SARS-CoV-2 Versus Influenza-associated Acute Respiratory Distress Syndrome Requiring Veno-venous Extracorporeal Membrane Oxygenation Support

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Abstract: No study has compared patients with COVID-19-related refractory ARDS requiring veno-venous extracorporeal membrane oxygenation (V-V ECMO) to a relevant and homogenous control population. We aimed to compare the outcomes, the clinical characteristics, and the adverse effects of COVID-19 patients to a retrospective cohort of influenza patients. This retrospective case-control study was conducted in the ICUs of Lille and Rouen University Hospitals between January 2014 and May 2020. Two independent cohorts of patients with ARDS requiring V-V ECMO infected with either COVID-19 (n = 30) or influenza (n = 22) were compared. A 3-month follow-up was completed for all patients. Median age of COVID-19 and influenza patients was similar (57 *vs.* 55 years; p = 0.62). The 28-day mortality rate did not significantly differ between COVID-19 (43.3%) and influenza patients (50%, p = 0.63). There was no significant difference considering the cumulative incidence of ECMO weaning, hospital discharge, and 3-month survival. COVID-19 patients had a lower SAPS II score (58 [37–64] *vs.* 68 [52–83]; p = 0.039), a higher body mass index (33 [29–38] *vs.* 30 [26–34] kg/m²; p = 0.05), and were cannulated later (median delay between mechanical support and V-V ECMO 6 *vs.* 3 days, p = 0.004) compared with influenza patients. No difference in overall adverse events was observed between COVID-19 and influenza patients (70% *vs.* 95.5% respectively; p = 0.23). Despite differences in clinical presentation before V-V ECMO implantation, 28-day and 3-month mortality rate did not differ between COVID-19 and influenza patients. Considering the lack of specific treatment for COVID-19, V-V ECMO should be considered as a relevant rescue organ support. *ASAIO Journal* 2021; 67;125–131

Key Words: COVID-19, acute respiratory distress syndrome, extracorporeal membrane oxygenation, influenza

Coronavirus disease-2019 (COVID-19) is an infectious disease caused by a betacoronavirus, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which may lead to severe lower respiratory tract infections. Since November 2019 and the first cases in Wuhan, China, this pandemic has infected over 25 million people around the world, killing more than 840,000 of them.[1] Among hospitalized COVID-19 patients, 26% needed admission in intensive care units (ICU),[2] of whom 88% needed mechanical ventilation for acute respiratory distress syndrome (ARDS).[3] Some of them, refractory to conventional care that included lung protective mechanical ventilation, required veno-venous extracorporeal membrane oxygenation (V-V ECMO) assistance, as recommended by the extracorporeal life support organization (ELSO).[4]

In a context of stressed health care systems and scarce resources, selecting patients most likely to benefit from V-V ECMO has been a tremendous challenge for physicians all over the world. Following early reports, concern was raised about high mortality rate in COVID-19 patients supported with V-V ECMO.[5] However, more recent studies found that V-V ECMO may be useful in selected critically ill patients.[6–8] Finally, the thrombotic complications,[9] hyperinflammatory state, and lack of data on recovery rate complicated the assessment of the risk-benefit ratio.

Since the beginning of the outbreak, there is no specific comparison of COVID-19-related ARDS patients to a relevant and homogenous control cohort in order to confirm the relevancy of V-V ECMO in this setting. Influenza A/B-related ARDS is the most frequent and well-known viral refractory ARDS to date. In the absence of a randomized control trial to definitely settle the question, this population may be the most valuable control.

The primary objective of this study was to compare the 28-day mortality of COVID-19 patients with refractory ARDS requiring V-V ECMO to a retrospective cohort of influenza (A or B) patients supported by similar strategy. The secondary objective was to describe the main characteristics before

cannulation, the outcomes, and the prevalence of adverse events in both populations.

Material and Methods

Study Design

We retrospectively included all patients referred to the ICUs of Lille and Rouen University Hospitals, France, for severe ARDS due to COVID-19 or influenza, requiring V-V ECMO support, during at least 48 hours. Patients were included between January 1, 2014, and February 6, 2020, and between March 9, 2020, and May 6, 2020, for influenza and COVID-19, respectively. Viral infection diagnoses were confirmed using reverse transcription polymerase chain reaction (RT-PCR) test for SARS-CoV-2 (RT-PCR, Institut Pasteur, France), and multiplex RT-PCR for influenza A/B (AllPlex Respiratory Pannel, Seegene, Republic of Korea) on respiratory samples. A 3-month follow-up was completed for all patients.

Patients eligible for V-V ECMO had to fulfill ARDS criteria.[10] Before publication of the EOLIA trial,[11] indications for V-V ECMO were severe persistent hypoxemia ($PaO_2/FiO_2 < 100$ mm Hg) and hypercapnic respiratory acidosis with an inability to maintain a protective ventilation despite an optimal medical treatment, including neuromuscular blockade, prone positioning, protective ventilation, and high positive end-expiratory pressure (PEEP). Since the EOLIA trial publication, physicians were strongly encouraged to rely upon its indications ($PaO_2/FiO_2 < 50$ mm Hg during more than 3 hours or $PaO_2/FiO_2 < 80$ mm Hg during more than 6 hours or pH<7.25 with $PaCO_2 > 60$ mmHg during more than 6 hours, with the respiratory rate increased to 35 breaths per minute and mechanical ventilation settings adjusted to keep a plateau pressure of ≤32 cm of water) and to discuss early V-V ECMO implantation (*i.e.,* before day-7 of mechanical ventilation). Contraindications for V-V ECMO implantation were an age older than 70 years and severe comorbidities (advanced respiratory or cardiac failure, Child Pugh class C cirrhosis, hematological malignancies, and metastatic cancer), prolonged cardiac arrest, and refractory multiorgan failure. However, the final decision was taken after multidisciplinary discussion.

This study was approved by our institutional review board. Patient data were anonymized before analysis, according to French national data protection authority, National Commission on Informatics and Liberty's recommendations, after authorization request **N° DEC20-151.**

V-V ECMO Procedures

Cardiovascular surgeons were strongly encouraged to perform an ultrasound-guided percutaneous cannulation. Blood drainage with a large cannula (25–27 Fr) inserted into the common femoral vein, and returned through the right internal jugular vein (19 Fr) was recommended in first intention. Pump speed was adjusted to obtain a blood-oxygen saturation of 90% or more. Cannula position was guided by ultrasonography and verified by chest x-ray. For highly unstable patients in other regional hospitals, our mobile ECMO retrieval teams, comprising a cardiovascular surgeon and a perfusionist, were sent to the patient's bedside for ECMO cannulation. Once

ECMO had been implanted, the patient was transferred to one of our high-volume specialized centers.

After an initial bolus of 50–100 IU/kg, systemic anticoagulation was maintained using unfractioned heparin for a targeted anti-Xa activity between 0.2–0.3 UI/mL for the influenza group and a higher target of 0.3–0.5 UI/mL for COVID-19 patients due to early reports of high thrombotic complication rate.[12,13] This objective was decreased in high risk of bleeding and hemorrhagic patients.

Ultraprotective mechanical ventilation targeting lower tidal volume, respiratory rate, and driving pressure[14] was recommended for the first days of V-V ECMO initiation. Prone positioning under ECMO and early spontaneous breathing were left at the physician's discretion.

Data Collection

Data were collected from our electronic health records (IntelliSpace Critical Care and Anesthesia (ICCA), Philips Healthcare). The data before V-V ECMO cannulation included demographic characteristics (age and sex), comorbidities, laboratory tests, indication for V-V ECMO, mechanical ventilation parameters, adjuvant treatment, and prognostic scores. Outcomes (mortality rate, ECMO duration and weaning, catecholamine and mechanical ventilation free days, ICU and hospital length of stay) and adverse events (ischemic stroke, hemorrhagic stroke, major bleeding, thrombotic complications, and acute kidney injury) were also recorded. Major bleeding was defined according to ELSO guidelines.[15] Thrombotic complications included pulmonary embolism, cannula, membranous, and deep venous thrombosis. A KDIGO score of III defined acute renal failure.[16]

Statistical Analyses

Data were reported as median (interquartile range) for quantitative variables and numbers (percentage) for categorical variables. Between-group comparisons were done using Chi-square test (or Fisher's exact test when the expected cell frequency was inferior to 5) for binary outcomes or by using Mann-Whitney U test for quantitative variables. No statistical comparisons were done for categorical variables with one modality frequency lower than 5. For censored outcomes (ECMO duration, ICU and hospital length of stay [LOS]), we used a competing risk survival analysis approach by estimating the cumulative incidence of ECMO weaning and hospital discharge alive considering death as competing event. Cumulative incidences were estimated by the Kalbfleisch and Prentice method and were compared between the 2 groups using the Gray's test. Finally, the 3-month overall survival was estimated using Kaplan-Meier method and compared by using log-rank test. Statistical testing was performed at the 2-tailed α level of 0.05. Data were analyzed using the SAS software package, release 9.4 (SAS Institute, Cary, NC).

Results

During the study period, 58 patients required a V-V ECMO assistance for ARDS related to influenza or COVID-19 pneumonia. Six patients (3 in the COVID-19 group and 3 in the influenza group) had an ECMO course shorter than 48 hours

and were excluded from the analysis. Among the 52 remaining patients, 30 presented with COVID-19 and 22 had influenza infection (18 influenza A and 4 influenza B virus). The flow chart of the study is reported in **Figure 1**.

Patient Characteristics

Median age of COVID-19 and influenza patients was similar (57 *vs.* 55 years; $p = 0.62$). Subjects were mostly male (38/52 [73.1%]) with no significant difference between groups (80 *vs.* 63.6% for COVID-19 and influenza respectively; $p = 0.19$). COVID-19 patients had more frequently a history of hypertension, diabetes, and dyslipidemia compared to the influenza group. At the time of V-V ECMO initiation, the median PaO_2/FiO_2 ratio was identical in patients with COVID-19 and influenza (69 [63–75] *vs.* 68 [56–81] mm Hg; $p = 0.87$) (Table 1). Bacterial coinfection was more frequent in influenza patients (31.8% *vs.* 6.7%). The median sequential organ failure assessment (SOFA) and Simplified Acute Physiology Score II (SAPS

II) scores of COVID-19 patients were 10 and 58, respectively, lower than the scores of 11 ($p = 0.37$) and 68 ($p = 0.04$) of influenza patients (Table 2).

The main indication for V-V ECMO was hypoxemia (PaO_2/FiO_2 less than 80 mm Hg for more than 6 hours) refractory to optimal medical treatment in patients with COVID-19 (89.6%) and in patients with influenza (90%). Only 2 patients were placed under V-V ECMO for indication not included in EOLIA trial inclusion criteria. One COVID-19 patient was cannulated for pulmonary hypertension leading to acute right heart failure and *foramen ovale* reopening, while 1 influenza patient was implanted for low respiratory system compliance without respiratory acidosis. The median time from mechanical support to V-V ECMO was significantly lower in patients with influenza (3 [1–5] days) compared with patients with COVID-19 (6 [4–9] days; $p = 0.004$). There was no significant difference in mechanical ventilation parameters between the 2 groups before V-V ECMO initiation. Every patient received neuromuscular blocking agents and a large proportion of patients
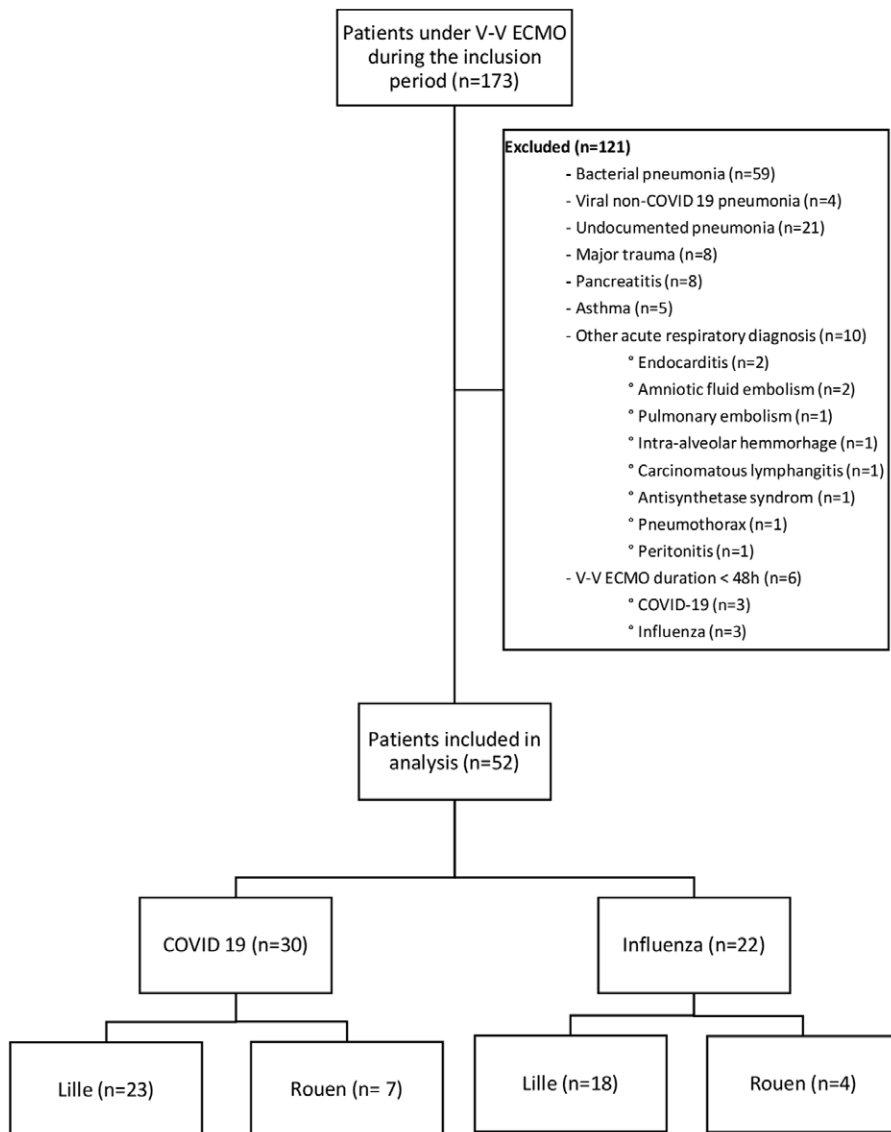

Figure 1. Flow-chart of the study.

Table 1. Patients' Characteristics at Veno-venous Extracorporeal Membrane Oxygenation (V-V ECMO) Initiation in COVID-19 and Influenza Patients

	COVID-19 (n=30)	Influenza (n=22)	P
Demographics			
Age, years	57 (47–62)	55 (48–60)	0.62
Men	24 (80.0)	14 (63.6)	0.19
Comorbidities			
Body mass index, kg/m²	33 (29–38)	30 (26–34)	0.05
Hypertension	16 (53.3)	7 (31.8)	0.12
Diabetes	10 (33.3)	2 (9.1)	0.04
Dyslipidemia	7 (23.3)	1 (4.5)	0.12
Smoking	1 (3.3)	5 (22.7)	0.07
Coronary arterial disease	0 (0.0)	1 (4.5)	NA
Asthma/COPD	3 (10.0)	2 (9.1)	1.00
Chronic respiratory insufficiency	0 (0.0)	2 (9.1)	NA
Immunocompromised condition	3 (10.0)	1 (4.5)	NA
Biological data at V-V ECMO initiation			
pH*	7.37 (7.32–7.41)	7.35 (7.27–7.43)	0.36
PaO₂/FiO₂†, mmHg	69 (63–75)	68 (56–81)	0.87
PaCO₂‡, mmHg*	52 (46–60)	45 (35–63)	0.27
Lactates§, mmol/L	1.3 (1.1–1.8)	1.8 (1.2–2.4)	0.08
Creatinine¶, µmol/L	80 (62–194)	168 (80–230)	0.09
Bilirubin‖, µmol/L	12 (9–24)	12 (9–24)	0.96
ASAT#, UI/L	65 (35–103)	79 (60–203)	0.06
ALAT¶, UI/L	48 (31–73)	43 (33–100)	0.98
Platelets**, 10⁹/L	280 (242–352)	122 (60–239)	0.001
aPTT§, ratio	1.4 (1.2–1.8)	1.6 (1.2–1.7)	0.66
Fibrinogen††, g/L	7.8 (7.2–9.2)	4.5 (3.5–6.2)	<0.001

Values are number (%) or median (interquartile range).
*4 missing values (1 in COVID-19 group).
†3 missing values (1 in COVID-19 group).
‡5 missing values (1 in COVID-19 group).
§8 missing values (3 in COVID-19 group).
¶2 missing values (1 in COVID-19 group).
‖3 missing values (2 in COVID-19 group).
#4 missing values (3 in COVID-19 group).
**2 missing values (0 in COVID-19 group).
††14 missing values (6 in COVID-19 group).
ALAT, alanin aminotransferase; aPTT, activated partial thromboplastin time; ASAT, aspartate aminotransferase; COPD, chronic obstructive pulmonary disease; FiO₂, fraction of inspired oxygen; NA, not applicable.

(94.2%) were prone-positioned before V-V ECMO implantation. Almitrine use was the only significant difference in medical management before V-V ECMO initiation (33.3% *vs.* 4.5% for COVID-19 and influenza patients respectively; $p=0.02$) (Table 2).

V-V ECMO Characteristics

Patients with influenza had more percutaneous cannulation (100%) compared with patients with COVID-19 (76.7%, $p=0.03$). The femorojugular configuration was mostly used (n=50/52). Only one patient with influenza had a femorosubclavicular configuration and 1 patient with COVID-19 had a double lumen cannula in jugular position. Our mobile ECMO retrieval team brought back more influenza than COVID-19 patients (54.5% *vs.* 26.7%; $p=0.05$).

Outcomes and Adverse Effects

The 28-day and 3-month mortality rate did not significantly differ between COVID-19 patients (43.3% and 53.3%, respectively) and influenza patients (50%; $p=0.63$ and 50%;

Table 2. Veno-Venous Extracorporeal Membrane Oxygenation (V-V ECMO) Indications, Adjuvant Treatments and Prognostic Scores in COVID-19 and Influenza Patients

	COVID-19 (n=30)	Influenza (n=22)	P
Indication for V-V ECMO			
PaO₂/FiO₂ < 50 mmHg	1 (3.4)	3 (15.0)	NA
PaO₂/FiO₂ [50–80] mmHg	25 (86.2)	15 (75.0)	0.46
pH < 7.25 and PaCO₂ > 60 mmHg*	5 (17.2)	4 (20.0)	1.00
Other	1 (3.4)	1 (5.0)	NA
Mechanical ventilation data			
Time from MV to V-V ECMO, days	6 (4 to 9)	3 (1 to 5)	0.004
Tidal volume†, ml/kg IBW	6.5 (5.7 to 6.9)	6.3 (6.0 to 6.8)	0.98
Respiratory rate†, bpm	30 (26 to 32)	30 (28 to 30)	0.98
Plateau pressure‡, cmH₂O	30 (26 to 31)	32 (28 to 36)	0.18
PEEP§, cmH₂O	14 (12 to 16)	14 (9 to 16)	0.53
Driving pressure‡, cmH₂O	15 (13 to 20)	20 (12 to 24)	0.16
Treatment before V-V ECMO initiation			
Prone positioning	30 (100.0)	19 (86.4)	NA
Neuromuscular blocking agents	30 (100.0)	22 (100.0)	NA
Glucocorticoids	4 (13.3)	2 (9.1)	1.00
Inhaled nitric oxide	22 (73.3)	18 (81.8)	0.47
Almitrine	10 (33.3)	1 (4.5)	0.02
Norepinephrine	15 (50.0)	16 (72.7)	0.10
Prognostic scores before V-V ECMO initiation			
SAPS II	58 (37 to 64)	68 (52 to 83)	0.04
SOFA	10 (7 to 12)	11 (8 to 13)	0.37
PRESERVE	3 (2 to 3)	4 (2 to 6)	0.04
RESP	1 (0 to 2)	2 (0 to 3)	0.73
PRESET	5.5 (4 to 6)	5.5 (4 to 7)	0.41

Values are number (%) or median (interquartile range)
*2 patients in COVID-19 group and 1 patient in influenza group had also PaO₂/FiO₂ [50-80] mmHg.
†3 missing values (0 in COVID-19 group).
‡16 missing values (11 in COVID-19 group).
§2 missing values (0 in COVID-19 group).
IBW, ideal body weight; MV, mechanical ventilation; PEEP, positive end-expiratory pressure; PRESERVE score, PRedicting dEath for SEvere ARDS on VV-ECMO; PRESET score, PREdiction of Survival on ECMO Therapy score; RESP score, Respiratory Extracorporeal membrane oxygenation Survival Prediction score; SAPS II, simplified acute physiology score; SOFA, sepsis-related organ failure assessment.

$p=0.81$, respectively) (Table 3). The 6-month mortality rate was still at 50% for influenza patient. There was no significant difference considering cumulative incidence of ECMO weaning (**Figure 2A**), hospital discharge (**Figure 2B**), and 3-month survival (**Figure 2C**). The median time on ECMO for patients alive at ICU discharge was 9 (6–13) days in 14 COVID-19 patients and 10 (6–14) days in 12 influenza patients ($p=0.67$).

No difference in overall adverse events rate under V-V ECMO between COVID-19 and influenza patients was found (70.0 *vs.* 95.5%; $p=0.23$). We observed a nonsignificant higher thrombosis event rate in COVID-19 group (33.3%) *vs.* influenza patients (13.6%; $p=0.11$) with more pulmonary embolism, oxygenator failure, and oxygenator thrombosis. Despite a higher rate of bleeding event in COVID-19 patients, the occurrence of major bleeding was similar in both groups: 43.3% in patients with COVID-19 *vs.* 40.9% in patients with influenza ($p=0.86$).

Discussion

Our study is the first to compare SARS-CoV-2- and influenza-infected patients requiring V-V ECMO and to report a 3-month

Table 3. Complications and outcomes in COVID-19 cases and controls treated by veno-venous extracorporeal membrane oxygenation (V-V ECMO)

	COVID-19 (n = 30)	Influenza (n = 22)	P
Complication under V-V ECMO	25 (70.0)	21 (95.5)	0.23
Ischemic stroke	1 (3.3)	0 (0.0)	NA
Hemorrhagic stroke	3 (10.0)	5 (22.7)	0.26
Acute kidney injury	15 (50.0)	12 (54.6)	0.75
Blood stream infection	4 (13.3)	2 (9.1)	1.00
Bleeding			
Overall	22 (73.3)	14 (63.6)	0.45
Major bleeding	13 (43.3)	9 (40.9)	0.86
Cannula insertion site	14 (46.7)	5 (22.7)	0.08
Thrombosis			
Overall	10 (33.3)	3 (13.6)	0.11
Deep venous thrombosis	3 (10.0)	3 (13.6)	0.69
Pulmonary embolism	2 (6.7)	0 (0.0)	NA
Oxygenator failure	6 (20.0)	0 (0.0)	0.03
Oxygenator thrombosis	2 (6.7)	0 (0.0)	NA
Outcomes			
Mortality			
28-day	13 (43.3)	11 (50.0)	0.63
Intensive Care Unit	16 (53.3)	10 (45.5)	0.57
Hospital	16 (53.3)	10 (45.5)	0.57
Catecholamine free days *,†	16 (8 to 26)	16 (11 to 30)	0.46
Mechanical ventilation free days ‡	3 (0 to 7)	4 (0 to 8)	0.91
V-V ECMO duration, days	11 (7 to 14)	11 (6 to 19)	0.92
V-V ECMO weaning	15 (50.0)	14 (63.6)	0.33
Length Of Stay, days			
Intensive Care Unit	27 (20 to 39)	31 (22 to 38)	0.68
Hospital	29 (21 to 47)	33 (23 to 45)	0.91

Values are number (%) or median (interquartile range).
*Defined from ICU admission to ICU discharge.
†1 missing value (0 in COVID-19 group).
‡Defined from initiation of mechanical ventilation to ICU discharge.

follow-up for COVID-19 patients. Mortality rate, cumulative incidence of survival, V-V ECMO weaning, hospital discharge, and adverse events rate were not different between the 2 populations.

On the one hand, according to SAPS II score, COVID-19 patients were less severe than the patients with influenza at V-V ECMO initiation, possibly because of a lower rate of bacterial coinfection. On the other hand, they presented more comorbidities, such as hypertension, diabetes, dyslipidemia, and obesity, as previously reported in a general population of SARS-CoV-2 infected hospitalized patients.[2] Moreover, COVID-19 patients were cannulated 3 days later than influenza patients while early cannulation (i.e., <6 days of mechanical ventilation) could reduce mortality.[17] The physician's decision to initiate V-V ECMO support may have been delayed in COVID-19 patients by the higher rate of almitrine infusion and prone positioning that could temporarily improve PaO_2/FiO_2 ratio. Despite all these differences, 28-day and 3-month mortality rate did not differ between the 2 groups.

We report here a retrospective cohort of influenza ARDS requiring V-V ECMO with a hospital-mortality rate of 45.5%, higher than the 27.6% reported in a previous metaanalysis.[18] One of the most likely explanation could be the higher median age (55 years old vs. 39.7,[19] 34.4,[20] 36.5,[21] and 42[22]) and SOFA score (11 vs. 9[21,22]) of our population in comparison with previous cohort studies. Our hospital-mortality rate of 53.3% in COVID-19 patients is consistent with the 46% provided by the

ELSO registry on COVID-19 cases.[23] Interestingly, the middle-term follow-up showed that all patients discharged from the hospital were still alive at 3 months. Recently, Schmidt et al.[8] reported a 60-day mortality rate of 31% in 83 COVID-19 patients under V-V ECMO. As highlighted by the authors, this encouraging result could have several explanations: a large proportion of patients (79/83) were hospitalized in a very high volume center (Pitié-Salpétrière Hospital ICU), ultraprotective ventilation resulting in a drastic decrease in mechanical power and 81% of the patients were prone-positioned under V-V ECMO. Compare with our cohort, patients were younger (49 vs. 57 years old), were cannulated earlier (4 vs. 6 days), had a higher RESP Score (4 vs. 1), and a lower SAPS II score (45 vs 58). Furthermore, only 13/30 (43.3%) of our COVID-19 patients benefited from prone-positioning under V-V ECMO. It is also important to notice that we reported in-hospital mortality after a complete 3-month follow-up whereas the 36% hospital mortality reported by Schmidt et al. at 90 days account as alive the 18 patients lost in follow-up of the latest weeks.

In our cohort, RESP and PRESET scores seemed more accurate to predict survival or mortality compared to PRESERVE score. Our populations had a high proportion of obese patients (median BMI of 33 in patients with COVID-19), and obesity is known to increase mortality in patients hospitalized for SARS-CoV-2.[24] Conversely, a $BMI > 30 \, kg/m^2$ reduces the PRESERVE score because low BMI was associated with poor outcome. This could explain the gap between PRESERVE score predicted mortality and the observed one in our study. Anyway, prognostic scores before V-V ECMO initiation (i.e., PRESERVE, PRESET, RESP scores) must be used with caution in COVID-19 patients. Indeed, all these scores lack external validity to be used in COVID-19 patients (neither their derivation cohort nor their validation cohort had included these patients).

Our data showed no between-groups difference in overall adverse events rate. However, we observed more thrombotic complications in COVID-19 patients. This is consistent with previous data[8,9] and could reflect the interplay between the hyperinflammatory state, the prothrombotic trend, and the pathophysiological adaptation to V-V ECMO of COVID-19 patients.[25] The limited size of our population may also have underpowered this analysis. Larger scale analysis is needed to confirm this information. Moreover, as these thrombotic events occurred despite increased anticoagulation target, optimal anticoagulation strategy for COVID-19 patients is yet to be found.

Among the several limits of our study, the first is the limited size of our population and the retrospective setting resulting in underpowered analyses and exposing to confounders. Second, the statistical analysis performed to compare the characteristics of the patients at the time of cannulation or adverse events rate must be interpreted with caution regarding the small sample size in each group and the multiple testing issue. Only assumptions can be made about their meaning. Furthermore, our study was not designed to highlight differences in adverse events rate, especially for thrombotic complications adjusted on anticoagulant doses. Moreover, we can not exclude differences in ARDS management over the years. Centers' experience has certainly improved overtime, guidelines have been modified,[26] and pivotal publications have recently emerged and modified further our practice.[11,14] Of note most patients (14/22) in the influenza group were admitted in less than 15 months
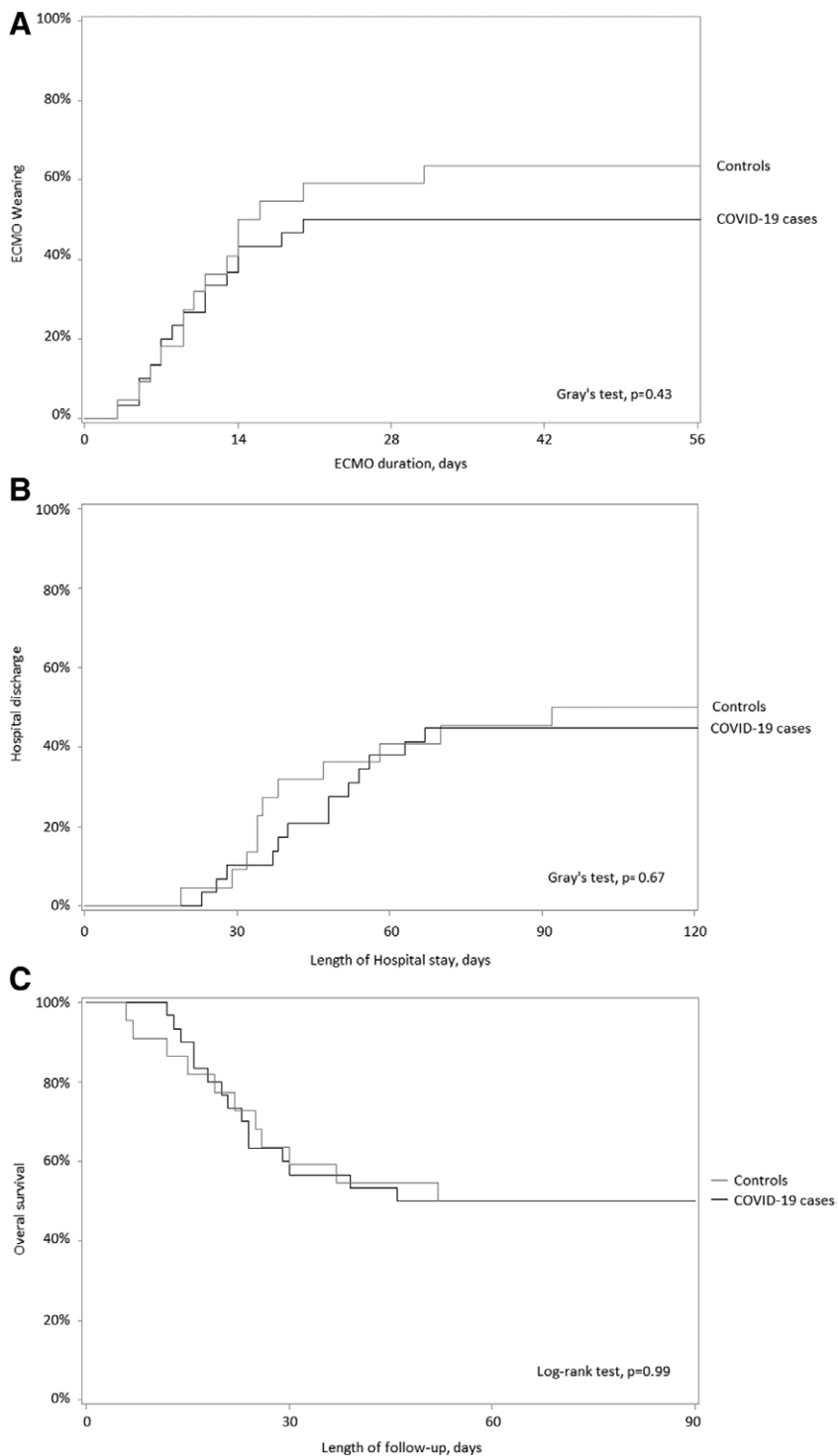
Figure 2. Cumulative incidence of extracorporeal membrane oxygenation weaning (A), hospital discharge (B), and 3-month overall survival (C) in COVID-19 cases and controls (patients suffering Influenza A or Influenza B viral ARDS requiring V-V ECMO).

before the COVID-19 outbreak, limiting the effect of this possible bias. The other controls were included in the 5 years preceding the COVID outbreak (1 patient in 2014, 4 patients in 2016, 3 patients in 2017). Due to the small size sample of our cohort, we could not perform subgroup statistical analyses to assess for ARDS management discrepancies before V-V ECMO cannulation. Nevertheless, the use of prone positioning and neuromuscular blockade, in accordance with PROSEVA[27] and ACURASYS trials results,[28] seemed to be the same over the years. Finally, the pandemic setting and overstressed ICU resources might have distorted our results. However, we provide here a first comparative study of COVID-19 and influenza ARDS requiring V-V ECMO with a complete 3 months follow-up.

Conclusions

We compared for the first time SARS-CoV-2 and influenza patients requiring V-V ECMO for refractory ARDS and observed no difference in 28-day and 3-month mortality rates. The cumulative incidence of ECMO weaning and hospital discharge were also similar among groups, as were overall adverse events. Considering the lack of specific treatment for COVID-19, V-V ECMO should be considered as a relevant rescue organ support as a bridge to lung recovery or lung transplant.

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