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Predictors of poor outcome in critically ill patients with COVID-19 pneumonia treated with extracorporeal membrane oxygenation

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Abstract

Introduction: We aimed to identify risk factors associated with ICU mortality in critically ill patients with COVID-19 pneumonia treated with Extracorporeal membrane oxygenation (ECMO). We also aimed to assess protocol violations of the local eligibility criteria of ECMO initiation.

Methods: All 31 consecutive adult patients with confirmed COVID-19 pneumonia admitted to ICU and treated with ECMO from March 13th 2020 to 8 December 2021 were enrolled. Eligibility criteria for ECMO initiation were: P/F-ratio<50 mmHg >3 hours, P/F-ratio<80 mmHg >6 hours or pH<7.25 + PaCO2>60 mmHg >6 hours, despite maximal protective invasive ventilation. Primary outcome was ICU mortality. Univariate logistic regression analyses were performed to identify predictors of ICU mortality.

Results: 12 out of 31 patients (38.7%) did not survive ECMO treatment in ICU. Half of the non-survivors suffered from acute kidney failure compared to 3 out of 19 survivors (15.79%) (p = .04). Half of the non-survivors required CRRT treatment versus 1 patient in the survivor group (5.3%) (p < .01). Higher age (2.45 (0.97–6.18), p = .05), the development of AKI (5.33 (1.00–28.43), p = .05), need of CRRT during ICU stay (18.00 (1.79–181.31), p = .01) and major bleeding during ECMO therapy (0.51 (0.19–0.89), p < .01) were identified to be predictors of ICU mortality.

Conclusion: Almost 60% of patients could be treated successfully with ECMO with sustained results at 3 months. Predictors for ICU mortality were development of AKI and need of CRRT during ICU stay, higher age category and major bleeding. Inadvertent ECMO allocation was noted in almost one in five patients.

Keywords

COVID-19, extracorporeal membrane oxygenation, intensive care unit, predictor, mortality

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the cause of the ongoing pandemic of coronavirus disease (COVID-19). The spectrum of disease severity of patients infected with SARS-CoV-2 is very wide: from an asymptomatic carrier state to severe pneumonia and the development of acute respiratory distress syndrome (ARDS).[1]

Conventional treatment options established for ARDS include lung-protective mechanical ventilation, neuromuscular blockade, and prone positioning.[2] Depending on the availability of resources, International guidelines also recommend the consideration of venovenous (VV)

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extracorporeal membrane oxygenation (ECMO) in selected patients with COVID-19 who develop severe ARDS and hypoxemia that is refractory to optimal ventilator management and prone positioning.[2–4] According to the Rescue Lung Injury in Severe ARDS (EOLIA) trial criteria,[5] VV ECMO should be timely considered in selected patients if they meet one of the following three criteria despite maximal conservative therapy: a ratio of partial pressure of arterial oxygen (Pao2) to the fraction of inspired oxygen (Fio2) < 50 mmHg for more than 3 h, PaO2/Fi02 Ratio (P/F Ratio) < 80 mmHg for more than 6 h or pH < 7.25+PaCO2 > 60 mmHg for more than 6h. Veno Arterial (VA) ECMO should be considered in selected patients with coexistence of refractory cardiogenic shock.[4]

On the downside, ECMO therapy is a resource-demanding procedure with an average cost exceeding 70.000USD[6] and carries an increased risk of bleeding and thromboembolic events[7] which may counteract its beneficial effects. The first results of ECMO therapy in COVID-19 patients from small Chinese cohorts were discouraging, reporting a very high mortality.[8,9] Other studies however show more promising results with a reported cumulative in-hospital mortality rate between 31% and 58.9%.[10,11] Finally, ECMO exemplifies a scarce resource that requires thoughtful risk-benefit evaluation and allocation strategy. A national survey demonstrated that the majority of US citizens advocate for the continued use of ECMO to treat COVID patients during periods of resource scarcity but would prioritize those with the highest likelihood of recovery.[12]

As a result, there is a need for a more in-depth understanding of the risk factors associated with poor outcomes in critically ill patients with COVID-19 pneumonia treated with ECMO. In this respect, the association of medical history, demographic factors, laboratory results, point-of-care echocardiography data, ventilator settings, ventilator-derived parameters, and treatment factors with outcomes in these patients needs to be analyzed. An optimal characterization of these patients with the highest likelihood of recovery can lead to improved ECMO resource utilization. ECMO resource utilization can further be improved by minimizing the risk of inadvertent ECMO allocation to patients not meeting the eligibility criteria for ECMO candidacy.

Hence, the primary aim of this study was to identify predictors of ICU mortality in a cohort of critically ill patients with COVID-19 pneumonia treated with extracorporeal membrane oxygenation.

Materials and methods

This single-center, investigator-initiated, longitudinal, ambispective, cohort study was performed at Jessa Hospital, Hasselt, Belgium. This study is approved by the ethical committee of Jessa Hospital, Hasselt, Belgium on 8 September 2021, and registered on clinicaltrials. gov (NCT05158816). In light of the urgent need to collect data on the ongoing pandemic and the retrospective nature of this study, written informed consent was waived. This study is reported according to the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) statement.[13]

Study population

All adult patients with acute hypoxaemic respiratory failure due to diagnosed COVID-19 pneumonia admitted to ICU and treated with ECMO from 13 March 2020 until 8 December 2021 were included in the study. Following the World Health Organisation (WHO) protocol,[14] laboratory confirmation of COVID-19 infection was defined as a positive result on polymerase chain reaction (PCR) assays of nasopharyngeal swab samples or bronchoalveolar lavage. Only laboratory-confirmed patients were included in the analysis. From 13 March 2020 until 8 December 2021, data from 363 consecutive patients admitted to the ICU were prospectively entered into a customized database that included medical history, demographic data, clinical symptoms and signs, laboratory results, ventilator settings, ventilator-derived parameters, echocardiographic parameters, and clinical outcomes. This database was retrospectively reviewed. APACHE II and IV scores were calculated at admission to ICU.[15,16] The Sequential Organ Failure Assessment (SOFA) score[17] was evaluated daily.

At admission, all patients were classified into 3 categories: 1) full code with ECMO, 2) No ECMO, and 3) Do-not-intubate (DNI). Inclusion criteria for ECMO candidacy during the first wave were: age < 60 years, clinical frailty scale 1 or 2, sustained severe hypoxemia or hypercapnia despite maximum ventilator support, prone ventilation, and neuromuscular blockade. Sustained severe hypoxemia was defined as "a P/F < 50 mmHg for more than 3 h or a PaO2/Fi02 Ratio (P/F Ratio) < 80 mmHg for more than 6 h. Sustained severe hypercapnia was defined as a pH < 7.25+PaCO2 > 60 mmHg for more than 6 h. After the first wave, inclusion criteria were extended to age>70 years (with age between 70 and 80 years a relative contra-indication) and clinical frailty scale < 5. Exclusion criteria for ECMO were severe bleeding, active malignancy, hepatic cirrhosis Child-Pugh B or C, COPD GOLD IV, cardiac arrest, multiple organ failure, severe neurological injury, or cognitive impairment (including CVA or dementia).

Patients were classified into two groups, i.e. the "early ECMO group" and the "late ECMO group". The early ECMO group included the group of patients who began ECMO within 24h or even before meeting the EOLIA trial criteria.[5] The delayed ECMO group referred to the patients that did not begin ECMO until more than 24h after meeting one of the EOLIA trial criteria.

Extracorporeal membrane oxygenation approach

A standard ECMO/ECLS circuit was used for all patients, including a LivaNova Stöckert console with a Revolution centrifugal pump system, a Sechrist gas blender, a Medtronic Biotrend SvO2 meter, and a Hico Variotherm 550 heater/cooler. The disposables consisted of a heparin-coated VA-tubing set with a PMP fiber ECMO oxygenator (LivaNova EOS ECMO or Eurosets A.L. ONE ECMO) and a LivaNova Revolution centrifugal pump head with a line pressure control on 3 places: P1 negative drainage pressure, P2 pre-oxygenator pressure and P3 post-oxygenator pressure. 5000IU of UFH were administered IV before cannulation according to our protocol. Placement of the cannulae was performed by the cardiac surgeon in collaboration with the cardiac anesthesiologist. After disinfection and preparing the groin, a 21Fr. or 25Fr. Medtronic multistage venous cannula was introduced percutaneously through the femoral vein by the Seldinger technique and positioned in the inferior caval vein at the subdiaphragmatic level. After the puncture of the internal jugular vein under echo guidance, the arterial return cannula is positioned in the superior caval vein with the tip at the level of the caval ostium. Attention is taken to avoid recirculation, this is supported by transoesophageal guidance. Simultaneously, the venous return cannula (Edwards Optisite 20Fr. or 22Fr.) was inserted by a cardiac anesthesiologist into the RIJV (right internal jugular vein) with the tip positioned towards the tricuspid valve. ECMO was initiated after an ACT check and ultrasound control of the position of both cannulas. Blood flow was increased with a target of 2,4 LPM CI (cardiac index), taking the limitations of negative venous drainage pressures into account. The weaning strategy for VV-ECMO consists of following parameters: sweep gas flow 0 L/min, ECMO FiO_2: 21%, pump flow 2–3 l/min, bloodgas: PaO2> 60 mmHG and SpO2> 90%, PCO2: <55 mmHg, FiO_2 ventilator <60%, Pinsp plateau <30 mmHg, RR < 30/min and duration of trial: minimal 1–2 h, maximal 12 h. The magnitude of the pandemic resulted in limited alterations to our conventional weaning strategy. Those alterations can be seen as "more tolerant to both hypoxia and hypercapnia" in comparison to our conventional weaning strategy.

Outcome parameters

The primary outcome was ICU mortality. As a result, the study population was divided into participants who had died during their ICU stay and participants who were discharged from the ICU alive. All participants reached the primary outcome. Secondary outcomes included the incidence of acute kidney injury (AKI) and continuous renal replacement therapy (CRRT), complications during ECMO, length of stay (LOS) in the ICU, hospital LOS and protocol violations of the local eligibility criteria for ECMO initiation. The data set was closed on 1 April 2022.

Point-of-care echocardiography data

All collected data originated from pre-ECMO transthoracic echocardiography (TTE). Five echocardiographic parameters assessing right ventricular (RV) function were included: tricuspid annular plane systolic excursion (TAPSE), right ventricular systolic pressure (RVSP) calculated from continuous wave Doppler by peak velocity over tricuspid regurgitant jet, right ventricle free wall global longitudinal strain (RVfwLS), right ventricular fractional area change (FAC) and right ventricle end-diastolic diameter/left ventricle end-diastolic diameter (RV EDA/LV EDA). RVSP and RV EDA/LV EDA were determined in the apical 4 chamber view whereas FAC TAPSE and RVfwLS were calculated from the apical focused RV view. Cut-off values were TAPSE of 17 mm, RVSP of 35mmHg, RV GLS of −20, RV FAC of 35% and RV EDA/LV EDA of 0,6.[18,19]

Definitions

Acute kidney failure was diagnosed according to the KDIGO clinical practice guidelines.[20] ARDS was diagnosed according to the Berlin Definition.[21] Sepsis and septic shock were defined according to the 2016 Third International Consensus Definition for Sepsis and Septic Shock.

COVID-19 waves

The date of ICU admission was categorized according to the COVID-19 wave. Waves 1 and 2 in Belgium were caused by the D614 G variant, wave 3 by the alpha variant, and wave 4 by the delta variant. These virus variants may differ in disease severity and consequently mortality rate.

Statistical analysis

Continuous data are shown as mean±standard deviation (SD) and categorical data are presented as frequencies (%). Comparisons between groups were performed with

the Student's t-tests for normally distributed data and with the Mann Whitney U test for nonnormally distributed data. Categorical variables were analyzed with a Chi-Square test. The following variables were tested for significance: medical factors, demographics, laboratory results, point-of-care echocardiography data, ventilator settings, ventilator-derived parameters, treatment variables, and secondary outcome variables. To predict ICU mortality, univariate logistic regression was performed for the binary variables and univariate linear regression was performed for the continuous variables. A p-value < 0.05 was considered statistically significant. All analyses were performed with SPPS Version 27.

Results

Patient characteristics

Between 13 March 2020, and 8 December 2021, 363 COVID-19 patients were admitted to the ICU, of which 31 patients were treated with ECMO therapy. A STROBE flowchart depicting the inclusion and exclusion of patients is presented in Figure 1. Detailed baseline characteristics of all COVID-19 patients supported by ECMO therapy, stratified for survival, are presented in Table 1. Patients admitted to the ICU had a mean age of 56.03 ± 10.40 years. Four out of 12 patients in the non-survivor group (33.3%) were active or former smokers, versus none in the survivor group (p = .02).

Outcome measures, progress, and complications

Details on the progress, complications, and outcomes are shown in Table 2.

In total, 12 patients did not survive ICU admission (38.7%) and one patient did not survive until a 90-day follow-up (41.9%). Six patients (19.4%) did not fulfill the local eligibility criteria for ECMO therapy. Of these patients, only 1 patient did not survive ICU admission (p = .04).

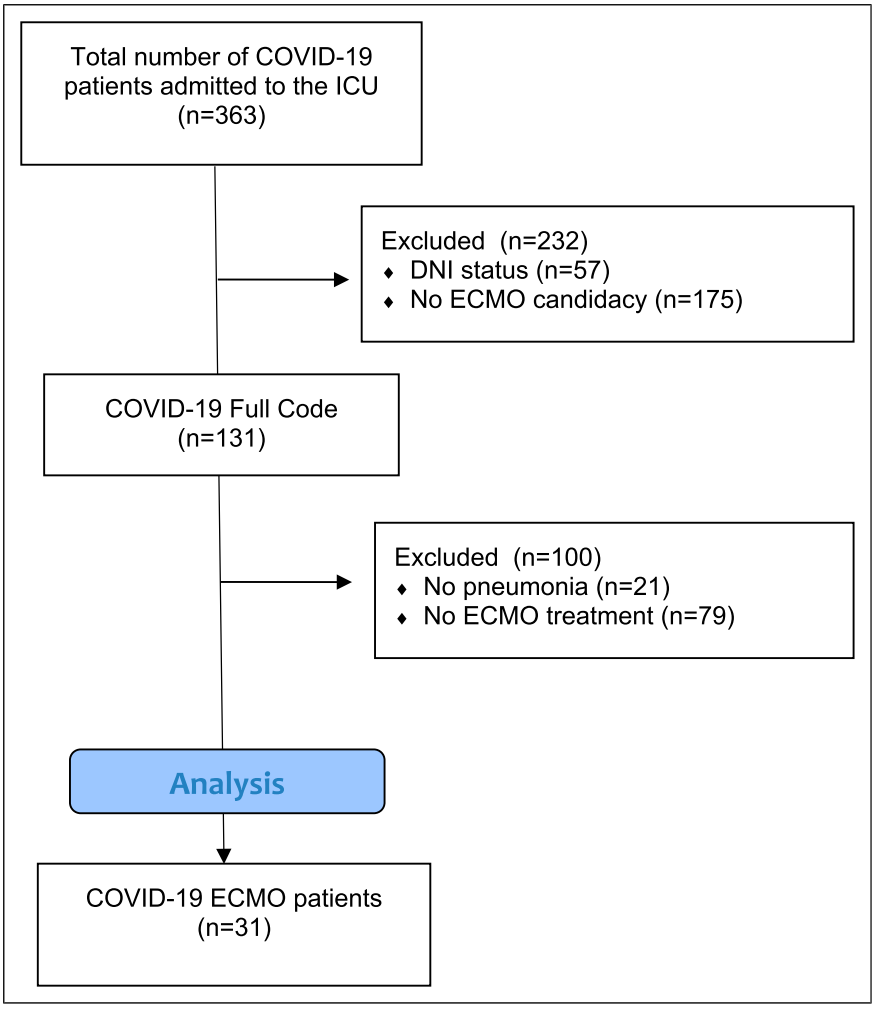

Figure 1. STROBE flowchart depicting inclusion and exclusion.

Table 1. Baseline characteristics.

	COVID-19 ECMO patients (n = 31)	COVID-19 ECMO survivors (n = 19)	COVID-19 ECMO non-survivors (n = 12)	p-value
Demographics				
Age (years)	56.03 ± 10.40	53.32 ± 10.82	60.33 ± 8.40	0.09
Age categories:				
<50	10 (32.3%)	8 (42.1%)	2 (16.7%)	0.23
51–60	9 (29.0%)	6 (31.6%)	3 (25.0%)	
61–70	11 (35.5%)	5 (26.3%)	6 (50.0%)	
>71	1 (3.2%)	0 (0.0%)	1 (8.3%)	
Gender (males/females)	23 (67.6%)/8 (23.5%)	14 (73.68%)/5 (26.32%)	9 (75%)/3 (25%)	0.93
BMI (kg/m^2)	32.43 ± 8.71	32.73 ± 9.57	31.96 ± 7.53	0.98
BMI categoires:				
Normal and overweight (18.50–29.99)	17 (54.8%)	10 (52.6%)	7 (58.3%)	0.92
Moderate obesity (30.00–39.99)	9 (29.0%)	6 (31.6%)	3 (25.0%)	
Severe obesity (>40)	5 (16.2%)	3 (15.8%)	2 (16.7%)	
Date of inclusion				0.06
Wave 1 (March 2020 - August 2020)	3 (9.7%)	3 (15.8%)	0 (0.0%)	0.92
Wave 2 (September 2020 -December 2020)	9 (29.0%)	6 (31.6%)	3 (25.0%)	
Wave 3 (January 2021 - April 2021)	10 (32.3%)	3 (15.8%)	7 (58.3%)	
Wave 4 (May 2021 - October 2021)	9 (29.0%)	7 (36.8%)	2 (16.7%)	
Scoring systems				
SOFA score at admission	4.03 ± 2.67	4.06 ± 3.02	4.08 ± 2.31	0.67
Rockwood clinical frailty index	2.06 ± 1.12	2.00 ± 1.29	2.17 ± 0.83	0.66
Apache II	10.23 ± 5.05	10.16 ± 5.50	10.33 ± 4.48	0.93
Apache IV	37.90 ± 19.20	36.68 ± 15.56	39.83 ± 17.66	0.62
Charlson comorbidity index	1.77 ± 0.88	1.68 ± 0.89	1.92 ± 0.90	0.48
Admission parameters				
PaO_2 At admission	65.97 ± 18.10	67.42 ± 13.92	63.67 ± 23.81	0.53
$PaCO_2$ At admission	40.84 ± 13.78	42.95 ± 15.64	37.50 ± 9.89	0.27
pH at admission	7.42 ± 0.10	7.39 ± 0.12	7.45 ± 0.05	0.34
SaO_2 at admission	91.19 ± 5.76	92.05 ± 4.22	89.93 ± 7.26	0.73
Lactate at admission	1.63 ± 0.65	1.47 ± 0.53	1.87 ± 0.77	0.09
P/F ratio at admission	88.78 ± 55.85	85.82 ± 60.67	93.49 ± 49.44	0.44
Comorbidities				
Smoking (no/yes/ex)	27 (87.1%)/1 (3.2%)/3 (9.7%)	19 (100%)/0 (0%)/0 (0%)	8 (66.7%)/1 (8.3%)/3 (9.7%)	**0.02**
Cardiovascular disease	4 (12.9%)	3 (15.8%)	1 (8.3%)	0.55
Hypertension	10 (29.4%)	4 (21.0%)	6 (50.0%)	0.90
Diabetes	4 (12.9%)	3 (15.8%)	1 (8.3%)	0.55
Respiratory disease	3 (9.6%)	3 (15.8%)	0 (0.0%)	0.15
Malignancy	2 (5.9%)	2 (10.5%)	0 (0.0%)	0.25
Chronic kidney disease	0 (0.0%)	0 (0.0%)	0 (0.0%)	1.00
Chronic liver disease	0 (0.0%)	0 (0.0%)	0 (0.0%)	1.00
Chronic bowel disease	1 (3.2%)	0 (0.0%)	1 (8.3%)	0.20
Chronic nervous disease	0 (0.0%)	0 (0.0%)	0 (0.0%)	1.00
Cerebrovascular disease	5 (16.2%)	4 (21.0%)	1 (8.3%)	0.35
HIV/AIDS	0 (0.0%)	0 (0.0%)	0 (0.0%)	1.00
Hematological disease	1 (3.2%)	1 (5.3%)	0 (0.0%)	0.42
Rheumatological disease	3 (9.6%)	2 (10.5%)	1 (8.3%)	0.84
Dementia	0 (0.0%)	0 (0.0%)	0 (0.0%)	1.00
Obesity	14 (45.2%)	8 (42.1%)	6 (50.0%)	0.67

Data are expressed as mean ± standard deviation or as frequencies. A p-value <0.05 is considered statistically significant.

Half of the non-survivors suffered from AKI versus 3 out of 19 patients (15.79%) in the survivor group (p = .04). These non-survivors (50%) required CRRT treatment during the ECMO therapy versus only 1 survivor (5.3%) (p < .01). Three patients in the non-survivor group (25%) suffered from a stroke, compared to none of the survivors (p = .02). Major bleeding (71%) was noted in all 12 non-survivors compared to about half of the survivors (p < .01).

Ventilatory parameters are presented in Table 3.

Table 2. Progress, complications and outcomes.

	COVID-19 ECMO patients (*n*=31)	COVID-19 ECMO survivors (*n*=19)	COVID-19 ECMO non-survivors (*n*=12)	*p*-value
Progress				
ECMO signals:				**0.04**
No signal	6 (19.4%)	5 (27.8%)	1 (8.4%)	0.20
pF ratio <80 mmHg	11 (35.5%)	8 (42.1%)	3 (25.0%)	0.33
pH <7.25	4 (12.9%)	0 (0.0%)	4 (33.3%)	**<0.01**
No information (externally placed)	10 (32.2%)	6 (31.2%)	4 (33.3%)	
ECMO (early/late)	13 (41.9%)/18 (58.1%)	9 (47.4%)/10 (52.6%)	4 (33.3%)/8 (66.7%)	0.44
P/F ratio during ICU stay	85.82 ± 56.78	81.02 ± 61.88	93.41 ± 49.23	0.21
Invasive mechanical ventilation	31 (100.0%)	19 (100%)	12 (100%)	
Number of days	31.37 ± 25.57	34.44 ± 28.61	26.75 ± 20.48	0.49
Prone ventilation	31 (100%)	19 (100%)	12 (100%)	1.00
Neuromuscular blocker before ECMO	26 (100%) (*n*=26)	17 (100%) (*n*=17)	9 (100%) (*n*=9)	1.00
Vasopression	30 (96.77%)	18 (94.7%)	12 (100%)	0.42
Highest SOFA score	11.81 ± 2.09	11.03 ± 2.30	12.67 ± 1.50	0.09
Complications				
CVA/Stroke	3 (9.7%)	0 (0.0%)	3 (25.0%)	**0.02**
Major bleeding	22 (71.0%)	10 (54.5%)	12 (100%)	**<0.01**
Catheter dislocation	0 (0.0%)	0 (0.0%)	0 (0.0%)	1.00
HIT	2 (6.5%)	1 (5.3%)	1 (8.3%)	0.73
Acute kidney failure	9 (29.03%)	3 (15.79%)	6 (50.00%)	**0.04**
CRRT during ECMO	7 (22.6%)	1 (5.3%)	6 (50%)	**<0.01**
Acute heart failure	11 (35.18%)	7 (36.80%)	4 (33.33%)	0.84
Sepsis	29 (93.55%)	17 (89.50%	12 (100%)	0.25
Thromboembolism	18 (58.06%)	10 (52.60%)	8 (66.70%)	0.48
DVT	17 (54.84%)	9 (47.40%)	8 (66.7%)	
Lung	1 (3.20%)	1 (100%)	0 (0.00%)	
Outcomes				
Length of ECMO (days)	18.43 17.35	17.17 ± 14.78	20.33 ± 21.19	0.92
Duration of ECMO ≥28 days	8 (25.8%)	5 (27.8%)	3 (25.0%)	0.86
LOS before ICU (days)	4.65 ± 6.14	4.42 ± 7.08	5.00 ± 4.53	0.28
LOS ICU (days)	41.03 ± 29.74	49.83 ± 31.74	30.50 ± 22.67	0.09
LOS total (days)	46.27 ± 31.32	60.94 ± 33.7	35.50 ± 22.62	**0.01**
ICU mortality	12 (38.71%)			
90-days mortality	13 (41.93%)			

Data are expressed as mean ± standard deviation or as frequencies. A *p*-value <0.05 is considered statistically significant.

Table 3. Ventilatory parameters.

	COVID-19 ECMO survivors (n = 19)	COVID-19 ECMO non-survivors (n = 12)	p-value
Parameters measured immediately before placement ECMO			
PaO2	64.78 ± 17.36	65.80 ± 10.13	0.52
PaCO2	49.72 ± 16.23	55.30 ± 14.47	0.16
pH	7.32 ± 0.11	7.31 ± 0.08	0.58
SaO2	89.06 ± 4.69	90.10 ± 3.79	0.59
Lactate	1.93 ± 2.80	1.60 ± 1.03	0.77
P/F ratio	66.44 ± 17.89	70.45 ± 21.92	0.44
Platelets	307.59 ± 121.70	246.00 ± 73.34	0.09
GFR	87.94 ± 29.71	90.80 ± 28.0	0.95
aPTT	47.56 ± 30.48	43.89 ± 16.88	0.94
WBC	13.93 ± 7.52	12.30 ± 2.94	0.87
Haemoglobin	11.72 ± 2.39	11.44 ± 1.30	0.61
Days of prone ventilation	5.53 ± 5.32	6.89 ± 6.37	0.49
PEEP	10.60 ± 1.50	11.22 ± 2.68	0.63
Tidal Volume	0.54 ± 0.13	0.44 ± 0.18	0.09
PIP	24.87 ± 3.85	22.22 ± 5.67	0.20
Lung compliance	42.47 ± 23.43	38.57 ± 32.86	0.45
Days mechanical ventilation	5.23 ± 7.27	4.89 ± 4.46	0.51
Days of ICU	7.61 ± 7.01	7.33 ± 5.79	0.92
Parameters measured immediately after placement ECMO			
PaO2	86.37 ± 29.02	82.18 ± 19.83	0.79
PaCO2	45.00 ± 13.50	42.45 ± 8.87	0.76
pH	7.40 ± 0.07	7.43 ± 0.08	0.25
SaO2	95.42 ± 2.34	94.91 ± 4.08	0.70
Lactate	1.70 ± 1.32	2.38 ± 1.74	0.11
P/F ratio	145.95 ± 59.35	155.73 ± 50.40	0.77
PEEP	8.95 ± 2.12	10.00 ± 2.00	0.28
Tidal Volume	0.37 ± 0.15	0.26 ± 0.14	0.07
PIP	27.16 ± 8.42	23.91 ± 6.86	0.33

Data are expressed as mean ± standard deviation or as frequencies. A p-value <0.05 is considered statistically significant.

Seven patients (22.6%) needed a second ECMO treatment. Four patients survived both ECMO treatments (p = .79). 30 patients were treated with VV ECMO, while 1 patient received VA ECMO. In order to facilitate mobilization of patients with very long VV-ECMO runtimes, three out of six patients with a VV-ECMO runtime of >1 month were converted to a single dual lumen cannula.

Predictors of ICU mortality

Univariate analysis of risk factors for ICU mortality is presented in Table 4. Higher age (2.45 (0.97–6.18), p = .05), the development of AKI (5.33 (1.00–28.43), p = .05), the need for CRRT during ICU stay (18.00 (1.79–181.31), p = .01) and major bleeding during ECMO therapy (0.51 (0.19–0.89), p < .01) were identified to be predictors of ICU mortality.

Point-of-care echocardiography data

Table 5 presents the detailed echocardiographic data from pre-ECMO TTE. No significant differences were found.

Discussion

In this monocentric cohort study involving 31 consecutive critically ill COVID-19 patients requiring ECMO therapy, the ICU mortality was 39.7% and the 90-day mortality was 41.93%.

Patients with a history of smoking were overrepresented in the non-survivor group. All 4 patients were treated with ECMO because of low arterial pH (<7.25) and poor lung compliance and all 3 patients who suffered from stroke didn't survive ICU admission. Hospital LOS was significantly longer in the survival group. Univariate regression analysis showed the development of AKI and the need for CRRT during ICU stay, higher

Table 4. Univariate regression analysis.

	OR (95% CI)	*p*-value
Age	1.08 (0.99–1.17)	0.07
Age categories	**2.45 (0.97–6.18)**	**0.05**
BMI	0.99 (0.91–1.08)	0.81
BMI categories	0.92 (0.34–2.42)	0.86
Rockwood clinical frailty index	1.14 (0.59–2.12)	0.68
SOFA at admission	1.01 (0.77–1.33)	0.93
Gender	0.93 (0.18–4.9)	0.94
Wave	1.22 (0.57–2.6)	0.61
LOS before ICU	1.01 (0.90–1.14)	0.79
Length of ECMO	1.01 (0.97–1.06)	0.62
Early versus Late ECMO	0.55 (0.12–2.49)	0.44
Lung compliance before ECMO	0.99 (0.96–1.03)	0.72
pH before ECMO	0.22 (0.00–717.79)	0.71
Days of mechanical ventilation before ECMO	0.99 (0.86–1.14)	0.89
PF < 80	0.46 (0.09–2.25)	0.34
CRRT during ECMO	**18.00 (1.79–181.31)**	**0.01**
Acute kidney failure	**5.33 (1.00–28.43)**	**0.05**
Major bleeding	**0.51 (0.19–0.89)**	**<0.01**

Data are expressed as OR (95% CI). A *p*-value <.05 is considered statistically significant.

Table 5. Point-of-care echocardiography data.

	COVID-19 ECMO survivors (*n* = 19)	COVID-19 ECMO non-survivors (*n* = 12)	*p*-value
TAPSE	1/14 (7.1%)	1/9 (11.1%)	0.74
RVSP	1/8 (12.5%)	0/5 (0.0%)	0.41
RV EDA/LV EDA	10/14 (71.4%)	6/9 (66.7%)	0.81
RV FAC	6/14 (42.9%)	3/9 (33.3%)	0.65
RVfwLS	4/14 (28.6%)	1/9 (11.1%)	0.32

Data are expressed as numbers (frequencies). A *p*-value <.05 is considered statistically significant.

age category, and major bleeding to be predictors of ICU mortality. Protocol violations of the local eligibility criteria of ECMO initiation were noted in 6 (19.4%) patients.

The association between advanced age and mortality in COVID-19 patients treated with ECMO is well documented in the literature, as five different multicenter cohort studies also observed this association.[22–26] This association is not surprising because older age is also known to be a strong independent risk factor for COVID-19 mortality.[27]

The association between the development of AKI and ICU mortality observed in this study is also supported by literature, as a large multicenter cohort study of 292 patients also concluded that renal dysfunction is an independent predictor of in-hospital mortality.[26]

The observation in this study that patients with an arterial pH lower than 7.25 before initiation of ECMO are overrepresented in the non-survivor group echoes the finding of Biancari et al. that decreased arterial pH before ECMO is independently associated with increased risk of mortality.[23] These findings support the hypothesis that ECMO initiation because of ventilatory failure due to decreased lung compliance is associated with a lower chance of survival compared to ECMO initiation because of oxygenation failure.

In the present study, we couldn't detect a correlation between BMI and ICU mortality. Two other large multicenter studies also failed to demonstrate a correlation between BMI and ICU mortality in COVID-19 patients treated with ECMO therapy.[26,28] In contrast, a large single-center observational cohort study including 76 COVID-19 patients treated with ECMO concluded that obesity is an independent factor associated with improved 90-day survival. Conversely, in-hospital death in a multicenter cohort of 171 COVID-19 patients requiring ECMO in Poland was independently associated

with higher BMI. Future research is needed to clarify these inconsistencies.

Dreier et al. showed that patients with COVID-19 induced ARDS might need prolonged (≥28 days) ECMO support and that prolonged ECMO support is not associated with poor outcomes.[29] Our study supports these conclusions since 5 out of 8 (62.5%) patients treated with prolonged ECMO support in our cohort survived ICU admission. Conversely, a large meta-analysis found that ECMO duration was associated with increased mortality.[30] These contradictory findings might be explained by the so-called self-fulfilling prophecy effect. Beliefs of poor prognosis for critically ill patients with prolonged ECMO support may become self-fulfilling if life-sustaining treatment or resuscitation is subsequently withheld in some centers based on that belief. Prolonged ECMO support might also be associated with an increased risk of complications in a time-dependent manner.

Contrary to Li et al., who found that early initiation of ECMO was associated with decreased mortality, we couldn't detect a difference in outcome between the "early ECMO group" and the "delayed ECMO group" in the present study.[31] The retrospective nature of the former study has the disadvantage that significant biases may affect the selection of controls which may explain these conflicting results.

ICU scoring systems, such as the SOFA, the APACHE II, and IV scores have been validated as prognostic tools to predict mortality in severely ill ICU patients.[32,33] The prognostic value of these scoring systems to predict poor outcome seems rather limited in a critically ill COVID-19 population supported with ECMO. A multicenter study reported that the prognostic accuracy for the APACHE II score and SOFA score was low with an area under the receiver operating characteristic (AUC) of 0.572 and 0.602, respectively.[34] In the present study, we couldn't find a significant difference in APACHE II, APACHE IV, or SOFA admission scores between survivors and non-survivors. Daviet et al. were also unable to detect a significant difference in SOFA admission scores between survivors and non-survivors.[25] On the contrary, Bergman et al. reported a higher SOFA score before cannulation to be a risk factor for mortality.[24]

The association between the somatic variable major bleeding and ICU mortality found in the present study seems logical and is in line with the literature, as Bergman et al. reported an increased number of transfusions to be a risk factor for mortality.[24] Albeit, the observation that all patients who died in the present study experienced major bleeding during their ICU stay, may suggest that balancing the increased and competing risks of clotting and bleeding in these patients is very difficult and that the applied anticoagulation strategy was too aggressive in individual cases.

In the present study, we couldn't find an association between five pre-ECMO echocardiographic point-of-care parameters assessing RV function and ECMO survival. This is surprising since Mustafa et al. showed improved survival after VV-ECMO cannulation with the ProTek duo cannula, functionally acting as a right ventricular assist device (RVAD).[28] As consequence, determining RV dysfunction on TTE may facilitate tailored management between classic VV-ECMO and RVAD VV-ECMO. Kopanczyk pointed out RV FAC and GLS but not TAPSE to be aberrant on VV-ECMO patients.[35] Unfortunately, the author did not examine any association with outcome. In a retrospective study on 35 patients treated with VV-ECMO, Lazzeri et al. found pre-ECMO left ventricular ejection fraction (LVEF), RV EDA/LV EDA, and TAPSE not to be predictors for mortality.[36] Importantly, in the latter study, 30% of patients were diagnosed with RV failure based on TAPSE and RV EDA/LV EDA, normalization of these RV values was observed after ECMO initiation, and all survived.[36]

As consequence, reversibility of RV echocardiographic findings after EMCO initiation may be another predictor for survival. However, in our study, we tried to identify predictors to aid decision-making in the process before ECMO insertion.

This study has several limitations. First, the ambivalent single-center design with relatively low numbers of patients negatively impacts the generalizability of our findings. Second, multivariate prediction analysis is not performed due to the low number of included patients. Third, there is a potential impact of the increasing knowledge of pathophysiology and treatment options in COVID-19 over time, which leads to frequent changes in therapeutic strategies, creating a heterogeneous patient population.

In conclusion, these results suggest that almost 60% percent of patients with need for VV-ECMO due to severe COVID-19 pneumonia can be treated successfully with ECMO with sustained results at 3 months. Predictors for ICU mortality were the development of AKI and the need for CRRT during ICU stay, higher age category, and major bleeding. Inadvertent ECMO allocation was noted in almost one in five patients. These results may help to improve ECMO resource utilization in times of scarcity.

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Ethical approval

This study is approved by the ethical committee of JESSA Hospital Hasselt, Belgium.

Consent to participate

Written informed consent was waived in light of the urgent need to collect data in the ongoing pandemic.

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Supplemental Material

Supplemental material for this article is available online.

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Appendix

List of abbreviations

ARDS	acute respiratory distress syndrome
MVA	maximum ventilation alone
DVT	deep vein thrombosis
VTE	venous thromboembolism
IMV	invasive mechanical ventilation
ICU	intensive care unit
LMWH	low-molecular-weight-heparine
NMBA	neuromuscular blocking agents
PEEP	positive end expiratory pressure
P/F ratio	ratio of arterial oxygen partial pressure to fractional inspired oxygen concentration
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SD	standard deviation