

Thromboembolic and Bleeding Events in COVID-19 Patients receiving Extracorporeal Membrane Oxygenation

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Abstract

Background Extracorporeal membrane oxygenation (ECMO) is a potential treatment option in critically ill COVID-19 patients suffering from acute respiratory distress syndrome (ARDS) if mechanical ventilation (MV) is insufficient; however, thromboembolic and bleeding events (TEBE) during ECMO treatment still need to be investigated. **Methods** We conducted a retrospective, single-center study including COVID-19 patients treated with ECMO. Additionally, we performed a univariate analysis of 85 pre-ECMO variables to identify factors influencing incidences of thromboembolic events (TEE) and bleeding events (BE), respectively.

Results Seventeen patients were included; the median age was 57 years (interquartile range [IQR]: 51.5–62), 11 patients were males (65%), median ECMO duration was 16 days (IQR: 10.5–22), and the overall survival was 53%. Twelve patients (71%) developed TEBE. We observed 7 patients (41%) who developed TEE and 10 patients (59%) with BE. Upper respiratory tract (URT) bleeding was the most frequent BE with eight cases (47%). Regarding TEE, pulmonary artery embolism (PAE) had the highest incidence with five cases (29%). The comparison of diverse pre-ECMO variables between patients with and without TEBE detected one statistically significant value. The platelet count was significantly lower in the BE group ($n = 10$) than in the non-BE group ($n = 7$) with 209 (IQR: 145–238) versus 452 G/L (IQR: 240–560), with $p = 0.007$.

Conclusion This study describes the incidences of TEE and BE in critically ill COVID-19 patients treated with ECMO. The most common adverse event during ECMO support was bleeding, which occurred at a comparable rate to non-COVID-19 patients treated with ECMO.

Keywords

- COVID-19
- SARS-CoV-2
- ARDS
- ECMO
- thrombosis
- bleeding

* Both authors contributed equally to this study.

Introduction

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) already caused over 10 million infections and 500,000 deaths as reported in July 2020.¹ SARS-CoV-2 infection causes hyperactivity of immune and nervous systems and an activation of the coagulation cascade associated with severe hypercoagulability, leading to multiple organ failure.² The hypercoagulability leads to an increased risk of venous and arterial thromboembolism with a reported incidence of 31% for intensive care unit (ICU) patients with COVID-19.^{3,4} Furthermore, COVID-19 acute respiratory distress syndrome (ARDS) patients developed significantly more thrombotic complications than non-COVID-19 ARDS patients (11.7 vs. 2.1%, $p < 0.008$).⁵ Certain laboratory parameters, such as D-dimer and fibrin degradation products (FDP), have been shown to identify patients at risk of thromboembolic and bleeding events (TEBE).^{2,6,7} Thereupon studies investigated different regimes for prophylactic anticoagulant therapy in COVID-19 patients at risk of TEBE. The use of heparin is associated with a significantly lower mortality and better prognosis.⁸

Extracorporeal membrane oxygenation (ECMO) plays a role as a rescue therapy.^{9,10} In severe non-COVID-19-induced ARDS patients, there is existing conclusive evidence linking (venovenous [V-V]) ECMO support to better patient outcomes and decreased mortality.^{11–13} However, ECMO treatment itself increases the risk of TEBE¹⁴ and experience of ECMO treatment in COVID-19 patients remains limited.^{9,15–17}

The aim of this study was to describe TEBE in critically ill COVID-19 patients receiving ECMO support. Furthermore, we aimed to identify pre-ECMO characteristics that influence the incidence of TEBE in COVID-19 patients treated with ECMO.

Materials and Methods

Patients and COVID-19 Diagnosis

This single-center retrospective observational study included all adult inpatients (≥ 18 years) between March 1 and April 20, 2020, who were diagnosed with COVID-19 according to the WHO interim guidance¹⁰ and developed severe COVID-19 disease with ARDS requiring ECMO support. Severe cases of COVID-19 with ARDS were identified according to the Berlin Definition of the European Society of Intensive Care Medicine from 2011.

The study was approved by the local ethic commission and the requirement for informed consent was waived by the ethical board due to emerging worldwide public health crisis and retrospective nature of the study.

Data Collection

Beside demographics, medical history, and treatment regimes, time course of laboratory, mechanical ventilation (MV) parameters, and ECMO settings were collected through the entire length of hospital stay (LOS) and outcomes were extracted from our patient data management systems (Philips IntelliSpace Critical Care and Anesthesia and Siemens Medico). Outcomes comprised mortality and complications such as TEBE, organ

failure, super infections, and other pathologies. We also gathered data about the amount of packed red blood cells (PRBC) and albumin units. PRBC units contained 200 to 300 mL and albumin units were 100 mL with a concentration of 20%.

Laboratory Analysis

Detailed laboratory analyses were performed daily and included complete blood count electrolytes; measures of hemostasis; hemolysis markers; biochemical tests of cardiac, renal, and liver function; NT-pro-brain natriuretic peptide (NT-proBNP); interleukin-6 (IL-6); procalcitonin (PCT); C-reactive protein (CRP); fibrinogen; and D-dimers. Blood gas analyses were performed in intervals of 1 to 2 hours. The data were collected afterward, and some laboratory parameters were not always documented in the system over the entire ICU stay. However, the pre-ECMO documentation was complete and missing values exist only in measurements after ECMO initiation.

Extracorporeal Membrane Oxygenation Settings

Critically ill COVID-19 patients, who presented with commonly accepted ECMO indications as suggested by the Extracorporeal Life Support Organization (ELSO),¹⁸ in whom all other treatments options have been exhausted (lung protective invasive MV; prone positioning; neuromuscular blockade; and inhaled nitric oxide [iNO] rescue therapy) were considered for ECMO treatment. Decision on initiation of ECMO treatment was judged by consensus following discussion in the ECMO team consisting of internal medicine intensivist, cardiothoracic surgeon, and pneumologist.

The type of ECMO engines were iLA ACTIVVE XLUNG kits (XENIOS, Heilbronn, Germany) and Cardiohelp HLS systems Version 7.0 (Maquet Cardiopulmonary GmbH, Rastatt, Germany). Data about ECMO settings, utilization (i.e., V-V or veno-arterial [V-A]), cannulation sites, utilization switch (i.e., from V-V to V-A or V-VA), and details on ECMO's weaning were extracted. Our standard approach for the treatment of isolated respiratory failure is V-V ECMO.

Anticoagulation Regime

Hemostasis parameters were measured daily and included activated partial thromboplastin time (aPTT), international normalized ratio (INR), platelet count, fibrinogen, anti-thrombin, d-dimer, and activated clotting time (ACT). aPTT was measured three times daily and ACT was measured four times daily as a control for adequate coagulation and not as a target value. In addition, factor XIII was measured three times a week. Although these measurements were performed and controlled regularly, the documentation in the system was not complete for all variables.

In all patients with VV-ECMO, we primarily administered 400 IE/h of unfractionated heparin (UFH) if no other relevant indications for a higher anticoagulation target, like atrial fibrillation or mechanical heart valve prosthesis, were present. If no bleeding complications occurred, we tolerated an ACT up to 180 seconds. If necessary, UFH was reduced or paused. Other target values were an aPTT between 40 and under 60 seconds, platelet count above 50 G/L, and fibrinogen above 150 mg/dL, and we kept the INR under 1.5. In case

of bleedings, we adjusted the target values by using fresh frozen plasma or PRBC. We reduced the ACT under 160 seconds, normalized the INR, and raised the platelet count to at least 80 G/L and fibrinogen to more than 200 mg/dL.

Thromboembolic and Bleeding Events

TEBE include all thromboembolic events (TEE) and bleeding events (BE) that occurred during ECMO therapy. TEE comprised pulmonary artery embolism (PAE), venous or arterial thrombosis, and ischemic or hemorrhagic stroke. For BE, we documented upper respiratory tract (URT) bleedings and divided them into endobronchial and mucosal bleedings. We also reported the incidence of pericardial tamponade, hemothorax, and cannulation side or gastrointestinal bleedings (GIB).

Screening of the above-mentioned complications was conducted daily due to our standard clinical documentation. BE were differentiated into major and minor in case of URT or cannulation side bleedings. Therefore, all bleedings that led to the use of two or more units of whole blood or red blood cells and/or a fall in hemoglobin more than 1.24 mmol/L were identified as major according to the definition of a major bleeding from the International Society on Thrombosis and Haemostasis (ISTH).¹⁹ We chose the ISTH classification due to its applicability for patients treated with anticoagulants and ECMO being a nonsurgical treatment.

Transfusion of PRBC was very frequent and in most patients, we aimed to maintain a hemoglobin value of 9 g/dL. However, as our main ECMO target aside from ultra-protective ventilation would be a sufficient oxygen delivery, we calculated the ratio of oxygen delivery (Do_2) to oxygen consumption (Vo_2) several times daily and aimed for a ratio of $\geq 4:1$ or at least $3:1$. Thus, in some patients, a transfusion of PRBC was required due to low $\text{Do}_2:\text{Vo}_2$ ratios even if hemoglobin was around 10 g/dL.

Confirmation of SARS-CoV-2

Throat-swab specimens, tracheal secretions, or bronchoscopic alveolar lavage were obtained for SARS-CoV-2 from each suspected patient immediately at hospital admission. The real-time reverse transcription polymerase chain reaction (RT-PCR) assay was used to confirm COVID-19 infections.

Statistical Analysis

Categorical variables are presented as absolute numbers (n) and percentages (%). Continuous variables were tested for normal distribution with the Kolmogorov-Smirnov test and presented as median and interquartile range (IQR).

For comparison between patients with and without TEE or BE, univariate analyses were performed using the Mann-Whitney U test for continuous variables and Fisher's exact test for categorical variables.

All statistical comparisons were two-sided. A p value < 0.05 was considered significant. Statistical analysis was performed with SPSS Version 26 (IBM Corp., Armonk, New York, United States). The figure for time courses of laboratory

parameters using mean values was created with Microsoft Excel for Mac, Version 16.41 (Microsoft, Redmond, Washington, United States).

Results

Baseline Characteristics

We included 17 patients with COVID-19 who received ECMO from March 1 to April 20, 2020. The median age was 57 years (IQR: 52–62), median BMI was 28 kg/m^2 (IQR: 25–32), 6 patients (35%) were female, and the most prevalent comorbidity was arterial hypertension in 13 patients (76%). Nine patients (53%) had fever at admission and the most prevalent typical COVID-19 symptom was dyspnea with 12 patients (71%). Four patients (24%) were nicotine users, and 3 patients (18%) were suffering from COPD. Data on MV and laboratory tests prior to receiving ECMO showed a median $\text{PaO}_2/\text{FiO}_2$ ratio of 0.82 (IQR: 0.68–1.04) and the median duration of MV before ECMO was 3 days (IQR: 2.5–17). Eight patients (47%) had iNO inhalation prior to ECMO support and all patients received antibiotic and prone position treatment. We found a median PaO_2 of 68 mm Hg (IQR: 54–74), PaCO_2 of 66 mm Hg (IQR: 45–78), d-dimer of $4547 \text{ } \mu\text{g/dL}$ (IQR: 1,720–15,395), and fibrinogen of 656 mg/dL (IQR: 421–717). Furthermore, we found a median platelet value of 226 (IQR: 189–421) and the median PTT was 33 seconds (IQR: 28–37). The Respiratory ECMO Survival Prediction (RESP) score was estimated before ECMO therapy and predicted a median score of -1 (IQR: -3 to 1). Further parameters and details are presented in ►Table 1.

During ECMO therapy, we observed TEE in 7 patients and BE in 10 patients. We compared the TEE group ($n = 7$) with a non-TEE group ($n = 10$), and the BE group ($n = 10$) with a non-BE group ($n = 7$). Besides patient characteristics, we included laboratory measurements, MV parameters, ECMO settings, and ICU risk scores before ECMO implantation. Baseline characteristics of all groups are provided in ►Table 1.

In the first comparison between the TEE group and the non-TEE group, we found no statistically significant differences. However, there were several notable differences. In the seven patients with TEE, we found fewer female patients (14 vs. 50%, $p = 0.160$), more patients suffering from atrial fibrillation (57 vs. 20%, $p = 0.162$), and less utilization of cytokine absorption (29 vs. 60%, $p = 0.335$). Furthermore, the TEE group had higher median pCO_2 values with 77 (IQR: 55–80) versus 60 (IQR: 34–70), with $p = 0.088$; and the group also had lower median RESP score values with -2 (IQR: -4 to 0) versus 0 (-3 to 2), $p = 0.315$.

As for the 10 patients with BE, we found one statistically significant difference and some notable differences regarding coagulation parameters. The median platelet count was significantly lower in the BE group than in the non-BE group with 209 (IQR: 145–238) versus 452 (IQR: 240–560), $p = 0.007$. The BE group also had a longer median PTT with 35 (IQR: 28–39) versus 29 (IQR: 28–34) seconds, $p = 0.193$; and the group also had a lower median INR with 1.2 (IQR: 1.2–1.3) versus 1.3 (IQR: 1.3–1.4), $p = 0.133$.

Table 1 Baseline characteristics (pre-ECMO)

Variable	Total (n = 17)	TEE (n = 7)	No TEE (n = 10)	p-value ^a	BE (n = 10)	No BE (n = 7)	p-value ^a
Age (y), median (IQR)	57 (52–62)	58 (55–67)	57 (47–62)	0.364	57 (50–61)	60 (53–62)	0.536
Female sex, n (%)	6 (35)	1 (14)	5 (50)	0.160	4 (40)	2 (29)	1.000
BMI (kg/m ²), median (IQR)	28 (25–32)	26 (25–31)	30 (26–36)	0.193	28 (25–33)	30 (25–31)	0.887
LVEF (%), median (IQR)	55 (50–56)	54 (49–57)	55 (50–55)	0.740	55 (50–56)	55 (50–56)	0.740
LOS pre-ECMO (d), median (IQR)	5 (4–19)	5 (3–21)	5 (4–14)	1.000	4.5 (4–14)	13 (3–21)	0.740
Arterial hypertension, n (%)	13 (76)	5 (71)	8 (80)	1.000	7 (70)	6 (86)	0.603
Coronary artery disease, n (%)	1 (6)	0 (0)	1 (10)	1.000	0 (0)	1 (14)	0.412
Diabetes mellitus, n (%)	5 (29)	2 (29)	4 (40)	1.000	3 (30)	3 (43)	0.644
Peripheral arterial disease, n (%)	1 (6)	1 (14)	0 (0)	0.412	1 (10)	0 (0)	1.000
Cerebrovascular disease, n (%)	0 (0)	0 (0)	0 (0)	1.000	0 (0)	0 (0)	1.000
Nicotine users, n (%)	4 (0.24)	1 (14)	3 (30)	0.603	1 (10)	3 (43)	0.250
History of pneumonia, n (%)	5 (0.29)	1 (14)	4 (40)	0.278	2 (20)	3 (43)	0.593
COPD, n (%)	3 (0.18)	1 (14)	2 (20)	1.000	1 (10)	2 (29)	0.537
Hyperlipoproteinemia, n (%)	2 (0.12)	1 (14)	1 (10)	1.000	2 (20)	0 (0)	0.485
Atrial fibrillation, n (%)	6 (0.35)	4 (57)	2 (20)	0.162	3 (30)	3 (43)	0.644
Chronic kidney disease, n (%) ^b	2 (12)	1 (14)	1 (10)	1.000	1 (10)	1 (14)	1.000
Prior myocardial infarction, n (%)	1 (06)	0 (0)	1 (10)	1.000	0 (0)	1 (14)	0.412
Prior PCI, n (%)	1 (6)	0 (0)	1 (10)	1.000	0 (0)	1 (14)	0.412
Prior pulmonary hypertension, n (%)	2 (12)	1 (14)	1 (10)	1.000	1 (10)	1 (14)	1.000
Prior cardiac surgery, n (%)	1 (6)	1 (14)	0 (0)	0.412	1 (10)	0 (0)	1.000
Prior lung surgery, n (%)	1 (6)	0 (0)	1 (10)	1.000	0 (0)	1 (14)	0.412
History of malignancy, n (%)	1 (6)	0 (0)	1 (10)	1.000	0 (0)	1 (14)	0.412
Immunosuppressive medication, n (%)	1 (6)	0 (0)	1 (10)	1.000	0 (0)	1 (14)	0.412
Typical symptoms, n (%)	17 (100)	5 (71)	6 (60)	1.000	6 (60)	5 (71)	1.000
Fever at admission, n (%)	9 (53)	4 (57)	5 (50)	1.000	5 (50)	4 (57)	1.000
Temperature (°C), median (IQR)	38.6 (37.1–38.9)	38.6 (36.9–38.8)	38.3 (37.3–39.1)	0.669	38.3 (36.8–38.9)	38.7 (37.3–38.9)	0.740
Cough, n (%)	10 (59)	5 (71)	5 (50)	0.622	6 (60)	4 (57)	1.000
Dyspnea, n (%)	12 (71)	6 (86)	6 (60)	0.338	8 (80)	4 (57)	0.593
Diarrhea, n (%)	3 (18)	1 (14)	2 (20)	1.000	2 (20)	1 (14)	1.000
Antiviral treatment, n (%)	3 (18)	2 (29)	1 (10)	0.537	2 (20)	1 (14)	1.000
Inotropes, n (%)	12 (71)	4 (57)	8 (80)	0.593	7 (70)	5 (71)	1.000
Vasopressor, n (%)	15 (88)	6 (86)	9 (90)	1.000	8 (80)	7 (100)	0.485
iNO inhalation, n (%)	8 (47)	3 (43)	5 (50)	0.581	6 (60)	2 (29)	0.335

(Continued)

Table 1 (Continued)

Variable	Total (n = 17)	TEE (n = 7)	No TEE (n = 10)	p-value ^a	BE (n = 10)	No BE (n = 7)	p-value ^a
Mechanical ventilation settings							
MV pre-ECMO (d), median (IQR)	3 (2.5–17)	3 (3–20)	3.5 (1.8–12)	0.536	3.5 (2.8–13)	3 (2–20)	0.962
pO ₂ :FiO ₂ (ratio), median (IQR)	0.82 (0.68–1.04)	0.76 (0.6–0.83)	0.97 (0.7–1.2)	0.161	0.91 (0.7–1)	0.83 (0.5–1)	0.813
Pinsp (mbar), median (IQR)	28 (25–30)	28 (26–30)	28 (25–30)	0.536	28 (27–30)	26 (22–30)	0.536
PEEP (mbar), median (IQR)	14 (11–15)	14 (13–15)	13.5 (9.5–15)	0.669	14 (13–15)	12 (10–15)	0.315
VTe (mL), median (IQR)	320 (219–477)	347 (295–500)	293 (153.8–455)	0.193	338 (258–520)	295 (157–440)	0.193
Vf (n/min), median (IQR)	24 (22–30)	24 (22–24)	25 (21.3–31.3)	0.813	24 (22–27)	24 (19–35)	1.000
CVP (mm Hg), median (IQR)	14 (11–15.5)	11 (10–15)	15 (13–17)	0.109	14 (11–15)	15 (10–18)	1.000
ECMO settings							
V-V, n (%)	16 (0.94)	6 (86)	10 (100)	0.412	9 (90)	7 (100)	1.000
V-A, n (%)	1 (0.06)	1 (14)	0 (0)	0.412	1 (10)	0 (0)	1.000
Fem.-Jug., n (%)	7 (0.41)	3 (43)	4 (40)	1.000	3 (30)	4 (57)	0.350
Fem.-Fem., n (%)	1 (0.06)	1 (14)	0 (0)	0.412	1 (10)	0 (0)	1.000
Right IJV dual cannula, n (%)	9 (0.53)	3 (43)	6 (60)	0.637	6 (60)	3 (43)	0.637
Cytokine absorption, n (%)	8 (47)	2 (29)	6 (60)	0.335	5 (50)	3 (43)	1.000
Blood gas and laboratory tests							
pO ₂ (mm Hg), median (IQR), (ref. 80–105)	68 (54–74)	68 (58–82)	65 (52–71)	0.364	68.5 (62–77)	55 (49–72)	0.161
pCO ₂ (mm Hg), median (IQR), (ref. 35–45)	66 (45–78)	77 (55–80)	60 (34–70)	0.088	68 (51–77)	66 (32–88)	0.813
pH, median (IQR), (ref. 7.35–7.45)	7.3 (7.2–7.4)	7.3 (7.2–7.3)	7.3 (7.2–7.4)	0.364	7.3 (7.2–7.3)	7.3 (7.2–7.4)	0.475
BE (mmol/L), median (IQR), (ref. -2–2)	1.8 (-4.2 to 6.5)	2.3 (-5.5 to 6.5)	-1.6 (-4 to 6.8)	0.669	-1.6 (-5.5 to 6.8)	2.1 (-3.5 to 6.5)	0.536
HCO ₃ (mmol/L), median (IQR), (ref. 22–29)	26 (24–35)	31 (25–35)	25 (22–33)	0.270	26 (24–35)	31 (25–34)	0.813
Na ⁺ (mmol/L), median (IQR), (ref. 135–147)	145 (142–151)	145 (144–151)	143 (137–152)	0.536	144 (140–151)	146 (142–151)	0.601
K ⁺ (mmol/L), median (IQR), (ref. 3.5–5)	4.4 (3.8–4.65)	4.5 (4.2–4.7)	4.1 (3.8–4.7)	0.230	4.4 (3.8–4.6)	4.4 (3.8–5.1)	1.000
Hb (g/dL), median (IQR), (ref. 12–17.5)	9.3 (7.9–11)	9.4 (8.4–12.5)	8.5 (7.5–10.5)	0.230	9.2 (7.9–10.4)	9.9 (7–12.1)	0.887
WBC (/nL), median (IQR), (ref. 4.5–11)	11.1 (9.8–15.35)	10.4 (9.6–13.4)	12.4 (9.9–18.6)	0.315	10.2 (9.5–15.3)	13.2 (10.4–16)	0.315
Platelet (G/L), median (IQR), (ref. 150–450)	226 (180–421)	213 (145–290)	232.8 (192–471)	0.740	209 (145–238)	452 (240–560)	0.007 ^a
Creatinine (mg/dL), median (IQR), (ref. 0.84–1.21)	1.1 (0.8–1.7)	0.9 (0.8–1.8)	1.2 (0.9–2)	0.740	1.2 (0.9–2.3)	1.1 (0.7–1.6)	0.669
BUN (mg/dL), median (IQR), (ref. 7–20)	64 (41–114)	62 (29–116)	65 (44–116)	0.669	48.5 (33.5–135.5)	66 (62–77)	0.601
GLDH (U/L), median (IQR), (ref. 1–10)	8.6 (3.6–12)	5.6 (3.2–12)	8.7 (3.8–12.5)	0.887	7.1 (3–12.5)	8.8 (3.9–12)	0.740
CK (U/L), median (IQR), (ref. 22–198)	234 (60–657)	167 (45–234)	592 (66.3–1672.5)	0.193	201 (66–590)	598 (46–4155)	0.417
Ck-MB (U/L), median (IQR), (ref. 5–25)	21 (18–40)	27 (18–53)	19 (12–34)	0.270	22 (16.5–53.5)	20 (18–27)	1.000
TrpT (μg/mL), median (IQR), (ref. <22)	22 (12–59)	22 (9–52)	31.5 (11.8–73.3)	0.601	21 (13.5–56.8)	50 (10–65)	0.887
Bilirubin (mg/dL), median (IQR), (ref. 0.2–0.8)	0.5 (0.41–1.21)	0.4 (0.4–0.7)	0.7 (0.5–1.7)	0.109	0.5 (0.4–2.2)	0.6 (0.4–0.8)	0.887

Table 1 (Continued)

Variable	Total (n = 17)	TEE (n = 7)	No TEE (n = 10)	p-value ^a	BE (n = 10)	No BE (n = 7)	p-value ^a
ALT (U/L), median (IQR), (ref. 19–33)	37 (29–46)	39 (33–45)	32.5 (25.3–104.3)	0.740	34.8 (19.8–44.5)	39 (32–99)	0.364
AST (U/L), median (IQR), (ref. 5–40)	66 (38–140)	66 (37–91)	93.5 (36.5–174.3)	0.475	63.5 (37.8–108.5)	91 (35–153)	0.887
fHb (mg/L), median (IQR), (ref. <50)	36 (21–47)	25 (20–60)	36 (22.3–44)	0.887	30.5 (19.8–52.5)	36 (23–44)	0.740
LDH (U/L), median (IQR), (ref. 140–280)	403 (309.5–559.5)	403 (314–459)	398 (303–692)	0.813	382 (303–525.3)	403 (322–639)	0.887
PTT (s), median (IQR), (ref. 60–70)	33 (28–37)	35 (29–37)	33 (28–36)	0.740	35 (28–39)	29 (28–34)	0.193
INR, median (IQR), (ref. 2–3)	1.3 (1.2–1.3)	1.3 (1.2–1.3)	1.3 (1.2–1.3)	0.887	1.2 (1.2–1.3)	1.3 (1.3–1.4)	0.133
ATIII (%), median (IQR), (ref. 60–123)	66 (52–76)	66 (54–87)	68 (46.8–76)	0.887	66.5 (55.5–78.8)	55 (40–76)	0.475
IL-6 (µg/mL), median (IQR), (ref. 0–16.4)	256 (93–642)	122 (104–931)	286.8 (70.6–544.4)	1.000	253.7 (98.7–497.7)	317.6 (79.4–1329)	0.813
CRP (ng/mL), median (IQR), (ref. <10)	187 (116–284)	211 (162–280)	165 (108–295)	0.813	243 (86–295)	183 (120–276)	0.536
PCT (%), median (IQR), (ref. 0.22–0.24)	2.2 (0.56–6.14)	0.6 (0.5–5.6)	5.1 (0.8–7.1)	0.230	1.6 (0.6–5.8)	5.2 (0.4–9.1)	0.740
D-dimer (µg/dL), median (IQR), (ref. <250)	4,547 (1,720–15,395)	11,567 (1,876–25,097)	4,174 (1,626–7,950)	0.475	5,193 (1,732–34,031)	4,547 (1,420–12,046)	0.669
Fibrinogen (mg/dL), median (IQR), (ref. 200–400)	656 (421–717)	656 (432–721)	569 (382.5–712.5)	0.669	569 (426.3–723.8)	656 (303–717)	0.740
NT-proBNP (pg/mL), median (IQR), (ref. <300)	1,765 (522–4,274)	1,765 (438–7,365)	2,089 (495–4,199)	1.000	1,914 (389–4,668)	1,765 (605–4,425)	0.887
ICU risk scores							
Resp score, median (IQR)	–1 (–3 to 1)	–2 (–4 to 0)	0 (–3 to 2)	0.315	–0.5 (–2.5 to 0)	–2 (–3 to 2)	0.813
GCS, median (IQR)	3 (3–3)	3 (3–3)	3 (3–3)	0.669	3 (3–3)	3 (3–3)	0.740
NEMS, median (IQR)	39 (39–45)	39 (39–44)	39.5 (37.8–46.3)	0.475	39 (37–44)	39 (39–45)	0.601
NEMS + SAS, median (IQR)	43 (41–48)	42 (41–47)	46 (42–48)	0.230	43 (41–48)	47 (42–49)	0.315
RASS, median (IQR)	–4 (–4 to 4)	–4 (–4 to 4)	–4 (–4.6 to 4)	0.193	–4 (–4.1 to 4)	–4 (–4 to 4)	0.887
SAPS II, median (IQR)	46 (36–57)	52 (35–57)	42 (36.5–51.8)	0.475	49 (35–57.8)	44 (37–52)	0.740
SAS, median (IQR)	2 (2–3)	2 (2–2.5)	2.4 (1.9–3)	0.962	2 (2–3.3)	2.5 (2–3)	0.962
SOFA, median (IQR)	9 (7–12.5)	11 (7–13)	9 (7–11.5)	0.669	11 (7–13.8)	9 (7–11)	0.536
Core-10-TISS, median (IQR)	17 (14–21)	16 (10–21)	17.5 (14–21.3)	0.536	17 (13.8–21.3)	17 (14–21)	0.962

Abbreviations: ALT, alanine transaminase; AST, aspartate transaminase; ATIII, antithrombin III; BMI, body mass index (kg/m²); BUN, blood urea nitrogen; CK, creatine kinase; CK-MB, creatine kinase myocardial band; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein (mg/L); CVP, central venous pressure; ECMO, extracorporeal membrane oxygenation; Fem., femoral vein; fHb, free plasma hemoglobin; GLDH, glutamate dehydrogenase; Hb, hemoglobin; iNO, inhaled nitric oxide; ICU, intensive care unit; IJV, internal jugular vein; IL-6, interleukin-6; Jug., jugular vein; LDH, lactate dehydrogenase; LVEF, left ventricular ejection fraction; MPAP, mean pulmonary artery pressure; MV, mechanical ventilation; NT-proBNP, N-terminal pro-hormone of brain natriuretic peptide; PCT, procalcitonin; PHT, pulmonary hypertension; PCl, percutaneous coronary intervention; PTT, partial thromboplastin time; PEEP, positive end-expiratory pressure; PEEP, positive end-expiratory pressure; Pinsp, maximal inspiratory pressure; ref., reference value; RHF, right heart failure; Tpt, topotecan; Vt, ventilation frequency; VTe, expiratory tidal volume; WBC, white blood cells; TnT, troponin T; V-A, venoarterial; V-V, venovenous.

Abbreviations of risk score systems: Core-10-TISS, Therapeutic Intervention Scoring System; GCS, Glasgow Coma Score; INR, international normalized ratio; NEMS, Nine equivalents of Nursing Manpower Use Score; RASS, Richmond Agitation–Sedation Scale; RESP, The Respiratory Extracorporeal Membrane Oxygenation Survival Prediction; SAPS II, Simplified Acute Physiology Score II; SAS, Riker Sedation–Agitation Scale; SOFA, Sequential Organ Failure Assessment Score.

^ap-values are calculated between the two previous columns. Under 0.05 is considered significant.

^bIncluding all patients with a MDRD-GFR < 60 mL/min.

Outcome and Clinical Course

The median ECMO support in our 17 patients was 16 days (IQR: 10.5–22). As of June 1, 2020, nine patients (53%) have been weaned successfully from ECMO and survived to hospital discharge and eight patients (47%) died during ECMO treatment. Seven patients (41%) developed TEE and 10 patients (59%) had BE during ECMO treatment. Patients frequently developed both TEE and BE; thus, five patients (71%) of the TEE group had BE and five patients (50%) of the BE group had TEE. Furthermore, we observed acute kidney failure with renal replacement therapy in 12 patients (71%), bacterial superinfections in 8 patients (47%), and right heart failure in 7 patients (41%). More details can be found in ►Table 2.

Outcomes, usage of blood products, and hospitalization details between the investigated groups showed no statistically

significant differences (►Table 2). Nevertheless, some relevant differences could be found and are mentioned in this section.

Starting with the TEE group ($n = 7$) compared with the non-TEE group ($n = 10$), we found comparable values for mortality (43 vs. 50%, $p = 0.581$) and median ECMO duration with 16 days (IQR: 13–23) versus 14 days (IQR: 10–22), $p = 0.601$. However, the TEE group developed right heart failure more frequently with 71 versus 20% ($p = 0.058$) and the median ICU stay was longer with 37 days (IQR: 18–62) versus 23 days (IQR: 6–53), $p = 0.315$.

As for the BE group ($n = 10$), we found higher mortality rates than in the non-BE group ($n = 7$) with 60 versus 29% ($p = 0.335$) and more patients who developed a disseminated intravascular coagulation (DIC) with 40 versus 0%, $p = 0.103$. Usage of blood products during ECMO was higher in the BE

Table 2 Outcomes and clinical course

Variable	Total ($n = 17$)	TEE ($n = 7$)	No TEE ($n = 10$)	p -value ^a	BE ($n = 10$)	No BE ($n = 7$)	p -value ^a
Mortality, n (%)	8 (47)	3 (43)	5 (50)	0.581	6 (60)	2 (29)	0.335
TEE, n (%)	7 (41)	7 (100)	0 (0)	0.000 ^a	5 (50)	2 (29)	0.622
BE, n (%)	10 (59)	5 (71)	5 (50)	0.622	10 (100)	0 (0)	0.000 ^a
Right heart failure, n (%) ^b	7 (41)	5 (71)	2 (20)	0.058	4 (40)	3 (43)	1.000
Bacterial superinfection, n (%)	8 (47)	2 (29)	6 (60)	0.335	4 (40)	4 (57)	0.637
Fungal superinfection, n (%)	3 (18)	1 (14)	2 (20)	1.000	2 (20)	1 (14)	1.000
DIC, n (%)	4 (24)	2 (29)	2 (20)	1.000	4 (40)	0 (0)	0.103
Delirium, n (%)	4 (24)	1 (14)	3 (30)	0.603	2 (20)	2 (29)	1.000
Acute kidney failure, n (%) ^c	12 (71)	6 (86)	6 (60)	0.338	9 (90)	3 (43)	0.101
RRT initiated, n (%)	12 (71)	6 (86)	6 (60)	0.338	9 (90)	3 (43)	0.101
Blood products							
ECMO flow (L/min), median (IQR) ^d	4 (3.7–4.4)	4 (3.2–4.2)	4.2 (3.7–4.4)	0.417	4.2 (3.4–4.4)	4 (3.8–4.4)	0.887
Total PRBCs (units), median (IQR)	32 (24–46)	33 (26–39)	31 (15–55.3)	0.813	32 (25.5–43.5)	33 (12–52)	0.669
PRBCs during ECMO (units), median (IQR)	28 (3–69)	26 (16–35)	24 (14–48.5)	1.000	28 (23.8–36.5)	14 (8–35.8)	0.093
PRBC per ECMO (units/d), median (IQR)	1.52 (1.13–2.7)	1.51 (1.13–1.78)	1.56 (1.26–1.88)	0.669	1.64 (1.52–2.7)	0.76 (0.5–1.78)	0.270
Total albumin (units), median (IQR)	85 (4–266)	9 (1–251)	103 (9–300)	0.669	124 (8–365)	12 (0–167)	0.230
Hospitalization details							
Total LOS (d), median (IQR)	24 (11–56)	37 (14–64)	23 (6–41)	0.417	20 (6–56)	30 (14–65)	0.417
Total ICU stay (d), median (IQR)	24 (16–56)	37 (18–62)	23 (6–53)	0.315	30 (17–58)	24 (1–53)	0.669
ECMO duration (d), median (IQR)	16 (11–22)	16 (13–23)	14 (10–22)	0.601	16 (11–24)	16 (10–21)	0.669
iNO duration (d), median (IQR)	2 (0–4.5)	2 (0–5)	1.5 (0–5.5)	0.813	2.5 (0.8–7)	0 (0–3)	0.133

Abbreviations: BE, bleeding events; DIC, disseminated intravascular coagulation; ECMO, extracorporeal membrane oxygenation; ICU, intensive care unit; iNO, inhaled nitric oxide; IQR, interquartile range; LOS, length of stay; MI, myocardial infarction; MV, mechanical ventilation; PRBCs, packed red blood cell; RRT, renal replacement therapy; TEE, thromboembolic events.

^a p -values are calculated between the two previous columns. Under 0.05 is considered significant.

^bIncluding all patients with right heart failure in stage 3 or 4 by the American Heart Association guidelines.

^cIncluding all patients with acute kidney failure in stage 2 or 3 by Kidney Disease Improving Global Outcomes (KDIGO) guidelines.

^dWe presented the blood flow rate that was adjusted on the first day of ECMO therapy.

Table 3 Thromboembolic and bleeding events (TEBE)

Outcome variable	Total (n = 17)
Total TEBE, n (%)	12 (71)
TEE, n (%)	7 (41)
Pulmonary artery embolism	5 (29)
Thrombosis	3 (18)
arterial	1 (6)
venous	2 (12)
Ischemic or hemorrhagic stroke	0 (0)
BE, n (%)	10 (59)
Upper respiratory tract	8 (47)
endobronchial	5 (29)
major	2 (12)
minor	3 (18)
mucosal	7 (41)
major	2 (12)
minor	5 (29)
Pericardial tamponade	2 (12)
Cannulation side	5 (29)
major	2 (12)
minor	3 (18)
Gastrointestinal	1 (6)
Hemothorax	1 (6)

Abbreviations: BE, bleeding events; TEE, thromboembolic events.

group; we also found more units of PRBC per ECMO day with 1.64 (IQR: 1.52–2.7) versus 0.76 (IQR: 0.5–1.78), $p = 0.270$ and more units of albumin over the whole ICU stay with 124 (IQR: 8–365) versus 12 (IQR: 0–167), $p = 0.230$.

Thromboembolic and Bleeding Events

During ECMO therapy, we had 12 patients (71%) who developed TEBE and 5 patients (29%) had a clinical course without TEBE. We used anticoagulation with UFH in 16 patients (94%). One patient (6%) received the thrombin-inhibitor Argatroban instead of UFH, due to heparin-induced thrombocytopenia II (HIT II). This patient developed a PAE and a major endobronchial bleeding despite altered anticoagulation. Moreover, we found two patients (12%) who already had TEBE after hospital admission but prior to ECMO implantation, and both had PAE. During ECMO, these two patients suffered again from PAE and developed bleedings.

–Table 3 shows the incidence of different TEBE during ECMO in detail. We summarized the results here. TEE occurred in 7 patients (41%) and BE in 10 patients (59%).

Among the seven patients with TEE were five patients (29%) with a PAE. Three patients (18%) had thrombosis consisting of two venous cases (12%) and one arterial case (6%). Both venous cases were a thrombosis in the right vena jugularis. The patient with arterial thrombosis had a thrombus formation in the fingers of the right hand. Ischemic or hemorrhagic strokes did not occur.

Among the 10 patients with BE were 8 patients (47%) with a URT bleeding. To be precise, we observed seven patients (41%) with a mucosal URT bleeding, of which two cases (12%) were a major bleeding. Five patients (29%) had an endobronchial URT bleeding, of which two cases (12%) were major bleeding. There were five patients (29%) with a cannulation side bleeding from which two cases (12%) were a major bleeding. We also reported two patients (12%) with a pericardial tamponade, one patient (6%) with a GIB and one patient (6%) with a hemothorax.

Time Course of Coagulation Parameters

Multiple parameters were measured on a daily basis to adjust anticoagulation therapy, where necessary. Due to imperfect documentation after ECMO initiation, we could not present all parameters. However, four different variables had less than 10% missing values and could be used. Therefore, we displayed time courses of PTT, platelet count, INR, and d-dimer using mean values in ▶Fig. 1.

PTT values were between 32 and 35 seconds before ECMO implantation and had an increasing trend during the therapy in all groups.

Regarding platelet count, the BE group had less platelets compared with the non-BE group in the first 3 days. As mentioned before, the difference in platelet count before ECMO implantation was statistically significant. However, the platelet count in the BE group was continuously above 80 G/L. This threshold was used in ECMO patients with bleeding by our internal guidelines.

INR values were higher in patients with TEE and BE. During statistical comparison, we could not find significant differences.

D-dimer values decreased in the first day after ECMO initiation; after that, we observed an increasing trend until the end of ECMO therapy in all patient groups.

Discussion

ARDS in COVID-19 patients showed a higher risk for TEBE than in non-COVID-19 patients.⁵ Considering the WHO and ELSO guidelines,^{10,18} ECMO plays a role as a rescue therapy in case of critically ill COVID-19 patients suffering from hypoxemic respiratory failure. However, incidence and risk factors for TEBE in COVID-19 patients treated with ECMO are still uncertain.

In this study, we described TEBE in the first 17 critically ill COVID-19 patients who received ECMO in our center and reported the following key findings. TEBE occurred in 12 patients (71%) consisting of 7 patients (41%) with TEE and 10 patients (59%) with BE. PAE was the most frequent TEE with five cases (29%), and URT was the most common location for BE with eight cases (47%). Mortality between the TEE group ($n = 7$) and the non-TEE group ($n = 10$) was comparable (43 vs. 50%, $p = 0.581$), and higher in the BE group ($n = 10$) than in the non-BE group ($n = 7$), but without significance (60 vs. 29%, $p = 0.335$). From among 85 pre-ECMO variables, only platelet count was significantly lower between the BE group ($n = 10$) and the non-BE group ($n = 7$) with 209 (IQR: 145–238) versus 452 (IQR: 240–560), $p = 0.007$. However, we found other



Fig. 1 Time courses of PTT, platelet count, INR, and d-dimer using mean values.

interesting differences that are not statistically significant but mentionable. TEE seemed to be more frequent patients with male gender, atrial fibrillation, less utilization of cytokine absorption, higher pCO_2 values, and lower RESP score values. As for BE, we found longer PTT and lower INR values.

From among the TEBE, mainly BE were frequent. Regarding other studies about ECMO in patients suffering from severe ARDS without COVID-19, we also found a high incidence of BE. Two studies report BE in 46% of the patients; the first study included 124 patients and the second study had 214 patients.^{11,13} We compared it to the 10 patients (59%) with BE of our study and no statistically significant differences could be found using Fisher's exact test. Only few studies reported the incidence of TEBE for COVID-19 patients treated with ECMO; the outcomes are not detailed enough and accurate comparisons with our study cannot be made. Especially the BE

are more frequent in our study and this is probably due to the fact that we also reported minor bleedings. Nevertheless, we summarized the results of other studies in the following. Yang et al¹⁷ reported only 3 patients (14%) with bleeding complications, whereas we had 10 patients (59%). In an American study by Kon et al,²⁰ there was only 1 patient (4%) with clinically significant bleeding complications, 5 patients (19%) with deep vein thrombosis (DVT), and 5 patients (19%) who developed thrombocytopenia; ECMO-associated complications in general were noted in 11 patients (41%). Bleeding complications and general ECMO complications are again much less than those in our study. However, we found four patients (24%) with thrombosis as a comparable outcome. In the study of Jacobs et al,¹⁵ two patients (13%) died due to DIC and one patient (7%) died due to a cerebral bleeding. In another American study by Loforte et al²¹ with only four patients in

total, one patient (25%) suffered from GIB. In our study, we report also one patient (6%) with GIB.

We observed a successful weaning rate of 53% from ECMO and survival to hospital discharge. This is superior to the rate of other studies.^{11,15,22} In the study of Yang et al,²³ only one patient (17%) survived out of the six patients treated with ECMO.²³ Marullo et al⁹ analyzed data of multiple institutions and reported a lower mortality of only 17% from 333 COVID-19 patients treated with ECMO. However, the actual weaning rate is 18% and the remaining patients are still alive on ECMO.⁹ Different patient selection and small sample sizes probably contribute to differences in survival rates.

The platelet count was significantly lower in patients with BE and therefore needs to be discussed. As stated previously, we only had one patient who developed a moderate thrombocytopenia between 50 and 100 G/L. Nevertheless, thrombocytopenia is a common phenomenon found in ECMO patients and its underlying mechanisms are multifactorial.²⁴ A decrease of platelets during the first 7 days is frequently seen and the values of our patient group were not clinically abnormal.²⁴ We aimed for a platelet count above 80 G/L as recommended in the ELSO guidelines.²⁵

We did not find any relevant hemorrhagic or ischemic strokes; however, we found five patients with microscopic bleedings in magnetic resonance imaging (MRI) examinations of the brain. Neurological symptoms did not occur in all cases and it is a common finding in COVID-19 patients without ECMO therapy. Therefore, it cannot be regarded as an ECMO complication in this study.

As a retrospective study, there was potential bias in data acquisition. Because of a small sample size and short study period, doctors could control the gathered data and confirm its correctness as much as possible. Although our pre-ECMO and outcome variables were complete, we have missing values for laboratory parameters during ECMO therapy. Therefore, we could not display time courses of all parameters.

We studied the characteristics and outcomes of the first 17 COVID-19 patients from March and April 2020, but we did not gather enough patients to conduct a high-quality predictor analysis. Therefore, validation of our findings with larger samples is required.

Conclusion

The present study describes TEBE during ECMO therapy in selected critically ill COVID-19 patients suffering from ARDS. It provides novel data about very common complications during ECMO therapy in a new subpopulation and can be used as guidance for future studies that investigate risk factors.

Further analysis with larger samples is required to optimize patient selection and improve the outcomes of critically ill COVID-19 patients.

Authors' Contribution

Koray Durak has collected the data (60%), performed data Analysis (55%) and wrote the first version of the manu-

script (100%). Alex Kersten contributed to the Study design (50%), performed ECMO implantation (35%), collected the data (40%), performed data analysis (45%), supervised the writing process of the first version of the manuscript, critically revised the manuscript. The above mentioned contribution justify a contributed equally authorship of both authors Koray Durak and Alex Kersten.

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We identified 10 different authors with the following explanation. All authors substantially contributed to the conception and performance of the study, as well as data acquisition, subsequent statistical analysis, and interpretation. Furthermore, multiple authors participated in ECMO implantation, blood sampling, supervision, and critical revision of the manuscript. All authors have seen and approved the final version of the manuscript. Both authors contributed equally to this study.

Conflict of Interest

None declared.

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