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Original Article

Venovenous extracorporeal membrane oxygenation for COVID-19 and influenza H1N1 associated acute respiratory distress syndrome: A comparative cohort study in China

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ABSTRACT

Background: Venovenous extracorporeal membrane oxygenation (VV-ECMO) has been demonstrated to be effective in treating patients with virus-induced acute respiratory distress syndrome (ARDS). However, whether the management of ECMO is different in treating H1N1 influenza and coronavirus disease 2019 (COVID-19)-associated ARDS patients remains unknown.

Methods: This is a retrospective cohort study. We included 12 VV-ECMO-supported COVID-19 patients admitted to The First Affiliated Hospital of Guangzhou Medical University, Guangzhou Eighth People's Hospital, and Wuhan Union Hospital West Campus between January 23 and March 31, 2020. We retrospectively included VV-ECMO-supported patients with COVID-19 and H1N1 influenza-associated ARDS. Clinical characteristics, respiratory mechanics including plateau pressure, driving pressure, mechanical power, ventilatory ratio (VR) and lung compliance, and outcomes were compared.

Results: Data from 25 patients with COVID-19 (n=12) and H1N1 (n=13) associated ARDS who had received ECMO support were analyzed. COVID-19 patients were older than H1N1 influenza patients (P=0.004). The partial pressure of arterial carbon dioxide ($PaCO_2$) and VR before ECMO initiation were significantly higher in COVID-19 patients than in H1N1 influenza patients (P <0.001 and P=0.004, respectively). COVID-19 patients showed increased plateau and driving pressure compared with H1N1 subjects (P=0.013 and P=0.018, respectively). Patients with COVID-19 remained longer on ECMO support than did H1N1 influenza patients (P=0.015). COVID-19 patients who required ECMO support also had fewer intensive care unit and ventilator-free days than H1N1.

Conclusions: Compared with H1N1 influenza patients, COVID-19 patients were older and presented with increased $PaCO_2$ and VR values before ECMO initiation. The differences between ARDS patients with COVID-19 and influenza on VV-ECMO detailed herein could be helpful for obtaining a better understanding of COVID-19 and for better clinical management.

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Introduction

The ongoing coronavirus disease 2019 (COVID-19) pandemic resulted in 400 million laboratory-confirmed cases documented globally since December 2019.[1] Approximately 14–20% of COVID-19 patients developed severe illness, while 5% became critical, resulting in high mortality in the early pandemic.[2,3] In patients who developed acute respiratory distress syndrome (ARDS) and in whom conventional therapies failed, venovenous extracorporeal membrane oxygenation (VV-ECMO) was employed. VV-ECMO has become integral to rescue therapy in ARDS patients, particularly when invasive ventilation, prone positioning, and neuromuscular blockade fail to save patients with hypoxemia.[4,5]

According to data from the Extracorporeal Life Support Organization (ELSO), ECMO-supported respiratory failure patients induced by viral infections presented a 63% survival rate between 2015 and 2020, and over 90% of patients were treated with VV-ECMO support.[6] Among patients with influenza admitted to the intensive care unit, 22%–38% of patients received ECMO treatment with a survival rate of up to 72%.[7] In light of the successful use of ECMO in treating ARDS patients with viral infections, ECMO was also well employed as a rescue therapy in COVID-19 patients.[8,9] However, COVID-19-associated ARDS is considered an atypical ARDS.[10,11] The mortality rate in ECMO-supported COVID-19 patients in the early pandemic is about 70%[12] and it is around 50% to date.[13,14] To understand the factors contributing to the different mortality in H1N1 and COVID-19-associated ARDS patients supported by ECMO, detailed comparisons of clinical characteristics and management between ECMO-supported patients with H1N1 and COVID-19 are required.

In the present study, we compared the clinical characteristics, respiratory parameters such as plateau pressure, driving pressure, mechanical power, VR and lung compliance, and outcomes of VV-ECMO-supported patients with H1N1 influenza and those with COVID-19. The findings may raise further insight into applying extracorporeal life support (ECLS) for COVID-19-associated ARDS.

Methods

Patients

This is a retrospective cohort study. We included 12 VV-ECMO-supported COVID-19 patients admitted to The First Affiliated Hospital of Guangzhou Medical University, Guangzhou Eighth People's Hospital, and Wuhan Union Hospital West Campus between January 23 and March 31, 2020. Experts from The First Affiliated Hospital of the Guangzhou Medical University were dispatched to the participating sites for study coordination and oversight. For comparison, 13 patients with H1N1 influenza treated with VV-ECMO at The First Affiliated Hospital of Guangzhou Medical University were included between January 1, 2018, and December 31, 2019. ARDS was diagnosed based on Berlin's definition. [15] The study was approved by the Institutional Review Board of each participating institution (approval number: 202092). This study was conducted in conformity with the Declaration of Helsinki and adhered to data confidentiality principles. The informed consent was waived as it is a retrospective and non-interventional observational study.

Inclusion and exclusion criteria for ECMO support

Based on the Extracorporeal Membrane Oxygenation for Severe Acute Respiratory Distress Syndrome (EOLIA) study[16] and prior experience of treating COVID-19 and H1N1 influenza patients in our centers, the criteria for initiating ECMO support in this study were as follows: (1) Ratio of partial pressure of arterial oxygen (PaO_2) to a fraction of inspired oxygen (FiO_2) (P/F ratio) <80 mmHg for >6 h, or <50 mmHg for >3 h, at FiO_2 ≥0.8; and (2) arterial blood pH <7.30 with the partial pressure of arterial carbon dioxide ($PaCO_2$) ≥60 mmHg for >6 h with optimized ventilator settings (respiratory rate increasing to 30 breaths/min, plateau pressure of ≤30 cmH_2O despite ventilator optimization [defined as FiO_2 ≥0.80]), tidal volume of 6 mL/kg predicted body weight (PBW), and optimal positive end-expiratory pressure (PEEP). Physicians were encouraged to use neuromuscular blockers (NMBs) and prone positioning, but a recruitment maneuver was not recommended. ECMO was discouraged in patients aged >80 years or those with irreversible neurological pathology, a malignant disease anticipating poor long-term survival, or uncontrolled active bleeding. At least two intensive care unit (ICU) consultants decided to initiate ECMO, and was re-evaluated every 6–8 h.

ECMO-related management

All patients received percutaneous cannulation using the Seldinger technique. Briefly, a type 21 or 23 French cannula (BE-PVL 2155 or 2355, Maquet Cardiopulmonary GmbH, Rastatt, Germany) was placed in the femoral vein for drainage, and a 17 or 19 French cannula (BE-PAS 1715 or 1915, Maquet Cardiopulmonary GmbH, Rastatt, Germany) was inserted into the jugular vein for return. ECMO was maintained using ROTAFLOW or CARDIOHELP (Maquet Cardiopulmonary GmbH, Rastatt, Germany) with circuit BE-PLS 2050 or HLS Set Advanced 7.0 (Maquet Cardiopulmonary GmbH, Rastatt, Germany). Ventilator parameters were set based on the following VV-ECMO protocol employed at our facility: plateau pressure <27 cmH_2O, driving pressure <15 cmH_2O, PEEP 8–10 cmH_2O, and FiO_2 40–60%. Weaning from ECMO was initiated when patients showed consistent improvement in clinical parameters, and radiological studies increased pulmonary compliance. ECMO was withdrawn if PaO_2 >70 mmHg, $PaCO_2$ <50 mmHg, pH >7.35 at FiO_2 <60%, PEEP <10 cmH_2O, tidal volume >6 mL/kg PBW, and inspiratory plateau pressure <30 cmH_2O. All the patients received continuous intravenous heparin according to the test-activated partial thromboplastin time (APTT) test results. Target APTT was between 1 and 1.5 times the upper limit of normal. If bleeding occurred, the APTT was normalized, blood products were given as needed, and heparin was stopped when massive bleeding developed.

General management

ARDS patients were managed by Surviving Sepsis Guidelines[17] and ARDS management protocol.[18] Patients with H1N1 influenza were treated with the anti-viral medication oseltamivir. Patients with COVID-19 were treated according to

the Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia (version 7.0).[19] All respiratory parameters were measured without spontaneous breathing under volume control mode ventilation, including plateau pressure, peak pressure, Driving pressure, and PEEP. In patients without neuromuscular blockade, the practice was to give a small amount of remifentanil or sufentanil to temporarily control spontaneous breathing.

Outcomes

Outcomes included 90-day mortality, ventilator- and ICU-free days, and incidence of complications. Definitions of ECMO-related complications and outcomes were made according to definitions in the ELSO registry.[20]

Data collection

Data were retrospectively collected from the ICU patient database, including demographic characteristics, underlying diseases, comorbidities, laboratory tests, ECMO-related parameters, microbiologic findings, complications, and clinical outcomes. Ventilatory ratio (VR) was defined as (minute ventilation [mL/min] × $PaCO_2$ [mmHg])/(PBW[kg] × 100 [mL/min] × 37.5 [mmHg]).[21] Mechanical power (J/min) was calculated as (0.098 × tidal volume [L] × respiratory rate × [peak pressure – 0.5 × driving pressure]).[22] The severity of illness was rated using the Sequential Organ Failure Assessment (SOFA) and Acute Physiology and Chronic Health Evaluation II (APACHE II) scores on ECMO initiation. The prognostic ECMO score for respiratory failure was also reported.[23]

Statistical analysis

Medians and ranges (interquartile ranges [IQRs]) are used to express continuous variables and were compared using the Wilcoxon rank sum test. Categorical variables are shown as counts and percentages. No imputation was made for missing data. Proportions for categorical variables were compared using the Fisher exact test. All statistical analyses were performed using the R software package, version 3.5.1 (the R Foundation). The significance threshold was set at a two-sided *P*-value <0.05. The cumulative percentage curve was calculated using the "survival" and "survminer" functions in the R package, and the line was terminated on day 90.

Results

Baseline characteristics

Between January 23 and March 31, 2020, 156 adult patients with COVID-19 were admitted to our ICUs. Among these, 113 patients were male, 106 patients required invasive mechanical ventilation, and 14 patients received ECMO. One patient was transferred from another hospital and was initiated with VV-ECMO 9 days before the transfer. Two COVID-19 patients with coronary heart disease who received venous-arterial ECMO were not included in the study. All the other 12 COVID-19 patients received VV-ECMO due to severe ARDS. Thirteen H1N1 influenza patients who received VV-ECMO were included for comparison. Table 1 summarizes the general characteristics of the two groups of patients. Compared with H1N1 influenza patients, COVID-19 patients were significantly older (median [IQR]: 66 [56–72] years *vs.* 41 [32-44] years, *P*=0.004) and had a higher rate of hypertension (50.0% [6/12] *vs.* 15.4% [2/13], *P*=0.097). There was no significant difference in gender, body mass index, and other comorbidities between the two groups.

Respiratory parameters at 6 h before ECMO initiation and during ECMO support

Patient parameters at 6 h before ECMO initiation are detailed in Table 2. Patients with COVID-19 presented with elevated levels of $PaCO_2$ (65.4 [60.4–72.8] mmHg *vs.* 42.7 [39.9–46.4] mmHg, *P* <0.001) and bicarbonate (31.5 [27.7–38.8] mmol/L *vs.* 24.1 [21.6–28.7] mmol/L, *P*=0.049), but not higher pH values, compared with patients with H1N1 influenza. P/F in COVID-19 patients was higher than that in H1N1 influenza patients (96.67 [79.45–105.89] mmHg *vs.* 77.70 [62.55–81.55] mmHg, *P*=0.101), but this difference was not statistically significant. COVID-19 patients also had higher levels of plateau pressure (30[27-32] cmH_2O *vs.* 26[24-29] cmH_2O, *P*=0.013), driving pressure (21[17-27] cmH_2O *vs.* 16[14-19] cmH_2O, *P*=0.018), and VR (3.06 [2.30–3.22] *vs.* 1.57 [1.50–2.14], *P*=0.004) compared with H1N1 influenza patients. In addition, COVID-19 patients tended to have higher mechanical power than H1N1 patients before ECMO initiation, though the difference was not significant (20.40 [15.07–30.87] *vs.* 16.91 [13.57–22.29], *P*=0.053). Meanwhile, peak pressure was increased in COVID-19 patients as well (34[30-35] cmH_2O *vs.* 30[26-34] cmH_2O, *P*=0.247). However, tidal volume, minute ventilation, and PEEP were comparable between the two groups. There were no significant differences in mean arterial blood pressure and the use of vasoactive drugs between the two groups, while heart rate tended to be lower in COVID-19 patients (94 [78–116] beats/min *vs.* 121 [102–137] beats/min, *P*=0.057). The median blood flow and the sweep gas rate within 72 h of ECMO initiation are presented in Supplementary Table S1. Within 72 h of ECMO initiation, the median blood flow in COVID-19 patients was 4.19 (3.97–4.20) L/min, and the sweep gas rate was 2.33 (1.83–3.00) L/min. Median tidal volume was 6.00 (3.83–6.83) mL/kg, PEEP was 9.33 (8.67–10.00) cmH_2O, plateau pressure was 24 (18.67–26.67) cmH_2O, and driving pressure was 14.67 (12.00–20.00) cmH_2O. These parameters were not significantly different from those of H1N1 patients.

Patient characteristics within 24 h before ECMO initiation

Twenty-four hours before ECMO initiation, patients with COVID-19 showed markedly prolonged prothrombin time (16.4 [15.9–18.6] s *vs.* 15.0 [14.6–15.8] s, *P*=0.023) and lower lactate dehydrogenase levels (363.4 [343.8–477.7] U/L *vs.* 788.0 [624.0–1288.0] U/L, *P*=0.002) compared with H1N1 influenza patients. However, the two groups had no significant difference in the ranks of fibrinogen, D-dimer, or the remaining laboratory parameters. APACHE II, SOFA, and RESP scores did not differ significantly between the two groups.

Conjunctive therapy before ECMO

Patients with COVID-19 received a variety of antiviral treatments; 54.5% (6/11) were given lopinavir/ritonavir, 54.5%

Table 1
General characteristics of patients with COVID-19 and H1N1.

Demographics and comorbidities	Total (*n*=25)	COVID-19 (*n*=12)	H1N1 influenza (*n*=13)	*P*-value
Age (years)	56 (37–66)	66 (56–72)	41 (32–44)	0.004
Body mass index (kg/m^2)	22.76 (20.90–24.70)	22.31 (20.88–24.69)	23.51 (22.04–24.80)	0.550
Sex				
Female	10 (40.0)	4 (33.3)	6 (46.2)	0.688
Male	15 (60.0)	8 (66.7)	7 (53.8)	0.688
Comorbidities				
Hypertension	8 (32.0)	6 (50.0)	2 (15.4)	0.097
Diabetes	7 (28.0)	4 (33.3)	3 (23.1)	0.673
Coronary artery disease	5 (20.0)	2 (16.7)	3 (23.1)	1.000
Hypercholesterolemia	1 (4.0)	0 (0)	1 (7.7)	1.000
Chronic obstructive pulmonary disease	2 (8.0)	1 (8.3)	1 (7.7)	1.000
Chronic kidney disease	1 (4.0)	0 (0)	1 (7.7)	1.000
Chronic liver disease	1 (4.0)	1 (8.3)	0 (0)	0.480
Smoking history	5 (20.0)	3 (25.0)	2 (15.4)	0.920

Data are presented as median (Interquartile range) or *n* (%).
P-values: COVID-19 *vs.* H1N1 influenza.
COVID-19: Coronavirus disease 2019.

(6/11) ribavirin, and 27.3% (3/11) arbidol. Oseltamivir was administered to all the patients with H1N1. Higher numbers of patients who received systemic corticosteroids (81.8% [9/11] *vs.* 36.4% [4/11], *P*=0.081) and NMBs (90.9% [10/11] *vs.* 54.6 [6/11], *P*=0.149) were found in COVID-19 compared with H1N1. Additionally, the duration of symptom onset and intubation to ECMO support were considerably more significant in patients with COVID-19 than in H1N1 patients (8[4-14] days *vs.* 2[1-6] days, *P*=0.019) (Table 2).

Patient outcomes and complications

At 90 days after ECMO initiation, five COVID-19 patients had weaned from ECMO successfully, and six COVID-19 patients had died. The one who was still on ECMO support on day 90 was successfully weaned on day 111 of ECMO support. All the COVID-19 patients who successfully weaned from ECMO made it to hospital discharge. When compared with H1N1 influenza patients, the percentage of patients successfully weaned from ECMO within 90 days was significantly lower in COVID-19 patients (41.7% [5/12] *vs.* 92.3% [12/13], *P*=0.011) (Table 3). None of the COVID-19 and H1N1 patients required re-initiation of ECMO. A cumulative curve showing successful weaning from ECMO is provided in Figure 1. The 90-day mortality rate was not statistically different between the two groups (COVID-19 group 50.0% [6/11] *vs.* H1N1 group 23.1% [3/13], *P*=0.226). Within the 90-day period, patients with COVID-19 showed a significantly shorter duration of ventilator-free days (0 [0–0] days *vs.* 54 [0–63] days, *P*=0.002) and ICU-free days (0 [0–0] days *vs.* 40 [0–60] days, *P*=0.005) compared with H1N1 influenza patients. Among those who survived to day 90, patients with COVID-19 (*n*=6) had a significantly longer duration of ECMO support compared with H1N1 influenza patients (*n*=10) (36[34-70] days *vs.* 14[7-23] days, *P*=0.015).

More COVID-19 patients developed hemorrhage-related (91.7% [11/12] *vs.* 69.2% [9/13], *P*=0.322) and thrombotic (75.0% [9/12] *vs.* 23.1% [3/13], *P*=0.017) complications. No difference in the incidence of ECMO-related barotrauma between the two groups was observed. Two COVID-19 patients developed neurological complications: one developed cerebral infarction and was weaned from ECMO on day 70, while the other developed hemorrhagic shock and brain death. More

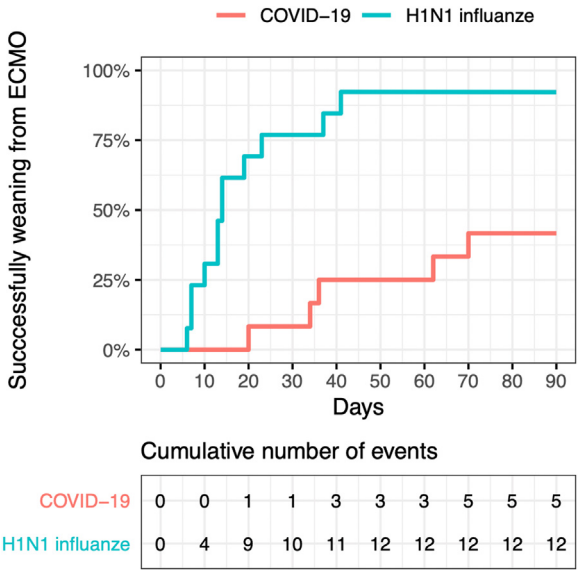

Figure 1. A cumulative curve shows successful weaning from ECMO. The green curve rose more rapidly and ended at a higher point than the red curve.
COVID-19: Coronavirus disease 2019; ECMO: Extracorporeal membrane oxygenation.

COVID-19 patients had infection-related complications (91.7% [11/12] *vs.* 30.8% [4/13], *P*=0.004), including more ventilator-associated pneumonia (58.3% [7/12] *vs.* 15.4% [2/13], *P*=0.041) (Table 3).

Discussion

Our retrospective clinical study showed that compared with ECMO-supported patients with H1N1 influenza, patients with COVID-19 were older and presented with increased $PaCO_2$ and VR values before ECMO initiation and had a longer time from symptom onset/mechanical ventilation to ECMO initiation. The percentage of COVID-19 patients weaned from ECMO was lower than that of H1N1 patients. COVID-19 patients also had fewer ICU- and ventilator-free days and longer ECMO treatment intervals among survivors. Overall, our findings are similar to the studies comparing outcomes of COVID-19 and H1N1 influenza

Table 2
Characteristics of patients before initiation of ECMO*.

Characteristics	Total (*n*=22)	COVID-19 (*n*=11)	H1N1 influenza (*n*=11)	*P*-value
Within 6 h before ECMO initiation				
pH	7.34 (7.28–7.39)	7.34 (7.28–7.36)	7.39 (7.28–7.47)	0.279
PaO_2 (mmHg)	77.9 (64.6–83.2)	81.0 (67.4–84.9)	77.7 (62.6–81.6)	0.439
$PaCO_2$ (mmHg)	53.7 (43.3–69.1)	65.4 (60.4–72.8)	42.7 (39.9–46.4)	<0.001
Bicarbonate (mmol/L)	27.7 (23.1–33.9)	31.5 (27.7–38.8)	24.1 (21.6–28.7)	0.049
P/F ratio (mmHg)	80.40 (64.60–100.37)	96.67 (79.45–105.89)	77.70 (62.55–81.55)	0.101
Lactate (mmol/L)	2.14 (1.66–3.01)	2.10 (1.74–2.91)	2.18 (1.65–2.94)	0.948
Plateau pressure (cmH_2O)	28 (26–30)	30 (27–32)	26 (24–29)	0.013
Peak pressure (cmH_2O)	31 (29–35)	34 (30–35)	30 (26–34)	0.247
Driving pressure (cmH_2O)	18 (16–22)	21 (17–27)	16 (14–19)	0.018
PEEP (cmH_2O)	9 (7–10)	9 (5–10)	10 (7–11)	0.303
Tidal volume (mL/kg of PBW)	6.35 (5.86–6.91)	6.30 (6.20–6.85)	6.37 (5.57–6.85)	0.949
Minute ventilation (L/min)	9.1 (8.1–10.4)	10.0 (8.9–10.5)	8.2 (7.8–9.4)	0.101
VR	2.19 (1.68–3.08)	3.06 (2.30–3.22)	1.57 (1.50–2.14)	0.004
Mechanical power	18.65 (13.57–30.87)	20.40 (15.07–30.87)	16.91 (13.57–22.29)	0.053
Respiratory-system compliance (mL/cmH_2O)	21.06 (16.50–24.99)	17.71 (15.66–23.79)	22.13 (18.55–24.77)	0.293
Respiratory rate (beats/min)	23 (20–25)	25 (22–25)	20 (20–25)	0.063
Heart rate (beats/min)	102 (87–124)	94 (78–116)	121 (102–137)	0.057
Mean arterial pressure (mmHg)	74.50 (56.75–89.75)	89.00 (49.17–98.33)	73.00 (61.50–75.67)	0.332
Use vasopressor	17 (77.27)	9 (81.82)	8 (72.73)	1.000
Use of norepinephrine	16 (72.73)	9 (81.82)	7 (63.64)	0.635
Dose of norepinephrine (μg/kg/min)	0.32 (0.10–0.58)	0.12 (0.05–0.57)	0.35 (0.20–0.55)	0.560
Within 24 h before ECMO initiation				
White blood cell ($\times10^9$/L)	10.7 (7.0–14.1)	9.9 (8.2–15.5)	11.6 (7.1–13.6)	0.870
Lymphocyte ($\times10^9$/L)	0.6 (0.4–0.7)	0.7 (0.4–0.7)	0.6 (0.4–0.8)	0.742
Hemoglobin (g/L)	91 (87–97)	91 (87–97)	92 (86–104)	0.411
Platelet ($\times10^9$/L)	146 (81–194)	108 (52–152)	155 (101–257)	0.045
Procalcitonin (ng/mL)	0.16 (0.12–0.25)	0.26 (0.13–1.32)	0.15 (0.12–0.18)	0.101
Fibrinogen (g/L)	3.80 (2.71–5.15)	3.74 (2.64–4.52)	4.34 (2.98–5.96)	0.300
Prothrombin time (s)	15.9 (14.9–16.8)	16.4 (15.9–18.6)	15.0 (14.6–15.8)	0.023
D-dimer (ng/mL)	5502 (2670–10,001)	5940 (2050–10,001)	5502 (4858–8502)	0.895
Lactate dehydrogenase (U/L)	536.5 (366.5–1115.8)	363.4 (343.8–477.7)	788.0 (624.0–1288.0)	0.002
Alanine aminotransferase (U/L)	29.3 (21.2–56.0)	23.9 (17.4–32.6)	43.4 (25.8–58.6)	0.270
Creatinine (μmol/L)	93.7 (59.9–152.5)	67.7 (55.6–123.7)	101.0 (79.5–178.5)	0.224
SOFA score†	11 (9–13)	11 (9–14)	10 (8–13)	0.645
APACHE II score‡	22 (18–28)	22 (18–28)	21 (18–29)	0.805
RESP score§	1 (0–4)	1 (–1 to 2)	4 (0–5)	0.136
Antiviral therapy				
Oseltamivir	11 (50.0)	NA	11 (100)	
Lopinavir/ritonavir	6 (27.3)	6 (54.5)	NA	
Ribavirin	6 (27.3)	6 (54.5)	NA	
Arbidol	3 (13.6)	3 (27.3)	NA	
Conjunctive therapy before ECMO				
Neuromuscular blockade	16 (72.7)	10 (90.9)	6 (54.6)	0.149
Prone positioning	7 (31.8)	3 (27.3)	4 (36.4)	1.000
Glucocorticoids	13 (59.1)	9 (81.8)	4 (36.4)	0.081
Days from intubation to ECMO (days)	4 (2–8)	8 (4–14)	2 (1–6)	0.019
Days from symptom onset to ECMO (days)	16 (11–24)	23 (20–29)	11 (7–15)	0.003

Data are presented as median (Interquartile range) or *n* (%).
P-values: COVID-19 *vs.* H1N1 influenza.
* One COVID-19 patient and two H1N1 patients were transferred after ECMO initiation in other hospitals. The data before ECMO support were incomplete and not included in the analysis.
† Organ failure was assessed using a SOFA score on a scale from 0 to 24, with higher scores indicating increased severity of organ damage.
‡ Scores were obtained using the APACHE II range from 0 to 71, with higher scores indicating increased severity of illness.
§ Scores were obtained using the RESP scoring system in the range of –22 to 25; RESP is a relevant and validated tool to predict survival in patients receiving ECMO for respiratory failure, with higher scores indicating increased expected survival rate.
APACHE II: Acute Physiology and Chronic Health Evaluation II; COVID-19: Coronavirus disease 2019; ECMO: Extracorporeal membrane oxygenation; IQR: Interquartile range; NA: Not available; P/F ratio: The ratio of partial pressure of arterial oxygen to fraction of inspired oxygen;PBW: Predicted body weight; PEEP: Positive end-expiratory pressure; RESP: Respiratory Extracorporeal Membrane Oxygenation Survival Prediction; SOFA: Sequential Organ Failure Assessment; VR: Ventilatory ratio.

patients. Worse outcomes were observed in COVID-19 patients compared with patients with H1N1 influenza.[24–26]

Longer duration from disease onset/hospital or ICU admission/mechanical ventilation to ECMO initiation was found in COVID-19 patients in studies comparing COVID-19 and H1N1 influenza[24–26] and ours. A previous study by Karagiannidis et al.[27] indicated that COVID-19 patients who received ECMO within 3 days after mechanical ventilation initiation had lower mortality than the ones over 3 days. However, the reasons why COVID-19 patients had a longer duration of symptoms onset/ICU admission/mechanical ventilation to ECMO initiation than H1N1 patients and how this fact contributes to mortality remain unclear. Since several researches providing guidance for ECMO management in COVID-19 patients have been published,[28–30] and the main criteria for ECMO initiation are similar to those for traditional ARDS,[16] the decisions of clinicians might not be the significant reason to result in a later ECMO initiation. Instead, the natural course of disease progression should

Table 3
Patients' outcomes on day 90.

Items	Total (*n*=25)	COVID-19 (*n*=12)	H1N1 influenza (*n*=13)	*P*-value
Successful weaning from ECMO	17 (68.0)	5 (41.7)	12 (92.3)	0.011
90-day mortality	9 (36.0)	6 (50.0)	3 (23.1)	0.226
ICU-free days within 90 days	0 (0–40)	0 (0–0)	40 (0–60)	0.005
Ventilator-free days within 90 days	0 (0–54)	0 (0–0)	54 (0–63)	0.002
Renal replacement therapy during ECMO	13 (52.0)	8 (66.7)	5 (38.5)	0.238
Complications				
Bleeding (any)	20 (80.0)	11 (91.7)	9 (69.2)	0.322
Cannulation site	7 (28.0)	5 (41.7)	2 (15.4)	0.202
Gastrointestinal	8 (32.0)	3 (25.0)	5 (38.5)	0.673
Upper airway mucus	2 (8.0)	2 (16.7)	0 (0)	0.220
Intrathoracic	3 (12.0)	2 (16.7)	1 (7.7)	0.593
Intraperitoneal	1 (4.0)	1 (8.3)	0 (0)	0.480
Massive bleeding leading to emergent transfusion	7 (28.0)	5 (41.7)	2 (15.4)	0.202
Deep vein thrombosis	14 (56.0)	9 (75.0)	3 (23.1)	0.017
Barotrauma (any)	13 (52.0)	6 (50.0)	7 (53.9)	1.000
Pneumothorax	11 (44.0)	4 (33.3)	7 (53.9)	0.428
Mediastinal emphysema	4 (16.0)	3 (25.0)	1 (7.7)	0.322
Subcutaneous emphysema	6 (24.0)	3 (25.0)	3 (23.1)	1.000
Neurologic (any)	2 (8.0)	2 (16.7)	0 (0)	0.220
Brain infarction	1 (4.0)	1 (8.3)	0 (0)	0.480
Brain death	1 (4.0)	1 (8.3)	0 (0)	0.480
Infection (any)	15 (60.0)	11 (91.7)	4 (30.8)	0.004
Ventilator-associated pneumonia	9 (36.0)	7 (58.3)	2 (15.4)	0.041
Bloodstream infection	5 (20.0)	4 (33.3)	1 (7.7)	0.160
Intrathoracic infection	3 (12.0)	2 (16.7)	1 (7.7)	0.593
Urine tract infection	3 (12.0)	1 (8.3)	2 (15.4)	1.000

Data are presented as medians (Interquartile range) or *n* (%).
P-values: COVID-19 *vs.* H1N1 influenza.
COVID-19: Coronavirus disease 2019; ECMO: Extracorporeal membrane oxygenation; ICU: Intensive care unit.

be considered. Even symptoms that shortly appeared after Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, dyspnea, and ICU admission often occurred at about 7 days and 10 days after symptom onset in the typical clinical course.[31] Additionally, atypical COVID-19-associated ARDS and pathophysiology changes are different from other respiratory viral infections (e.g., H1N1 influenza, adenovirus, SARS-Cov-1), which may also contribute to the late onset of dyspnea. Besides, the use of multiple respiratory support recommended by COVID-19 guidance,[32] such as awake prone positioning, high flow nasal cannula (HFNC), and non-invasive ventilation, potentially prevents the progression of COVID-19 ARDS patients. An ELSO registry data analysis by Barbaro et al.[13] compared three groups of ECMO-supported patients during the pandemic in 2020 (from January 1 to December 31). Patients treated with ECMO between May 2 and December 31 had more pre-intubation non-invasive ventilation (HFNC, bilevel positive airway pressure, continuous positive airway pressure). Lastly, the early pandemic highly considered ethical issues and concerns about disease transmission in the hospital.

Notably, the COVID-19 patients in the present study had significantly elevated $PaCO_2$ before ECMO initiation compared with H1N1 patients, despite having normal minute ventilation. This finding is consistent with those derived in other studies.[25,26] In several large ECMO-supported COVID-19 cohort studies, an elevated $PaCO_2$ level, which is around 60 mmHg, was noticed.[13,32,33] The causes of CO_2 retention in ARDS patients include ultra-low tidal volume lung protective ventilation, increased CO_2 production, and elevated dead space.[34] As no evidence of insufficient tidal volume/minute ventilation or increased CO_2 production was noticed in the studies,[13,32,33] we looked into evidences of increased dead space. At the beginning of 2020, we reported that CO_2 retention was common in ventilated COVID-19 patients with increased VR.[35] VR is a simple bedside indicator of ventilatory efficiency, which has been shown to be well correlated with dead space. In addition, increased VR is associated with the mortality of ARDS patients.[36] We also calculated VR in the present study and found significantly increased VR in COVID-19 patients compared with those with H1N1. Increased VR was also found in an ECMO-supported French COVID-19 cohort.[32] The increased VR is probably a result of endothelial dysfunction[37] and coagulation disorder[38] caused by SARS-CoV-2 infection. In a systematic review by Hariri et al.[39] diffused alveolar damage (DAD) was found as the predominant histopathologic pattern in patients both with COVID-19 and H1N1 influenza. However, microthrombi were reported more frequently in patients with COVID-19. As we know, thrombosis results from endothelial injury, and endothelial activation causes the attachment of platelets. Thrombosis continuously consumes the coagulation proteins and platelets, leading to thrombocytopenia, prolonged prothrombin time, and coagulation disorders, which is consistent with our observed results. Significant microthrombi in pulmonary vascular might cause a high ventilation/blood flow ratio (V/Q) and increased pulmonary dead space fraction. Taken together, a significant increase in quiet space is critical to developing respiratory failure in critical COVID-19 patients. Therefore, assessments of end-tidal carbon dioxide (CO_2) concentration and titration of ventilation parameters should be considered when managing COVID-19 patients.

Elevated dead space and subsequent hypercapnia are potential risk factors for lung injury. Increased quiet space could result in decreased ventilatory efficiency. As such, higher tidal volume or minute ventilation is required to maintain sufficient physi-

ological alveolar ventilation and normal $PaCO_2$ levels. Higher minute ventilation potentially increases respiratory effort, causing patient-self-induced lung injury (P-SILI).[40,41] When respiratory effort is considered injurious at the bedside, NMBs are often introduced at the bedside. Interestingly, a high proportion of NMB usage was observed in COVID-19-associated ARDS patients. Even in mild COVID-19-associated ARDS ventilated patients, 70–82% were treated by NMBs.[42,43] Although the respiratory effort can be decreased by NMBs, adjustments of ventilator settings are also critical to minimize lung injury. In patients with CO_2 retention, tidal volume is usually increased with increased driving pressure. However, a lower PEEP is often chosen to maintain minute ventilation and treat respiratory acidosis but maintain plateau pressure at a level lower than 30–32 cmH_2O. Meanwhile, such titration can bring adverse effects. One is the increased risk of ventilator-induced lung injury caused by elevated driving pressure, potentially resulting in higher mortality.[44] It is demonstrated in the present study that patients with COVID-19 had higher plateau pressure, driving pressure, and increased mechanical power compared with H1N1 patients, as well as higher mortality. Therefore, for patients with increased CO_2 but not low oxygenation, attempting to increase driving pressure and respiratory rate to enhance CO_2 clearance could increase mechanical power, ultimately leading to worsening lung injury. So, extracorporeal techniques may be used in patients where mechanical ventilation cannot manage hypercapnic acidosis. Furthermore, such strategies may prolong the duration of invasive ventilation and delay ECLS initiation. Since CO_2 retention is common in ventilated COVID-19 patients before ECMO initiation, extracorporeal carbon dioxide removal ($ECCO_2R$) might be feasible for respiratory support for ventilated patients with increased $PaCO_2$. A few studies have already demonstrated the feasibility of CO_2 removal in COVID-19 patients[45,46]; however, whether $ECCO_2R$ is sufficient to reduce mortality in these patients remains to be further investigated.

Data from the ELSO registry[13,47] and others[24,26,32,48] reported that the median age among ECMO-supported COVID-19 patients was 48–60 years, while the median age of ECMO-supported H1N1 patients was 36–53 years.[7,24,26] Age is suggested as a severity and mortality risk factor in COVID-19 patients.[27,49] Fenelli et al.[26] reported that after multivariable adjustment (including age, disease severity, underline diseases, rescue therapies pre-ECMO, and ventilation setting pre-ECMO), mortality in COVID-19 patients was not significantly different compared with H1N1 influenza, suggesting the outcomes of viral infection related ARDS patients probably depend on patient selection rather than the different viral etiology. However, elderly patients (50–80 years old) are more likely to require ICU admission[50] and ECMO support. Even if ethical considerations might affect physicians' decisions during the COVID-19 pandemic,[51] indications of ECMO support for elderly patients with COVID-19 should still be cautiously considered as usual care. To further address this question, more real-world analysis on ECMO-supported COVID-19 patients in elderly patients is required.

Our study has several limitations. First, the study is a retrospective study with a relatively small sample size. Second, the data of the H1N1 cohort crossed 2 years, while the data of the COVID-19 cohort covered only a 2-month period, which may have caused estimation bias. Third, VR was calculated based on stable CO_2 production and cardiac function, and so the accuracy of dead space evaluation may be affected.

Conclusions

Compared with ECMO-supported H1N1 patients, ECMO-supported COVID-19 patients had older age, higher incidence of CO_2 retention, higher VR before ECMO initiation, and prolonged time from symptoms onset/mechanical ventilation to ECMO initiation. Clinicians managing VV-ECMO in these patients should consider the differences between ARDS patients with COVID-19 and influenza.

Author Contributions

Yonghao Xu, Yin Xi, Weijie Guan, Xiaoqing Liu, Yimin Li conceived and designed the study; Yin Xi, Shuijiang Cai, Jieyi Pan, Zhenting Liang, Ya Wang, Yuheng Yu, Weibo Liang, Shaofeng Kong, Zheng Lv collected the data; Hongkai Wu, Yonghao Xu, Yin Xi, Weijie Guan, Sibei Chen analyzed the data; Yonghao Xu, Yin Xi, Weijie Guan, Manshu Li draft the manuscript; Weibo Liang, Yin Xi, Shuijiang Cai, Yuheng Yu, Weiqun He, Xilong Deng, Yuanda Xu, Zheng Lv managed the patients; Rong Zhang, Xiaoqing Liu, Zheng Lv, Yimin Li reviewed and revised the manuscript. All authors read and approved the final manuscript.

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Ethics Statement

The study was approved by the Institutional Review Board of each participating institution (approval number: 202092).

Conflict of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data Availability

This published article and its supplementary information files include all data generated or analyzed during this study.

Supplementary Materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jointm.2023.07.003.

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