48 (16.7%)	0.283
7.35–7.45	27/65 (41.5%)	8/17 (47.1%)	19/48 (39.6%)	
<7.35	25/65 (38.5%)	4/17 (23.5%)	21/48 (43.8%)	
Highest arterial lactic acid, mmol/L	2.10 (1.50–3.00)	2.05 (1.31–2.80)	2.10 (1.50–3.60)	0.560
>ULN	29/50 (58.0%)	9/15 (60.0%)	20/35 (57.1%)	0.851
Treatments during ICU stay				
Requirement of inotropes or vasopressors before intubation	26/87 (29.9%)	8/26 (30.8%)	18/61 (29.5%)	0.906
Anti-viral treatment	52/88 (59.1%)	17/27 (63.0%)	35/61 (57.4%)	0.623
Anti-microbial treatment	87/88 (98.9%)	27/27 (100.0%)	60/61 (98.4%)	1.000
Anti-fungi treatment	58/88 (65.9%)	16/27 (59.3%)	42/61 (68.9%)	0.381
Convalescent plasma	19/88 (21.6%)	12/27 (44.4%)	7/61 (11.5%)	0.001
Corticosteroids	57/88 (64.8%)	20/27 (74.1%)	37/61 (60.7%)	0.224
IVIG	50/88 (56.8%)	16/27 (59.3%)	34/61 (55.7%)	0.758

Data are median (IQR) or *n* (%). *P* values were calculated by Mann-Whitney *U* test,  $\chi^2$  test, or Fisher's exact test, as appropriate. Upper limit of normal (ULN) and lower limit of normal (LLN) were defined according to the normal ranges of tests in each hospital. ALT: alanine transaminase; LDH: lactate dehydrogenase; NT-proBNP: N-terminal pro-brain natriuretic peptide; cTnI: cardiac troponin I; IL-6: interleukin-6; SOFA: sequential organ failure assessment; PEEP: positive end expiratory pressure; PaO<sub>2</sub>/FiO<sub>2</sub>: partial pressure of arterial oxygen/fraction of inspiration oxygen; PaCO<sub>2</sub>: partial pressure of arterial carbon dioxide; IVIG: intravenous immunoglobulin



**Fig. 2** Histogram of the number of patients concurrently treated with ECMO in Wuhan, China, from January 1 to June 30, 2020. Green and red histograms indicate the patients finally successfully weaned (weaned group) and failed to wean (non-weaned) from ECMO, respectively.

proBNP and cTnI concentrations indicative of an abnormal cardiac status (table 1). The median Murray score, which is used to assess the severity of ARDS, was 3.0 in both groups (table 1). The median sequential organ failure assessment (SOFA) score, which is used to evaluate the functions of extra-pulmonary organs, was 8.00 (IQR: 6.00–10.00).

The non-weaned group had a significantly higher peak respiratory rate and peak PaCO<sub>2</sub> at 24 h before ECMO initiation and a significantly lower minimum PaO<sub>2</sub>/FiO<sub>2</sub> and arterial pH than in the weaned group (table 1). There was no significant difference in peak

PEEP and arterial lactic acid values between the two groups (table 1). Approximately 30% of patients in both groups had an unstable hemodynamic status necessitating inotropes or vasopressors before intubation (table 1). Anti-viral, anti-microbial, and anti-fungal agents, corticosteroids, and intravenous immunoglobulin were administered at similar frequencies in both groups (table 1). Notably, more patients in the weaned group (44.4%) than in the non-weaned group (11.5%) received convalescent plasma (table 1).

## 2.2 Descriptive Data Related to Use of ECMO

Of the 88 enrolled patients, 79 received V-V ECMO therapy (table 2). Of the 7 patients who received veno-arterial (V-A) ECMO, 4 were weaned and 3 failed to wean (table 2). The two patients who received veno-arterio-venous (V-A-V) ECMO failed to wean from ECMO (table 2). One patient in each group underwent a switch of the ECMO mode (table 2). One patient in the weaned group received ECMO therapy while awake and without mechanical ventilation (table 2). Three patients in the weaned group and two in the non-weaned group had undergone repeated ECMO (table 2). Five patients in the weaned group and 7 patients in the non-weaned group experienced interhospital transportation with ECMO run (table 2). The blood flow velocities of ECMO were equivalent in the two groups (table 2).

During the ICU stay, patients in the weaned

**Table 2 ECMO-related parameters and therapies, and outcomes of patients with COVID-19 and supported with ECMO**

Parameters	All patients (n=88)	Weaned (n=27)	Non-weaned (n=61)	P value
<b>ECMO-related parameters</b>				
ECMO mode				0.194
V-V ECMO	79/88 (89.8%)	23/27 (85.2%)	56/61 (91.8%)	
V-A ECMO	7/88 (8.0%)	4/27 (14.8%)	3/61 (4.9%)	
V-A-V ECMO	2/88 (2.3%)	0/27 (0.0%)	2/61 (3.3%)	
Switch of ECMO mode	2/88 (2.3%)	1/27 (3.7%)*	1/61 (1.6%)†	0.522
Awake ECMO	1/88 (1.1%)	1/27 (3.7%)‡	0/61 (0.0%)	0.674
ECMO recommencement after weaning	5/88 (5.7%)	3/27 (11.1%)	2/61 (3.3%)	0.335
Interhospital transportation with ECMO run	12/88 (13.6%)	5/27 (18.5%)	7/61 (11.5%)	0.582
Blood flow of ECMO, L/min	3.70 (3.50–4.00)	3.67 (3.42–4.00)	3.70 (3.50–4.03)	0.798
<b>ECMO-related therapies</b>				
<b>Transfusion during ICU stay</b>				
Red blood cells, units	14.00 (4.00–26.25)	21.00 (10.75–35.25)	12.00 (4.00–24.00)	0.012
Plasma, mL	1200.00 (400.00–3162.50)	1550.00 (687.50–4550.00)	1050.00 (312.50–2797.50)	0.090
Platelet, units	1.00 (0.00–5.00)	0.00 (0.00–2.00)	2.00 (0.00–5.00)	0.128
CRRT	57/88 (64.8%)	17/27 (63.0%)	40/61 (65.6%)	0.813
Prone position ventilation during ICU stay	35/88 (39.8%)	12/27 (44.4%)	23/61 (37.7%)	0.551
Received tracheotomy	23/88 (26.1%)	15/27 (55.6%)	8/61 (13.1%)	<0.001
<b>Outcomes</b>				
Weaning of mechanical ventilation	15/87 (17.2%)	15/26 (57.7%)	0/61 (0.0%)	<0.001
Survival to hospital discharge	15/88 (17.0%)	15/27 (55.6%)	0/61 (0.0%)	<0.001
In-hospital death	65/88 (73.9%)	4/27 (14.8%)	61/61 (100%)	<0.001
Under hospitalization	8/88 (9.1%)	8/27 (29.6%)	0/61 (0.0%)	<0.001
<b>Durations</b>				
Symptom onset to intubation, days	20.00 (15.00–26.00)	20.00 (15.00–28.75)	19.00 (15.00–26.00)	0.714
Symptom onset to ECMO initiation, days	23.00 (17.00–31.50)	22.00 (17.50–27.50)	24.00 (17.00–33.00)	0.402
Intubation to ECMO initiation, days	3.00 (1.00–7.00)	2.00 (1.00–6.00)	4.00 (2.00–8.00)	0.108
Intubation to tracheotomy, days	25.00 (15.50–30.50)	25.00 (17.50–32.00)	19.00 (14.75–26.75)	0.194§
ECMO initiation to death, days	13.00 (4.00–24.00)	67.50 (53.50–80.75)	12.00 (3.00–21.00)	0.007
Cumulative ECMO support, days	13.00 (5.75–24.25)	14.00 (7.50–31.00)	12.00 (3.00–21.00)	0.049
Cumulative IMV support, days	22.50 (10.25–36.00)	37.00 (17.50–65.00)	19.00 (8.75–29.25)	<0.001
<b>Length of stay</b>				
ICU stay, days	25.00 (10.75–40.00)	45.00 (25.00–70.00)	17.00 (9.00–30.00)	<0.001
Hospital stay, days	30.50 (13.75–50.00)	56.00 (41.50–105.50)	21.00 (11.00–37.00)	<0.001
<b>Complications</b>				
<b>Nosocomial infection</b>				
Pulmonary infection	65/88 (73.9%)	21/27 (77.8%)	44/61 (72.1%)	0.578
Catheter related bloodstream infection	5/88 (5.7%)	3/27 (11.1%)	2/61 (3.3%)	0.335
<b>Acute organ injury</b>				
Cardiac injury	72/85 (84.7%)	20/26 (76.9%)	52/59 (88.1%)	0.319
Renal injury	58/86 (67.4%)	16/26 (61.5%)	42/60 (70.0%)	0.442
Liver injury	50/87 (57.5%)	11/27 (40.7%)	39/60 (65.0%)	0.034
DIC	6/88 (6.8%)	2/27 (7.4%)	4/61 (6.6%)	1.000
<b>Hemorrhage</b>				
Pulmonary hemorrhage	2/88 (2.3%)	0/27 (0.0%)	2/61 (3.3%)	1.000
Gastrointestinal hemorrhage	19/88 (21.6%)	8/27 (29.6%)	11/61 (18.0%)	0.223
Cannula hemorrhage	4/88 (4.5%)	2/27 (7.4%)	2/61 (3.3%)	0.762
Intra-cranial hemorrhage	4/88 (4.5%)	0/27 (0.0%)	4/61 (6.6%)	0.308
Spontaneous epistaxis	2/88 (2.3%)	0/27 (0.0%)	2/61 (3.3%)	1.000
<b>Other complications</b>				
Thrombosis	4/88 (4.5%)	3/27 (11.1%)	1/61 (1.6%)	0.158
Pneumothorax	9/88 (10.2%)	0/27 (0.0%)	9/61 (14.8%)	0.052
Hemothorax	1/88 (1.1%)	1/27 (3.7%)	0/61 (0.0%)	0.674
Pericardial tamponade	0/88 (0.0%)	0/27 (0.0%)	0/61 (0.0%)	

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Parameters	All patients (n=88)	Weaned (n=27)	Non-weaned (n=61)	P value
Cause of death				
Intractable respiratory failure	16/65 (24.6%)	3/4 (75.0%)	13/61 (21.3%)	0.069
Heart failure	22/65 (33.8%)	2/4 (50.0%)	20/61 (32.8%)	0.873
Lethal hemorrhage	6/65 (9.2%)	1/4 (25.0%)	5/61 (8.2%)	0.816
MODS	55/65 (84.6%)	4/4 (100.0%)	51/61 (83.6%)	0.869

Data are median (IQR) or *n* (%). *P* values were calculated by Mann-Whitney *U* test,  $\chi^2$  test, or Fisher's exact test, unless specified otherwise. CRRT: continuous renal replacement therapy; IMV: invasive mechanical ventilation; DIC: disseminated intravascular coagulation; MODS: multiple organ dysfunction syndrome. \*The patients underwent mode switch from V-V to V-A ECMO. †The patients underwent mode switch from V-A to V-A-V ECMO. ‡Awake ECMO indicates that the patient received ECMO therapy while awake and without mechanical ventilation. §*P* value was calculated by two-tailed Student's *t*-test.

group received more red blood cell transfusions, with a median of 21.00 units (IQR: 10.75–35.25; table 2). Plasma and platelet transfusions were similar in both groups (table 2). Up to 64.8% and 39.8% of patients received continuous renal replacement therapy and prone position ventilation, respectively, in the ICU. Tracheotomy was performed in 55.6% (*n*=15) of patients in the weaned group and 13.1% (*n*=8) in the non-weaned group.

### 2.3 Outcomes and Complications Associated with Use of ECMO

Of the 27 patients weaned from ECMO, 15 were further weaned from IMV, 15 were discharged from hospital, 4 died during hospitalization, and 8 remained in hospital (table 2). Of the 61 patients in the non-weaned group, all patients died during hospitalization (table 2). The median time to intubation and ECMO initiation after the onset of symptoms was 20.00 and 23.00 days, respectively, and there was no significant difference between the two groups (table 2). The median (IQR) duration of IMV support before ECMO initiation was 2.00 (1.00–6.00) days in the weaned group and 4.00 (2.00–8.00) days in the non-weaned group (table 2). The median (IQR) time from intubation to tracheotomy was 25.00 (15.50–30.50) days (table 2). The median (IQR) time from ECMO initiation to death was 67.50 (53.50–80.75) days in the weaned group, and 12.00 (3.00–21.00) days in the non-weaned group (table 3). The cumulative ECMO support, IMV support, ICU stay, and hospital stay durations were significantly shorter in the non-weaned group than in the weaned group (table 2), which was largely ascribed to the higher mortality rate in the former group.

Microbial culture-confirmed nosocomial pulmonary infection was evident in 73.9% of patients, and this rate was similar between the two groups (table 2). Cardiac injury was the most common type of acute organ injury, followed by renal and liver injury (table 2). Disseminated intravascular coagulation was observed in 6.8% of all patients (table 2). Gastrointestinal bleeding was the major hemorrhagic complication (table 2). Pneumothorax was observed exclusively in

the non-weaned group (table 2). The major causes of death were multiple organ dysfunction syndrome and heart failure (table 2).

### 2.4 Factors Associated with Odds of Successful Weaning from V-V ECMO

After excluding 9 patients who received V-A ECMO or V-A-V ECMO support (fig. 1), a logistic regression analysis was performed to identify factors associated with the likelihood of successful weaning from V-V ECMO. Factors identified as statistically significant (*P*<0.1) in a univariate analysis were entered into the multivariate logistic regression analysis. Notably, a lymphocyte count  $\leq 0.5 \times 10^9/L$ , D-dimer concentration  $>4 \times$  ULN at ICU admission and a peak PaCO<sub>2</sub>  $>60$  mmHg at 24 h before ECMO initiation were independently correlated with lower odds of successful weaning (table 3). A tracheotomy during the ICU stay was independently correlated with higher odds of ECMO weaning (table 3). In contrast, convalescent plasma infusion was significant in the univariate analysis but was not independently associated with the odds of weaning (table 3).

### 2.5 Comparison of Combined ECMO Therapy and IMV-only Therapy Using Propensity Score-matched Analysis

Recent EOLIA study questioned the necessity for ECMO to rescue ARDS<sup>[11]</sup>. We then evaluated the effectiveness of ECMO support (ECMO group) and IMV-only support (IMV-only group) for the treatment of COVID-19-related ARDS. To avoid confounding variables that might affect the outcomes of critically ill patients, we performed a propensity score-matched analysis (fig. 1). Moribund patients who died within 24 h after ECMO or IMV initiation were excluded (fig. 1). We matched 70 patients from the IMV-only group with 70 patients from the ECMO group at a ratio of 1:1 in the propensity score-matched analysis (table 4). The crude 120-day in-hospital mortality rates after ICU admission were 74.3% in the ECMO group and 80.0% in the IMV-only group (table 4). After applying an adjusted mixed-effect Cox model with the hospital site as a random effect and adjusting the imbalanced



**Table 3 Univariate and multivariate logistic regression analysis of variables between weaned and non-weaned groups**

Parameters	Weaned (n=23)	Non-weaned (n=56)	Univariate logistic analysis		Multivariate logistic analysis	
			OR (95% CI)	P value*	OR (95% CI)	P value†
Clinical characteristics on hospital admission						
Age ≥60, years	8/23 (34.8%)	33/56 (58.9%)	0.372 (0.135–1.020)	0.055	0.095 (0.008–1.174)	0.067
Female	8/23 (34.8%)	23/56 (41.1%)	0.765 (0.279–2.101)	0.603		
Major comorbidities	11/23 (47.8%)	28/56 (50.0%)	0.917 (0.347–2.422)	0.861		
Hypertension	7/23 (30.4%)	23/56 (41.1%)	0.628 (0.223–1.768)	0.378		
Diabetes mellitus	6/23 (26.1%)	10/56 (17.9%)	1.624 (0.512–5.153)	0.411		
Laboratory examinations on ICU admission						
Lymphocyte count ≤0.5×10 <sup>9</sup> /L	5/23 (21.7%)	26/56 (46.4%)	0.321 (0.104–0.984)	0.047	0.021 (0.001–0.756)	0.035
Platelet <LLN, ×10 <sup>9</sup> /L	5/23 (21.7%)	20/56 (35.7%)	0.500 (0.161–1.550)	0.230		
C-reactive protein ≥100 mg/L	11/22 (50.0%)	24/55 (43.6%)	1.292 (0.479–3.480)	0.613		
Total bilirubin >ULN, μmol/L	3/23 (13.0%)	17/56 (30.4%)	0.344 (0.090–1.315)	0.119		
LDH >1.5×ULN, U/L	18/20 (90.0%)	43/51 (84.3%)	1.674 (0.323–8.669)	0.539		
NT-proBNP or BNP >ULN, pg/mL	11/23 (47.8%)	23/55 (41.8%)	1.275 (0.480–3.391)	0.626		
Creatinine >ULN, μmol/L	5/23 (21.7%)	16/56 (28.6%)	0.694 (0.220–2.189)	0.534		
D-dimer >4×ULN, mg/L	12/23 (52.2%)	42/55 (76.4%)	0.338 (0.121–0.944)	0.038	0.020 (0.001–0.405)	0.011
Serum IL-6 ≥10×ULN, pg/mL	9/20 (45.0%)	17/42 (40.5%)	1.203 (0.411–3.525)	0.736		
Scores on ICU admission						
Murray score ≥3	16/23 (69.6%)	42/56 (75.0%)	0.762 (0.260–2.231)	0.620		
SOFA score ≥8	12/20 (60.0%)	26/48 (54.2%)	1.269 (0.440–3.662)	0.659		
24-h before ECMO initiation						
Highest PaO <sub>2</sub> /FiO <sub>2</sub> <80, mmHg	4/15 (26.7%)	17/39 (43.6%)	0.471 (0.127–1.740)	0.259		
Highest PaCO <sub>2</sub> >60, mmHg	2/15 (13.3%)	25/44 (56.8%)	0.117 (0.024–0.581)	0.009	0.015 (0.001–0.368)	0.010
Lowest arterial pH <7.30	3/15 (20.0%)	15/44 (34.1%)	0.483 (0.118–1.980)	0.312		
Highest arterial lactic acid >ULN, mmol/L	9/15 (60.0%)	18/33 (54.5%)	1.250 (0.362–4.318)	0.724		
Treatments during ICU stay						
Requirement of inotropes or vasopressors before IMV	7/23 (30.4%)	15/56 (26.8%)	1.196 (0.411–3.476)	0.743		
Prone position ventilation during ICU stay	11/23 (47.8%)	20/56 (35.7%)	1.650 (0.617–4.414)	0.319		
Received tracheotomy	14/23 (60.9%)	8/56 (14.3%)	9.333 (3.036–28.695)	0.000	29.021 (1.458–577.797)	0.027
Convalescent plasma	10/23 (43.5%)	6/56 (10.7%)	6.410 (1.966–20.900)	0.002	18.795 (0.108–3267.396)	0.265
Durations						
Intubation to ECMO initiation ≥7, days	4/22 (18.2%)	16/56 (28.6%)	1.800 (0.527–6.151)	0.348		

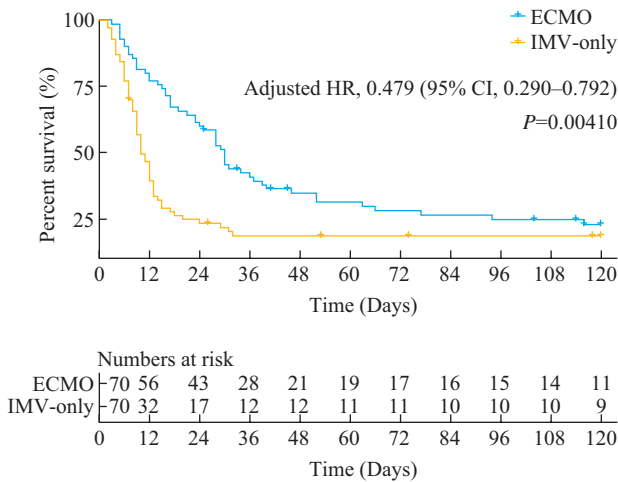
Data are n (%). Upper limit of normal (ULN) and lower limit of normal (LLN) were defined according to the normal ranges of tests in each hospital. LDH: lactate dehydrogenase; NT-proBNP: N-terminal pro-brain natriuretic peptide; BNP: brain natriuretic peptide; IL-6: interleukin-6; SOFA: sequential organ failure assessment; PaO<sub>2</sub>/FiO<sub>2</sub>: partial pressure of arterial oxygen/fraction of inspiration oxygen; PaCO<sub>2</sub>: partial pressure of arterial carbon dioxide; OR: odds ratio; CI: confidence interval. \*P values were calculated based on univariate logistic regression models. †P values were calculated based on multivariate logistic regression models.

parameters, the results demonstrated a significantly lower risk of 120-day in-hospital mortality after ICU admission in the ECMO group (adjusted HR, 0.479; 95% CI, 0.290–0.792,  $P=0.00410$ ) as compared with that in the IMV-only group (fig. 3).

### 3 DISCUSSION

Herein, we report the descriptive data collected from 7 ECMO centers in Wuhan during the COVID-19 pandemic, which included almost all of the ECMO cases in Wuhan. To the best of our knowledge, this is the largest cohort of ECMO-treated patients that has been reported since the COVID-19 outbreak. Altogether, 94

patients received ECMO treatment. Among them, 27 patients were successfully weaned from ECMO, 15 were fully recovered and discharged from the hospital, 8 remained in hospital, and 65 died. The crude in-hospital mortality rate of patients who received ECMO therapy in Wuhan during the COVID-19 pandemic was 73.9%. This rate is in contrast to a previous study that reported a mortality rate of 32% during the H1N1 pandemic in 2009<sup>[2]</sup> and another study that reported a mortality rate of 65% during the Middle East respiratory syndrome pandemic in 2012<sup>[12]</sup>. The relatively high mortality rate in this study might be attributable to the following factors. (1) Expert ECMO centers and experienced ECMO specialists were lacking during the



**Fig. 3** Kaplan-Meier curves of the cumulative probability of in-hospital mortality during the 120-day follow-up period after ICU admission (the primary endpoint) in the ECMO cohort and propensity-score matched IMV-only cohort. The blips on the curve indicate the censored cases during the 120-day follow-up period. An adjusted mixed-effect Cox model using the hospital site as a random effect was used to detect the hazard ratio (HR) regarding the primary endpoint. *P* value was calculated based on mixed-effect Cox model. HR, hazard ratio; CI, confidence interval

COVID-19 outbreak, especially during the early phases when medical systems were overwhelmed. From January 24 to March 8, 2020, multiple medical teams and additional ECMO resources were dispatched from all over the nation to Wuhan to combat COVID-19. On February 2, a stringent quarantine policy was implemented, resulting in a decreasing trend in the daily number of confirmed cases thereafter<sup>[13]</sup>. At that time, the shortages of medical resources began to be alleviated, especially in the ICUs. However, ECMO as a salvage therapy might not have been effective in critically ill patients for whom timely treatment had been delayed, leading to substantial irreversible hypoxemic injuries to various organs. (2) Knowledge regarding the etiology, progression dynamics, and effective therapies was scarce during the early phases of the COVID-19 outbreak. Deaths related to this limited experience were reflected by an ECMO-related mortality rate that approached 92% in January 2020. (3) Expertise in ECMO varied among hospitals, which led to significant 3- to 4-fold differences in successful weaning between hospitals (data not shown). Hence, centralized management of multidisciplinary care at high-volume ECMO therapy centers would be ideal.

**Table 4** Characteristics of patients receiving ECMO support and IMV-only support after propensity score matching

Parameters	ECMO (n=70)	IMV-only (n=70)	SD value*
<b>Clinical characteristics on hospital admission</b>			
Age ≥60, years	36/70 (51.4%)	43/70 (61.4%)	0.203
Female gender	28/70 (40.0%)	28/70 (40.0%)	<0.001
Any comorbidity	35/70 (50.0%)	36/70 (51.4%)	0.029
<b>Major comorbidities</b>			
Hypertension	28/70 (40.0%)	23/70 (32.9%)	0.149
Diabetes mellitus	15/70 (21.4%)	16/70 (22.9%)	0.034
Chronic lung disease	0/70 (0.0%)	3/70 (4.3%)	0.299
Cardiovascular disease (excluding hypertension)	7/70 (10.0%)	4/70 (5.7%)	0.160
Neurological disease	2/70 (2.9%)	1/70 (1.4%)	0.099
Chronic liver disease	2/70 (2.9%)	2/70 (2.9%)	<0.001
Chronic renal disease	0/70 (0.0%)	2/70 (2.9%)	0.243
<b>Laboratory examinations on ICU admission</b>			
Leukocyte count >10×10 <sup>9</sup> /L	47/70 (67.1%)	47/68 (69.1%)	0.042
Lymphocyte count ≤0.8×10 <sup>9</sup> /L	47/70 (67.1%)	47/68 (69.1%)	0.042
Platelet <LLN×10 <sup>9</sup> /L	22/70 (31.4%)	16/70 (22.9%)	0.194
C-reactive protein >100 mg/L	30/69 (43.5%)	23/57 (40.4%)	0.063
Total bilirubin >ULN, μmol/L	16/70 (22.9%)	19/67 (28.4%)	0.126
ALT >ULN, U/L	28/70 (40.0%)	24/66 (36.4%)	0.075
LDH >1.5×UNL, U/L	53/63 (84.1%)	59/66 (89.4%)	0.156
NT-proBNP or BNP >ULN, pg/mL	29/67 (43.3%)	26/60 (43.3%)	0.001
cTnI >ULN, pg/mL	28/67 (41.8%)	15/63 (23.8%)	0.390
Creatinine >ULN, μmol/L	17/70 (24.3%)	13/66 (19.7%)	0.111
D-dimer >4×ULN, mg/L	48/69 (69.6%)	46/61 (75.4%)	0.131
Serum IL-6 ≥10×ULN, pg/mL	22/55 (40.0%)	22/32 (68.8%)	0.603
PaO <sub>2</sub> <80, mmHg	27/59 (45.8%)	19/55 (34.6%)	0.230
PaCO <sub>2</sub> , mmHg			0.195
>50	22/59 (37.3%)	25/54 (46.3%)	
<35	10/59 (17.0%)	9/54 (16.7%)	

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Parameters	ECMO (n=70)	IMV-only (n=70)	SD value*
Arterial pH			0.667
>7.45	18/55 (32.7%)	13/21 (61.9%)	
<7.35	12/55 (21.8%)	4/21 (19.1%)	
Arterial lactic acid >ULN, mmol/L	29/48 (60.4%)	25/38 (65.8%)	0.112
Scores on ICU admission			
Murray score	3.00 (2.70–3.30)	3.33 (3.00–3.67)	0.432
Missing data	0/70 (0.0%)	0/70 (0.0%)	
SOFA score	8.00 (6.00–10.00)	8.00 (7.00–9.00)	0.026
Missing data	9/70 (12.9%)	21/70 (30.0%)	
Treatments during ICU stay			
CRRT	48/70 (68.6%)	27/70 (38.6%)	0.631
Prone position ventilation	28/70 (40.0%)	24/70 (34.3%)	0.118
Tracheotomy	21/70 (30.0%)	8/70 (11.4%)	0.471
Convalescent plasma	16/70 (22.9%)	3/70 (4.3%)	0.563
Outcomes			
Weaning of mechanical ventilation	13/70 (18.6%)	11/70 (15.7%)	0.076
Survival to hospital discharge	11/70 (15.7%)	10/70 (14.3%)	0.040
120-day all-cause mortality after ICU admission during hospitalization	52/70 (74.3%)	56/70 (80.0%)	0.136
Under hospitalization	7/70 (10.0%)	4/70 (5.7%)	0.160
Durations			
Symptom onset to first admission, days	14.00 (8.25–21.75)	10.00 (7.00–14.00)	0.520
Symptom onset to intubation, days	20.00 (15.25–25.75)	17.00 (14.00–23.00)	0.418
Intubation to tracheotomy, days	25.00 (16.00–29.00)	13.00 (11.00–31.00)	0.342
Cumulative IMV support, days	25.00 (13.25–37.00)	7.50 (5.00–12.00)	1.001
Length of stay			
ICU stay, days	28.00 (15.25–44.00)	10.00 (7.00–16.50)	0.877
Hospital stay, days	32.50 (16.25–52.25)	17.50 (10.00–26.00)	0.775

Data are median (IQR) or *n* (%). Upper limit of normal (ULN) and lower limit of normal (LLN) were defined according to the normal ranges of tests in each hospital. ALT: alanine transaminase; LDH: lactate dehydrogenase; NT-proBNP: N-terminal pro-brain natriuretic peptide; BNP: brain natriuretic peptide; cTnI: cardiac troponin I; IL-6: interleukin-6; PaO<sub>2</sub>: partial pressure of arterial oxygen; PaCO<sub>2</sub>: partial pressure of arterial carbon dioxide; CRRT: continuous renal replacement therapy; IMV: invasive mechanical ventilation. Age, gender, comorbidities (hypertension, diabetes mellitus), and laboratory examinations on ICU admission (lymphocyte count, C-reactive protein, creatinine, total bilirubin, ALT, LDH, NT-proBNP or BNP, and D-dimer) were used for propensity score matching. \*Standardized difference (SD) values were calculated to compare the mean of baseline covariate between ECMO and IMV-only groups.

During the later phases of the COVID-19 pandemic in Wuhan, ECMO patients were transferred between hospitals, leading to improvements in survival.

Our study revealed that a pre-ECMO PaCO<sub>2</sub> >60 mmHg was an independent risk factor for a failure to wean from ECMO. This result was consistent with previous studies in which hypercapnia was identified as a marker of poor prognosis related to ECMO therapy<sup>[14, 15]</sup>. Moreover, the pre-ECMO PaCO<sub>2</sub> was included in the Respiratory ECMO Survival Prediction-Score model used to predict the outcome of ECMO therapy<sup>[16]</sup>. As the COVID-19-induced ARDS progresses, disrupted vasoregulation and massive alveolar microthrombi increase the alveolar dead space and cause a high ventilation-perfusion ratio<sup>[17]</sup>. Additionally, sputum arising from proteinaceous and fibrinous exudates, pulmonary hemorrhage, cell debris, and nosocomial infection all contribute to airway obstruction and lobular consolidation<sup>[18]</sup>. Therefore, hypercapnia is an indicator of progression

from type 1 to type 2 respiratory failure and a potential signal of ventilation disorders and disease severity. These phenomena suggest that the reversibility of a COVID-19 patients with severe hypercapnia should be evaluated cautiously before ECMO implementation. In contrast, the implementation of ECMO at an early stage before hypercapnia may lead to a better prognosis.

Zhang *et al* reported that a D-dimer concentration of 4×ULN was the cutoff value for predicting the in-hospital death of a COVID-19 patient<sup>[19]</sup>. Our results showed that this D-dimer cutoff was independently correlated with decreased odds of weaning from ECMO, consistent with recent findings suggesting that an elevated D-dimer level predicts a poor outcome in COVID-19 patients<sup>[19–21]</sup>. Moreover, Tang *et al* demonstrated a correlation of prophylactic heparin use with reduced mortality in patients with D-dimer levels exceeding 3.0 mg/L<sup>[21]</sup>. D-dimer is a rational marker for disease severity and prognosis because (1) an elevated D-dimer level is caused mainly by inflammation

associated with COVID-19 and subsequent coagulation activity<sup>[19]</sup>, and (2) massive microvascular thrombosis formation in the alveolar capillaries secondary to vasculitis can trigger ARDS during COVID-19<sup>[18, 19]</sup>.

We and other researchers consistently noted that lymphopenia was an indicator of disease severity and a substantial predictor of an unfavorable outcome of COVID-19<sup>[17, 20]</sup>. Although the underlying mechanisms remain to be elucidated, the main reason likely involves the ability of COVID-19 to induce the exhaustion of lymphocytes, particularly T lymphocytes<sup>[22]</sup>. As lymphocyte repletion is pivotal in the recovery from COVID-19, ECMO-induced lymphopenia and impaired immunity should be carefully evaluated during treatment<sup>[23]</sup>.

Supportive care remains the mainstay of COVID-19 treatment in the absence of proven effective drugs. Most patients on ECMO also received prolonged IMV support, which requires meticulous airway management. In these patients, tracheotomy would reduce the need for sedation, enable oral intake, facilitate the efficient suction of secretions, allow for early rehabilitation, and facilitate weaning from IMV. We demonstrated that patients who received a tracheotomy had independently increased odds of ECMO weaning, even in the presence of greatly delayed therapy (median duration: 25 days post-intubation). Prolonged intubation and associated sedation would inevitably render the patient vulnerable to ventilator-associated pneumonia, which would further exacerbate the disease. The observed high mortality rate in the present study may be partially ascribed to the delay in tracheotomy. This delay may be attributable to (i) concerns about tracheotomy-provoked aerosol-mediated transmission due to a lack of knowledge about the transmission dynamics of SARS-CoV-2 during the early phases of the pandemic and (ii) concerns about uncontrollable bleeding due to heparinization. In fact, tracheotomy might be considered before ECMO initiation. Otherwise, the anticoagulation intensity should be reduced, and deep anesthesia would be required at the time of tracheotomy during an ECMO run<sup>[6]</sup>.

Our propensity score-matched analysis revealed that critically ill COVID-19 patients who received ECMO had a better survival outcome than those who received only IMV. Here, ECMO was frequently used as a last resort when IMV therapy failed to provide oxygenation support, and not as a prophylactic therapy. Our findings were consistent with those of the CESAR study<sup>[25]</sup> and an analysis of the application of ECMO for H1N1-related ARDS<sup>[3]</sup>. IMV strategies such as a higher PEEP, lung recruitment maneuvers, and a prone position might help during the early phase of refractory hypoxemia. However, most patients with COVID-19-related ARDS require a high driving pressure to

maintain satisfactory oxygenation and overcome a low lung compliance, which increases the risk of ventilator-induced lung injury. Although ECMO is expertise- and cost-intensive and carries a higher likelihood of complications, this option provides a full support for oxygenation and CO<sub>2</sub> removal, enables a “lung rest” ventilatory strategy, and provides time for virus clearance and lung recovery.

Our study has some limitations. First, the retrospective and uncontrolled nature increases the risk of bias in the study. Patients from 7 hospitals were enrolled, and each patient was treated at the discretion of the treating hospital or even the attending physicians, without a consensus or a standard clinical pathway. Second, the respirator parameters (e.g., plateau pressures, tidal volumes, or PEEPs) were not routinely recorded. This limitation prohibited us from evaluating the role of IMV in the outcome of ECMO use. Third, although we included nearly all ECMO patients in Wuhan, the sample size remained relatively small. Therefore, the strength of our findings might be limited.

Our study provides evidence that lymphocytopenia, a higher D-dimer concentration, and pre-ECMO hypercapnia predict a poor outcome of ECMO use in COVID-19 patients. Tracheotomy, even when delayed, could facilitate weaning from ECMO. Compared with IMV-only support, ECMO therapy was associated with a better survival outcome in critically ill patients with COVID-19-induced ARDS.

#### Conflict of Interest Statement

All authors declare no conflict of interest relevant to this study.

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