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Bleeding and thrombotic events in patients with severe COVID-19 supported with extracorporeal membrane oxygenation: a nationwide cohort study

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Abstract

Purpose: To describe bleeding and thrombotic events and their risk factors in patients receiving extracorporeal membrane oxygenation (ECMO) for severe coronavirus disease 2019 (COVID-19) and to evaluate their impact on in-hospital mortality.

Methods: The ECMOSARS registry included COVID-19 patients supported by ECMO in France. We analyzed all patients included up to March 31, 2022 without missing data regarding bleeding and thrombotic events. The association of bleeding and thrombotic events with in-hospital mortality and pre-ECMO variables was assessed using multivariable logistic regression models.

Results: Among 620 patients supported by ECMO, 29% had only bleeding events, 16% only thrombotic events and 20% both bleeding and thrombosis. Cannulation site (18% of patients), ear nose and throat (12%), pulmonary bleeding (9%) and intracranial hemorrhage (8%) were the most frequent bleeding types. Device-related thrombosis and pulmonary embolism/thrombosis accounted for most of thrombotic events. In-hospital mortality was 55.7%. Bleeding events were associated with in-hospital mortality (adjusted odds ratio (adjOR) = 2.91[1.94–4.4]) but not thrombotic events (adjOR = 1.02[0.68–1.53]). Intracranial hemorrhage was strongly associated with in-hospital mortality (adjOR = 13.5[4.4–41.5]). Ventilation duration before ECMO ≥ 7 days and length of ECMO support were associated with bleeding. Thrombosis-associated factors were fibrinogen ≥ 6 g/L and length of ECMO support.

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Conclusions: In a nationwide cohort of COVID-19 patients supported by ECMO, bleeding incidence was high and associated with mortality. Intracranial hemorrhage incidence was higher than reported for non-COVID patients and carried the highest risk of death. Thrombotic events were less frequent and not associated with mortality. Length of ECMO support was associated with a higher risk of both bleeding and thrombosis, supporting the development of strategies to minimize ECMO duration.

Keywords: ECMO, COVID-19, Bleeding, Thrombosis, Anticoagulation

Introduction

Veno-venous (VV) and veno-arterial (VA) extracorporeal membrane oxygenation (ECMO) are increasingly used in the management of refractory respiratory and circulatory failure [1–4]. However, ECMO complication rates remain high. Bleeding and thrombosis on ECMO are particularly frequent and carry a high risk of both morbidity and mortality [5–13]. They occur as a result of a complex interplay between the underlying critical illness, blood exposure to shear stress and non-biological surfaces and antithrombotic strategies.

Since the beginning of the SARS-CoV-2 pandemic, ECMO has been widely used for acute respiratory distress syndrome (ARDS) related to coronavirus disease 2019 (COVID-19) and, to a lesser extent, for COVID-19-associated circulatory failure [14–18]. Immunothrombosis is thought to be a key mechanism contributing to the pathogenesis of severe COVID-19 and to its high reported thrombotic risk [19–21]. This putative relationship has led to an ongoing research effort to evaluate optimal antithrombotic strategies and, frequently, to an intensification of anticoagulant dosing for COVID-19 patients in the intensive care unit (ICU) [22–26]. Although the rates and mechanisms of bleeding and thrombosis in COVID-19 patients have been extensively studied, relatively little is known about bleeding and thrombosis risks of COVID-19 patients on ECMO. The existing data are limited to small single-center series and one multicenter study [27–37].

Therefore, the goals of this prospective multicenter cohort study were: (1) to report bleeding and thrombotic events in patients receiving ECMO for severe COVID-19; (2) to evaluate their impact on in-hospital mortality; and (3) to identity factors associated with their occurrence. We hypothesized that bleeding and thrombotic events would be frequent and associated with worse outcomes.

Take-home message

In patients affected by coronavirus disease 2019 (COVID-19) supported by extracorporeal membrane oxygenation (ECMO), bleeding incidence was high and associated with mortality, with intracranial hemorrhage carrying the highest risk of death. Thrombotic events were less frequent and not associated with mortality. Length of ECMO support was associated with a higher risk of both bleeding and thrombosis.

Materials and methods

Data collection

The French national ECMOSARS registry (ClinicalTrials.gov Identifier: NCT04397588) was launched in April 2020 and is still currently recruiting COVID-19 patients supported by ECMO (VV or VA). The registry has been approved by the Rennes University Hospital ethics committee (n° 20.43). According to the French legislation, written consent was waived because of the observational design of the study. The data collection methodology has previously been described in the first report of the registry [17]. Briefly, data were collected by research assistants using an electronic case report form, and consistency tests were performed by data managers. Collected data included patient characteristics and comorbidities, management of COVID-related ARDS before ECMO cannulation, patient characteristics at ECMO cannulation and the day after, therapeutics, complications and patient outcomes on ECMO (see Supplementary Table S1 for the definition of the main variables). Patient and ECMO management, including anticoagulation, screening for bleeding/thrombosis complications and weaning protocol, was at the discretion of each center.

Study design and population

For the present study, we analyzed all consecutive patients included in the registry from the first patient included on February 25, 2020 up to March 31, 2022 without missing data regarding bleeding and thrombotic events. The analysis followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines (Supplementary Table S2).

Outcomes and variables

Our primary outcome was the incidence of thrombotic and bleeding events. Secondary outcomes were in-hospital mortality, mortality at day 28, mortality at day 90, ICU length of stay and hospitalization duration.

The ECMOSARS registry captures all clinically relevant bleeding and thrombotic events, irrespective of their assumed severity (see Supplementary Table S1 for the definition of bleeding and thrombotic events). No systematic screening was performed for both bleeding and thrombosis complications. Bleeding events included: intracranial bleeding, upper or lower gastrointestinal hemorrhage, peripheral cannulation site bleeding, retroperitoneal bleeding and pulmonary hemorrhage. Thrombotic events included: ischemic stroke, deep vein thrombosis, pulmonary embolism (or pulmonary thrombosis), acute mesenteric ischemia, acute limb ischemia, macroscopic thrombus of circuit and/or membrane without needing to change the circuit or the oxygenator, oxygenator failure requiring change due to clot formation, acute circuit thrombosis requiring change. In addition, the following variables were included in the present study: pre-ECMO patient-related variables (baseline demographics and comorbidities), pre-ECMO hospitalization related variables (center, Simplified Acute Physiology Score (SAPS) II, non-invasive ventilation, high-flow oxygen therapy, neuromuscular blocking agents, prone position, antiviral therapy, antibiotic therapy), variables at ECMO cannulation (ventilation duration, Sequential Organ Failure Assessment (SOFA) score, ARDS, vasoactive and inotropic drugs, lactatemia, pH, PaO_2/FiO_2 ratio, $PaCO_2$ change within 24 h after ECMO initiation, renal replacement therapy, anticoagulation, platelet count, prothrombin time (PT) expressed as percentage of standard value, fibrinogen), cannulation-related variables (retrieval and transport, type of ECMO), on-ECMO variables (antiplatelet agent, anticoagulation-related variables, antithrombin monitoring, length of ECMO support, transfusion requirements, vasoactive and inotropic drugs, acute kidney injury, infectious complications).

Statistical analysis

Patient characteristics are expressed as number (percentage) for categorical variables and median with interquartile range for continuous variables. For comparison between bleeding and thrombotic complications, a χ^2 test or a Fisher's exact test were used for categorical variables and a Kruskal–Wallis test for continuous variables. For comparison between VV and VA-ECMO and between epidemic waves, a χ^2 test or a Fisher's exact test were used.

A statistical analysis plan was made prior to accessing the data. No a priori statistical power calculation was conducted. Only pre-ECMO variables and variables at ECMO cannulation were included in the following multivariable analyses to prevent competing risk bias.

A directed acyclic graph was used to describe our model of causal associations between bleeding and thrombotic events (exposure variables), patient-related confounders, pre-ECMO hospitalization-related confounders, at ECMO cannulation confounders and in-hospital mortality, using DAGitty software (Supplementary Figure S1) [38]. No variables were analyzed as effect modifiers. The set of potential confounders sufficient for adjustment was: age, body mass index (BMI), center, PT at cannulation, type of ECMO (VV or VA), renal replacement therapy before ECMO, ventilation duration before ECMO and PaO_2/FiO_2 at cannulation. A multivariable logistic regression model was then used to estimate odd ratios between bleeding and thrombotic events (exposure variables) and in-hospital mortality. Confounders entered in the model were defined a priori using the directed acyclic graph. Centers were included in analysis as stratification factor. Patients who were still hospitalized at the time of database lock were not included in this analysis. Mortality at day 90 was also evaluated for any bleeding, any thrombosis and intracranial hemorrhage using the same model, as a post-hoc secondary analysis.

Multivariable logistic regression models were also used to identify variables independently associated with bleeding and thrombotic events. Variables entered in the models were defined a priori, based on published ECMO and COVID-19 literature [9, 10, 21, 27, 36, 37, 39–46]. No further variable selection was done. The set of variables entered in the model for bleeding events was: age, body mass index, type of ECMO, ventilation duration before ECMO, anticoagulation before ECMO, PT at cannulation, platelet count < 100 G/L at cannulation, fibrinogen < 1.5 g/L at cannulation, pH ≥ 7.25 at cannulation, PaO_2/FiO_2 ratio at cannulation, renal replacement therapy at cannulation, $PaCO_2$ change within 24 h after ECMO initiation and length of ECMO support. The set of variables entered in the model for thrombotic events was: age, body mass index, type of ECMO, ventilation duration before ECMO, anticoagulation before ECMO, PT at cannulation, platelet count ≥ 350 G/L at cannulation, fibrinogen ≥ 6 g/L at cannulation, pH ≥ 7.25 at cannulation, PaO_2/FiO_2 ratio at cannulation, renal replacement therapy at cannulation, $PaCO_2$ change within 24 h after ECMO initiation, length of ECMO support and history of venous thromboembolism. A sensitivity analysis was performed by removing from the multivariable models, the variables imputed with more than 30% of missing data (PT and fibrinogen).

Linearity of continuous independent variables and log-odds was checked. If not, those variables were transformed into categorical variables in accordance with previously published works [3, 9, 10, 17, 46].

Multiple imputation was used to account for missing values in variables. We used fully specified chained equations in the SAS MI procedure. For continuous variables, the regression method was used to impute missing values and discriminant function methods were used for binary and categorical variables. Passive imputation was used for the derived variables (BMI), meaning that each variable needed for the calculation was imputed prior to the calculation of the derived variable. Fifty imputed data sets were created and combined using standard between/within-variance techniques.

To describe the clinical management and outcomes over the course of the pandemic, a post-hoc analysis was performed by splitting the cohort between the first epidemic wave (up to July 1, 2020 [47]), and the next waves (from July 1, 2020 to March 31, 2022). Indeed, substantive changes were made regarding ICU management of COVID-19 patients in France after the first wave, including improved healthcare organization at a national scale, widespread use of Dexamethasone [48], increased use of non-invasive ventilation [49] and SARS-CoV-2 vaccination (starting January 2021).

All tests used two-tailed hypothesis. Statistical significance was achieved for $p < 0.05$. Statistical analyses were performed with SAS version 9.4 software (SAS Institute, Cary, North Carolina, USA).

Results

Study population

Among the 701 patients included in the ECMOSARS registry at the time of database lock, 81 had missing data regarding bleeding and thrombotic events, leaving 620 patients included in the present study (Fig. 1). Five hundred sixty-eight patients were supported by VV-ECMO, and 52 by VA-ECMO. Median age was 55 (47–61) years, 22.9% were females, and had a median body mass index of 30 (27–34) kg/m^2 (Table 1). Median SAPS II was 42 (31–57). ICU management before ECMO cannulation included non-invasive ventilation (32.5%), high-flow oxygen therapy (51.6%), neuromuscular blocking agents (94.8%), prone positioning (90.4%), antiviral therapy (49.2%) and antibiotics (90.1%). At the time of ECMO cannulation, 96% met Berlin criteria for ARDS with a median PaO_2/FiO_2 ratio of 68 (57–85) mmHg, and 11.9% were on renal replacement therapy.

Coagulation management

At ECMO cannulation, 90.1% (430/477) of patients had received anticoagulation (therapeutic-dose 45.3%, prophylactic-dose 44.9%). Median fibrinogen level was 7.4 (5.6–8.7) g/L, median PT was 73 (64–82)% and median platelet count was 255 (184–345) G/L (Table 2).

During ECMO support, the majority of patients received systemic anticoagulation (95.3%) and the preferred anticoagulant was unfractionated heparin (98.1%; $n = 468$). Unfractionated heparin was monitored using anti-factor Xa activity (91.6%), activated partial thromboplastin time (7.4%) and activated clotting time (ACT)

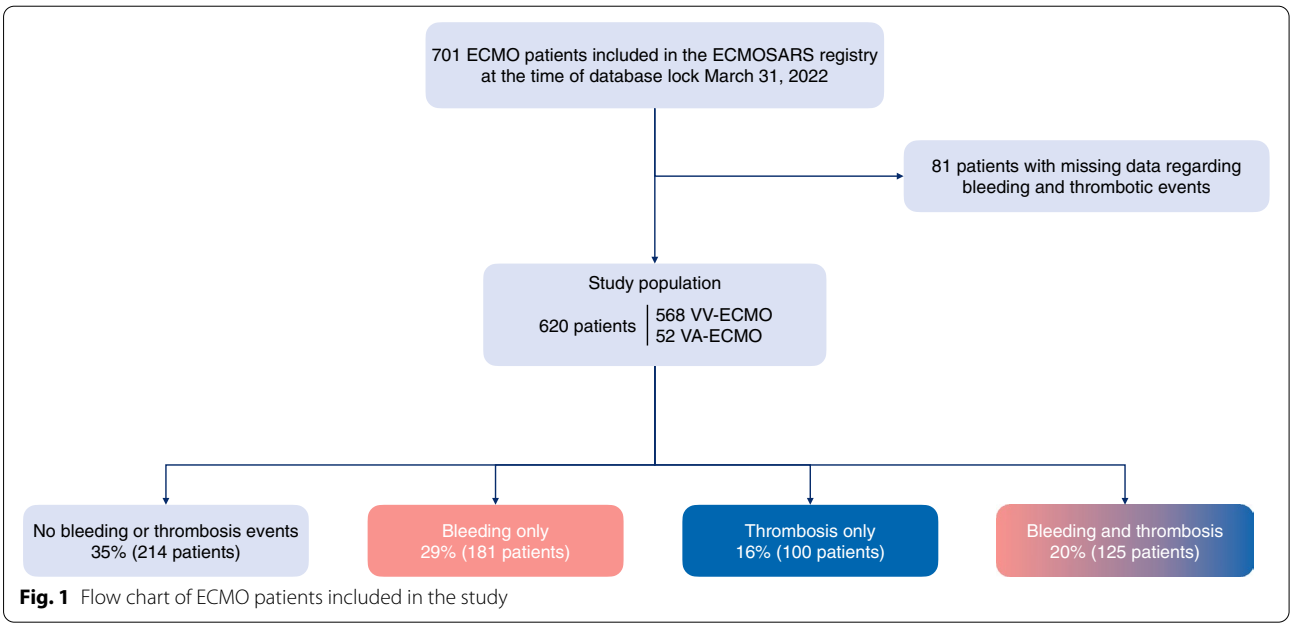

Fig. 1 Flow chart of ECMO patients included in the study

Table 1 Patient characteristics at the time of ECMO cannulation

Characteristics	No	All patients (*n* = 620)	Bleeding/thrombosis status				*p* value
			None (*n* = 214)	Bleeding (*n* = 181)	Thrombosis (*n* = 100)	Both (*n* = 125)	
Age—years	618	55 (46–61)	54 (44–61)	57 (50–62)	53 (46–59)	55 (48–60)	0.040
Female sex	620	142 (22.9)	56 (26.2)	36 (19.9)	26 (26)	24 (19.2)	0.291
Body mass index—kg/m^2	597	30 (27–34)	30 (27–35)	29 (26–33)	30 (26–35)	30 (27–34)	0.196
Comorbidities							
Chronic respiratory failure	620	19 (3.1)	10 (4.7)	5 (2.8)	2 (2)	2 (1.6)	0.441
Congestive heart failure	498	11 (2.2)	1 (0.7)	4 (2.5)	3 (3.9)	3 (2.6)	0.360
Coronary artery disease	620	34 (5.5)	9 (4.2)	10 (5.5)	8 (8)	7 (5.6)	0.593
Chronic kidney disease	499	24 (4.8)	9 (6)	9 (5.7)	3 (3.9)	3 (2.6)	0.579
Cancer	496	6 (1.2)	3 (2)	1 (0.6)	1 (1.3)	1 (0.9)	0.695
Hematological malignancy	496	5 (1)	2 (1.3)	2 (1.3)	0 (0)	1 (0.9)	0.935
Active smoker	614	27 (4.4)	10 (4.7)	8 (4.4)	3 (3)	6 (4.9)	0.929
History of venous thromboembolism	496	22 (4.4)	5 (3.4)	6 (3.8)	4 (5.2)	7 (6.2)	0.663
Pre-ECMO ICU management							
Simplified acute physiology score II	619	42 (31–57)	41 (29–56)	41 (31–58)	43 (34–55)	40 (29–56)	0.842
Delay from hospitalization to ICU	618	0 (0–0)	0 (0–0)	0 (0–1)	0 (0–1)	0 (0–0)	0.077
Non-invasive ventilation	615	200 (32.5)	60 (28.3)	70 (39.3)	24 (24)	46 (36.8)	0.020
High-flow oxygen therapy	496	256 (51.6)	72 (47.7)	85 (54.8)	38 (49.4)	61 (54)	0.574
Neuromuscular blocking agents	616	584 (94.8)	196 (92.5)	170 (95)	96 (96)	122 (97.6)	0.198
Prone position	617	558 (90.4)	187 (88.2)	165 (91.7)	90 (90)	116 (92.8)	0.501
Antiviral therapy	494	243 (49.2)	62 (41.9)	74 (47.4)	37 (48.1)	70 (61.9)	0.013
Antibiotic therapy	495	446 (90.1)	135 (91.2)	134 (85.4)	69 (89.6)	108 (95.6)	0.046
Characteristics at ECMO cannulation							
Ventilation time before ECMO—d	615	5 (2–8)	4 (1–7)	6 (3–9)	5 (3–8)	6 (3–8)	< 0.001
SOFA score	552	9 (8–12)	10 (8–12)	10 (8–12)	8 (6–11)	8 (7–12)	0.032
ARDS (Berlin criteria)	607	583 (96)	200 (95.7)	168 (94.9)	94 (95.9)	121 (98.4)	0.477
Vasoactive/inotropic drugs							
Norepinephrine	487	290 (59.5)	84 (57.5)	93 (60.8)	41 (54.7)	72 (63.7)	0.593
Epinephrine	494	29 (5.9)	8 (5.4)	11 (7.1)	3 (3.9)	7 (6.2)	0.815
Dobutamine	492	26 (5.3)	10 (6.7)	8 (5.2)	3 (3.9)	5 (4.4)	0.844
Lactatemia—mmol/L	543	1.7 (1.3–2.5)	1.8 (1.3–2.6)	1.7 (1.2–2.6)	1.7 (1.3–2.2)	1.6 (1.2–2.4)	0.362
pH	593	7.33 (7.25–7.4)	7.32 (7.24–7.4)	7.33 (7.24–7.4)	7.35 (7.26–7.42)	7.33 (7.25–7.38)	0.593
PaO_2/FiO_2 ratio—mmHg	586	68 (57–85)	66 (55–85)	69 (58–85)	72 (59–90)	67 (59–85)	0.233
ΔPCO_2	563	− 9 (− 21 to 0)	− 10 (− 21 to 1)	− 10 (− 22 to 1)	− 9 (− 19 to -1)	− 7 (− 17 to 2)	0.722
Renal replacement therapy	612	73 (11.9)	27 (12.8)	21 (11.7)	9 (9.1)	16 (13)	0.788
ECMO cannulation							
Retrieval and transport	617						0.383
Referral center		385 (62.4)	121 (56.8)	119 (66.1)	63 (63.6)	82 (65.6)	
Mobile ECMO unit, no transfer		45 (7.3)	14 (6.6)	13 (7.2)	8 (8.1)	10 (8)	
Mobile ECMO unit, transfer to referral center		187 (30.3)	78 (36.6)	48 (26.7)	28 (28.3)	33 (26.4)	
Type of ECMO	620						0.840
Veno-venous ECMO		575 (92.7)	201 (93.9)	166 (91.7)	93 (93)	115 (92)	
Veno-arterial ECMO		45 (7.3)	13 (6.1)	15 (8.3)	7 (7)	10 (8)	

Results are presented as *n*(%) or median (IQR)

SOFA, Sequential Organ Failure Assessment; ARDS, Acute Respiratory Distress Syndrome; PT, prothrombin time; PaO_2, partial pressure of oxygen; FiO_2, fraction of inspired oxygen; $\Delta PaCO_2$, difference between day 1 and cannulation partial pressure of carbon dioxide

Table 2 Hemostasis laboratory results and coagulation management pre- and during ECMO support

Clinical condition and management	No	All patients (*n* = 620)	Bleeding/thrombosis status				*p* value
			None (*n* = 214)	Bleeding only (*n* = 181)	Thrombosis only (*n* = 100)	Both (*n* = 125)	
At ECMO cannulation							
Anticoagulation	477						0.010
No		47 (9.9)	18 (12.5)	17 (11)	11 (15.5)	1 (0.9)	
Therapeutic-dose		216 (45.3)	60 (41.7)	76 (49)	25 (35.2)	55 (51.4)	
Prophylactic-dose		214 (44.9)	66 (45.8)	62 (40)	35 (49.3)	51 (47.7)	
Platelet count—G/L	477	255 (184–345)	253 (176–325)	250 (187–341)	264 (187–353)	257 (201–367)	0.663
PT—% [a]	411	73 (64–82)	75 (66–83)	73 (60–81)	74 (63–83)	72 (64–82)	0.646
Fibrinogen—g/L	398	7.4 (5.6–8.7)	7.1 (5.3–8.7)	7 (4.7–8.5)	7.87 (6.1–9)	7.6 (6.4–8.9)	0.032
During ECMO support							
Antiplatelet agents	492	48 (9.8)	11 (7.4)	18 (11.5)	11 (14.5)	8 (7.1)	0.235
Anticoagulation strategy	509						0.464
Without systemic anticoagulation		24 (4.7)	8 (5.4)	10 (6.4)	3 (3.5)	3 (2.5)	
Systemic anticoagulation		485 (95.3)	140 (94.6)	146 (93.6)	82 (96.5)	117 (97.5)	
Therapeutic-target-achieving time—hours	313	9 (4–44)	7 (4–28)	8 (4–28)	12 (2–60)	11 (4–48)	0.364
Type of anticoagulant	468						0.241
Unfractionated heparin		459 (98.1)	131 (96.3)	145 (99.3)	72 (97.3)	111 (99.1)	
Nonheparin Anticoagulants		9 (1.9)	5 (3.7)	1 (0.7)	2 (2.7)	1 (0.9)	
Unfractionated heparin monitoring method	431						0.682
Anti-Factor Xa activity		395 (91.6)	104 (88.1)	132 (93)	60 (93.8)	99 (92.5)	
aPTT		32 (7.4)	13 (11)	9 (6.3)	3 (4.7)	7 (6.5)	
ACT		4 (0.9)	1 (0.8)	1 (0.7)	1 (1.6)	1 (0.9)	
Antithrombin monitoring	476	130 (27.3)	32 (23)	46 (29.7)	21 (29.6)	31 (27.9)	0.587
Lowest antithrombin level—%	129	62 (50–73)	65 (54–77)	59 (50–73)	65 (57–70)	56 (45–74)	0.710
Antithrombin supplementation	471	40 (8.5)	6 (4.4)	15 (9.8)	5 (7)	14 (12.6)	0.118

Results are presented as *n*(%) or median (IQR)

PT, prothrombin time; aPTT, activated partial thromboplastin time; ACT, activated clotting time

[a] Expressed as percentage of the standard value

(0.9%; $n = 431$). Median time to achieve anticoagulation target defined by centers for each patient was 9 (4–44) h. The anti-factor Xa activity target was ≥ 0.3 IU/mL in 86.2% of patients ($n = 354$; Supplementary Tables S3 and S4). Antithrombin (AT) levels were monitored for 27.3% of patients ($n = 476$), for whom the lowest AT level was 62 (50–73) %. Forty patients (8.5%) received AT supplementation ($n = 471$). Anticoagulation management was not significantly modified over the course of the pandemic (Supplementary Table S4).

Incidence of bleeding and thrombosis

Overall, 406 (65.5%) patients suffered from bleeding or thrombosis during ECMO support (306 with bleeding and 225 with thrombosis), of whom 181 (29%) had only bleeding events, 100 (16%) only thrombotic events and 125 (20%) both bleeding and thrombotic events (Table 3; Fig. 1). Of 725 total events, 382 (53%) were bleeding events (Fig. 2A). Cannulation site (114 events, 18.4% of patients) and ear nose and throat (76 events, 12.3% of patients) were the most frequent bleeding types. Intracranial hemorrhage accounted for 6.8% of total events (49 events, 8% of patients). Ten percent of bleeding events (40 events) were associated with a massive transfusion (> 10U PRBCS/24 h). Device-related thrombosis accounted for most thrombotic events with 82 circuit changes due to acute thrombosis (13.2% of patients), 59 oxygenator failures (9.5% of patients) and 72 macroscopic thrombi of circuit or membrane without needing to change circuit or oxygenator (11.6% of patients). Pulmonary embolism/thrombosis was diagnosed in 9.4% of patients (58 events). No significant difference was observed between VV and VA-ECMO regarding overall incidence of bleeding and thrombosis (Supplementary Tables S5, S10 and S11). VA-ECMO support, however, was associated with a significant increase in gastrointestinal bleedings (15.4% vs 6.5%, $p = 0.043$), leg ischemia

Table 3 Bleeding and thrombotic events during ECMO support and associated in-hospital mortality

Characteristics	All patients (*n* = 620)	In-hospital mortality[a] (%)
Bleeding		
Any bleeding	306 (49.4)	71.3
No of events	382	
Cannulation site bleeding	114 (18.4)	67.6
ENT bleeding	76 (12.3)	69.9
Intracranial hemorrhage	49 (8)	93.9
Pulmonary bleeding	56 (9)	76.8
GI bleeding	45 (7.3)	80
Retroperitoneal bleeding	10 (1.6)	82.5
Other bleeding	32 (5.2)	70
Thrombosis		
Any thrombosis	225 (36.3)	57.4
No of events	343	
Circuit Change	82 (13.2)	65.9
Circuit clots	72 (11.6)	50
Oxygenator failure	59 (9.5)	74.6
Pulmonary embolism/thrombosis	58 (9.4)	60.3
Deep vein thrombosis	41 (6.6)	30
Leg ischemia	13 (2.1)	75
Ischemic stroke	10 (1.6)	70
Mesenteric infarction	8 (1.3)	100

Results are presented as *n* (%)

ENT, ear, nose and throat; GI, gastrointestinal

[a] In-hospital mortality was not available for 17 patients who were still hospitalized at the time of database lock (*n* = 603)

(13.5% vs 1.1%, $p < 0.001$) and ischemic stroke (9.6% vs 0.9%, $p < 0.001$). While thrombosis incidence remained stable over the course of the pandemic (32.7% vs 37.6%, $p = 0.267$, Supplementary Table S6), overall bleeding increased after the first epidemic wave (58.2% vs 46.2%, $p = 0.008$, Supplementary Table S6).

Outcomes and bleeding/thrombosis events

In-hospital mortality was 55.7% (336/603) with a median follow-up of 51 (34–78) days for survivors and 17 (8–28) days for deceased patients. Mortality at day 90 was 62.6% (330/527). Bleeding events were associated with higher in-hospital mortality with 71.8% for bleeding only, 69.4% for bleeding and thrombosis, 42.4% for thrombosis only and 40.3% for no bleeding or thrombosis ($p < 0.001$; Table 4). On multivariable analysis, overall bleeding was independently associated with in-hospital mortality (adjusted odds ratio (adjOR) = 2.91 [1.94–4.4]; Fig. 2B, Supplementary Table S7), unlike overall thrombosis which was not associated with increased in-hospital mortality (adjOR = 1.02 [0.68–1.53]; Fig. 2B, Supplementary Table S8). Likewise, mortality at day 90 was increased in patients with bleeding complications (adjOR = 3.21[2.03–5.1]; Supplementary Table S7). Among bleeding types, intracranial hemorrhage was independently associated with in-hospital mortality (adjOR = 13.5 [4.4–41.5]; Fig. 2B, Supplementary Table S9) and mortality at day 90 (adjOR = 23.9 [4.6–124.8]; Supplementary Table S9). Pulmonary bleedings were also independently associated higher in-hospital

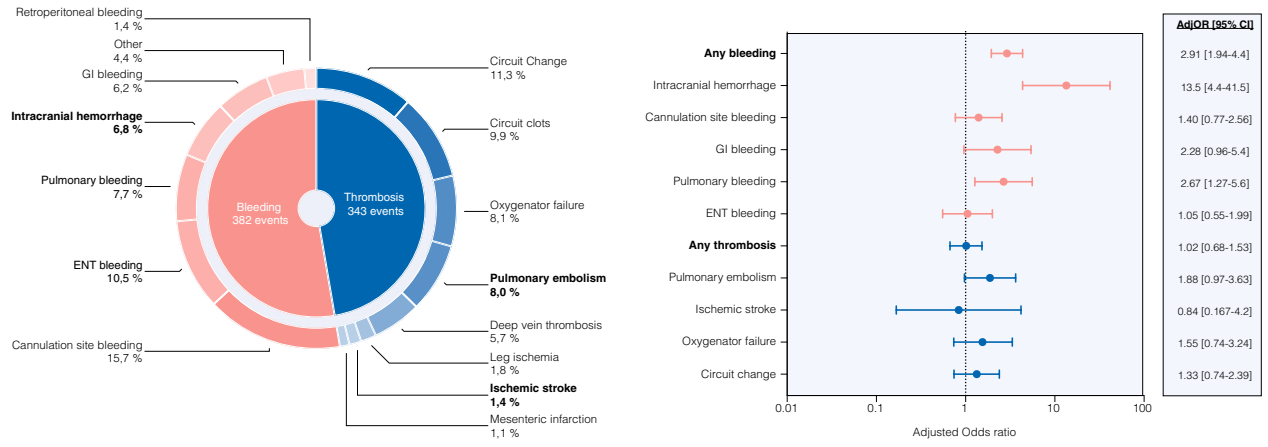

Fig. 2 Incidence and impact of bleeding and thrombotic events during ECMO support for severe COVID-19. **A**. Distribution of bleeding and thrombotic events on ECMO, expressed as percentage of total events (n = 725). Bleeding events are represented in red, thrombotic events in blue. **B**. Independent association of main bleeding and thrombotic events with in-hospital mortality. *GI, gastrointestinal*; *ENT, ear nose and throat*; *AdjOR, adjusted odds ratio*; *CI, confidence interval*

Table 4 Complications during ECMO support and outcomes

Characteristics	No	All patients (*n* = 620)	Bleeding/thrombosis status				*p* value
			None (*n* = 214)	Bleeding only (*n* = 181)	Thrombosis only (*n* = 100)	Both (*n* = 125)	
Complications on ECMO							
Length of ECMO support, days	541	12 (7–21)	11 (6–19)	13 (7–21)	13 (8–24)	18 (10–32)	< 0.001
Transfusion requirements on ECMO							
Number of PRBC transfused	476	4 (2–8)	2 (0–3)	6 (4–11)	2 (0–4)	9 (5–14)	< 0.001
Number of FFP transfused	469	0 (0–0)	0 (0–0)	0 (0–2)	0 (0–0)	0 (0–2)	< 0.001
Number of PC transfused	469	0 (0–0)	0 (0–0)	0 (0–1)	0 (0–0)	0 (0–2)	< 0.001
Vasoactive/inotropic drugs on ECMO							
Norepinephrine	492	422 (85.8)	123 (83.7)	139 (89.1)	51 (68)	109 (95.6)	< 0.001
Epinephrine	493	40 (8.1)	11 (7.4)	17 (10.8)	5 (6.6)	7 (6.3)	0.493
Dobutamine	493	40 (8.1)	13 (8.8)	12 (7.7)	4 (5.3)	11 (9.7)	0.717
Acute kidney injury on ECMO	615	292 (47.5)	86 (40.8)	95 (52.8)	39 (39)	72 (58.1)	0.003
Renal replacement therapy	288	225 (78.1)	65 (77.4)	77 (81.9)	27 (71.1)	56 (77.8)	0.596
Infectious complications on ECMO	616	307 (49.8)	109 (50.9)	77 (43)	55 (55.6)	66 (53.2)	0.151
Outcomes							
ICU length of stay—days	580	28 (15–45)	27 (15–45)	25 (12–41)	30 (15–48)	29 (17–46)	0.086
Hospitalization duration—days	565	34 (17–54)	40 (19–60)	28 (14–46)	39 (18–64)	33 (18–52)	0.003
Mortality at day 28	620	271 (43.7)	72 (33.6)	105 (58)	33 (33)	61 (48.8)	< 0.001
Mortality at day 90	527	330 (62.6)	82 (47.1)	122 (77.2)	42 (49.4)	84 (76.4)	< 0.001
In-hospital mortality	603	336 (55.7)	83 (40.3)	125 (71.8)	42 (42.4)	86 (69.4)	< 0.001

Results are presented as n (%) or median (IQR)

ECMO, extracorporeal membrane oxygenation; PRBC, packed red blood cells; FFP, fresh frozen plasma; PC, platelet concentrate; ICU, intensive care unit

mortality (adjOR = 2.67 [1.27–5.6]; Fig. 2B). Successive bleeding events in a patient were associated with higher mortality rates with adjusted odd-ratios of 1.87 [1.19–2.96] for one event, 3.84 [2.05–7.2] for two events and 3.63 [1.80–7.3] for three or more events. On univariate analysis, bleedings complications were associated with transfusion requirements on ECMO (packed red blood cells, fresh frozen plasmas and platelet concentrates) and acute kidney injury (Table 4).

Factors associated with the occurrence of bleeding and thrombotic events

Factors independently associated with the occurrence of all bleeding events were ventilation duration before ECMO ≥ 7 days (adjOR = 1.62 [1.09–2.41]) and length of ECMO support (per 5 days increase, adjOR = 1.08 [1.01–1.15]; Supplementary Table S10). Factors independently associated with the occurrence of all thrombosis events were fibrinogen ≥ 6 g/L at cannulation (adjOR = 1.94 [1.00–3.75]) and length of ECMO support (per 5 days increase, adjOR = 1.17 [1.09–1.26]; Supplementary Table S11). Sensitivity analyses removing PT and fibrinogen, imputed with more than 30% of missing data, from the variable selection did not change these results (Supplementary Tables S10 and S11).

Discussion

Our study reports bleeding and thrombotic events at a nationwide level in a large multicenter cohort of COVID-19 patients supported by ECMO. The main findings were as follows. First, bleeding complications were common, occurring in 49% of patients, and were independently associated with in-hospital mortality and mortality at day 90. Second, thrombotic events, while also common (36%), were associated with a fibrinogen ≥ 6 g/L at cannulation but not with mortality. Third, duration of ECMO support was associated with a higher risk of both bleeding and thrombosis. Fourth, intracranial hemorrhage was frequent (8%) and associated with high mortality rates (in-hospital and at day 90). And finally, the vast majority of the patients (95.3%) received a systemic anticoagulation with unfractionated heparin as the drug of choice (98.1%), mainly monitored by anti-factor Xa activity.

The incidence of bleeding complications in our study was high, with almost half of patients experiencing at least one bleeding event, which was higher than previously published studies on both COVID-19 and non-COVID patients supported by ECMO. This might,

however, be explained by the fact that the ECMOSARS registry captures all bleeding events, irrespective of their assumed severity (unlike Extracorporeal Life Support Organization (ELSO) registry or International Society on Thrombosis and Haemostasis (ISTH) major bleeding criteria) [3, 11–13, 16, 27, 28]. Overall, bleeding was independently associated with in-hospital mortality with a cumulative effect of bleeding recurrence, as already reported [11–13, 27]. In addition, our study demonstrates a sustained impact of bleeding on mortality at day 90. Finally, bleeding incidence seemed to increase over the course of the pandemic, which might be compared with the increased mortality previously reported [14, 47, 50, 51]. However, these findings will need to be confirmed in larger and more extensive studies.

Intracranial hemorrhage (ICH) incidence was higher than previously reported for both VV and VA-ECMO in non-COVID patients [3, 9, 11–13]. This seems, however, in line with recent data suggesting a higher incidence of ICH for COVID-19 patients supported by VV-ECMO [12–14, 16, 29–31, 34]. Notably, non-severe COVID-19 seems to be associated with a small but significant increase in the incidence of ICH [52, 53]. Unfortunately, many of these studies suffer from bias and heterogeneity in the diagnosis and reporting of intracranial hemorrhage, limiting their interpretation. The cause of the comparatively higher ICH incidence in COVID-19 patients on ECMO compared to other ECMO patients is not clear, but may be explained in part by the SARS-CoV-2 neurotropism hypothesis, or possibly by the intensification of anticoagulation in COVID-19 patients on ECMO [22, 26]. However, evidence for the link between anticoagulant dosing and bleeding remains limited for non-COVID patients on ECMO [11, 54], and therapeutic anticoagulation seems to be associated with only a non-significant trend for higher bleeding in COVID-19 patients [23–25, 55]. Finally, ICH was independently associated with mortality, in line with earlier studies on both COVID and non-COVID patients [12, 13, 27].

In addition to ICH, cannulation-related bleeding and ear nose and throat (ENT) bleeding accounted for more than a quarter of total events, but did not have a significant impact on in-hospital mortality. Compared to cannulation-related bleeds [12, 13], ENT bleeds, which are not included in the ELSO registry, have been rarely reported and their impact on mortality is largely unknown [11]. Moreover, the impact of the return cannula in a jugular position on the risk of ENT bleeding deserves further evaluation. In line with published data in non-COVID patients, pulmonary bleedings were frequent and independently associated with mortality [12, 13, 56]. Unlike previous reports, gastrointestinal bleeds, despite a trend towards higher mortality, did not reach statistical significance in multivariable analysis [12, 13].

Thrombosis incidence was lower than bleeding in our cohort, which contrasts with the recent ELSO report on VV-ECMO [12], even though our study included deep vein thrombosis and pulmonary embolism/thrombosis which are not recorded in the ELSO registry. Our results also differ from the high rates of thrombosis in early reports of COVID-19 patients on VV-ECMO [27, 28, 34]. Two factors might have influenced these results. First, as previously highlighted, intensification of anticoagulant dosing during the COVID-19 pandemic may have reduced thrombosis incidence, in particular circuit clotting and oxygenator failure [57]. Second, thrombosis reporting is highly dependent on clinical and radiological screening protocols. Systematic ultrasound or computed-tomography assessment of thrombosis on ECMO is likely accountable for the discrepancy between our results and recently published COVID-19 reports, especially regarding pulmonary embolism/thrombosis [27, 28, 34].

Unlike bleeding, neither overall thrombosis nor any thrombosis subtypes were significantly associated with in-hospital mortality. These results are partially in line with recent findings on COVID-19 ECMO patients [27] but differ from large multicenter studies in non-COVID ECMO patients which reported a significant impact of thrombosis on in-hospital survival, although weaker than bleeding [12, 13]. Two factors might explain these results. First, the use of a causal approach for model building using a directed acyclic graph (DAG) may have enabled a better control of confounding variables [38, 58]. Second, the smaller number of patients and events in our report might have underpowered the analysis.

We identified specific variables independently associated with the occurrence of bleeding or thrombosis. As already reported from the ELSO registry, the length of ECMO run was independently associated with both bleeding and thrombosis, supporting strategies aiming at minimizing ECMO duration, including daily assessment of readiness to liberate from ECMO [12, 13]. Longer duration of mechanical ventilation (MV) prior to ECMO ($\geq$ 7 days) was also independently associated with increased risk of bleeding. This may reflect a higher disease severity, nutritional deficiencies, increased inflammation and endothelial activation. This may also help to explain the reported association between survival and duration of MV before ECMO in both COVID and non-COVID patients [17, 18, 46]. Finally, a high fibrinogen level ($\geq$ 6 g/L) was associated with greater odds of thrombosis. Elevated fibrinogen levels have been associated with thrombosis risk in the general population [59, 60] but the evidence in ECMO patients remains scarce [61].

While fibrinogen, as inflammatory marker, is associated with COVID-19 severity and mortality [62], its ability to predict thrombosis appears low [39]. To date, only one single-center study, though limited in size, reported an association between high fibrinogen levels and thrombosis in COVID-19 patients supported by VV-ECMO [63].

Finally, we reported anticoagulation management practice during ECMO support at a nationwide level. As previously reported in an international survey [64], and in accordance with current international guidelines [65], the vast majority of the patients received a systemic anticoagulation, with unfractionated heparin being the drug of choice. Heparin was essentially monitored using anti-factor Xa activity, which contrasts with the international practice in adult ECMO [64]. Antithrombin monitoring and supplementation, though significant, was lower than previously published [64], which might reflect the negative results of a recent randomized control trial [66].

Our study has several strengths. First, we report bleeding and thrombosis for the first time in a large multicenter sample of COVID-19 patients, at a nationwide level. The excellent adherence to recommended medical interventions in ARDS patient management during the pre-ECMO period supports the generalizability of our results. Second, our registry captured data regarding ENT bleeding, venous thromboembolism and anticoagulation management practice that are not collected by the ELSO registry. Third, the use of a causal approach for multivariable model building and the sustained effect of bleeding on mortality up to day 90 strengthens confidence in our results.

Although the multicenter nature of this study prevented us from collecting high frequency clinical and biological data on ECMO, we were able to report important data regarding coagulation management, hitherto unpublished. These data highlight the considerable heterogeneity of practices and underline (1) the need for harmonization of procedures and practices across centers regarding hemostasis management on ECMO and (2) the crucial need for prospective interventional studies of anticoagulation management during both VA and VV-ECMO. To this extent, we believe our study reports valuable data that might help setting up prospective interventional studies.

Limitations

Our study has several limitations. The observational nature of this study prevented us from inferring causality. The timing of bleeding and thrombotic events occurrence was not available and sequential assessment of anticoagulation, ECMO parameters and biological markers on ECMO was not collected, precluding any time-to-event analysis. In addition, D-dimer levels, though described as markers of disease severity and thrombotic risk, were not available. Finally, the absence of systematic screening protocols for both bleeding and thrombosis before and during ECMO might have led to under-reporting of these events.

Conclusions

In a large nationwide cohort of patients supported by ECMO for severe COVID-19, bleeding incidence was high and associated with mortality. Besides, intracranial hemorrhage carried the highest risk of death. Thrombotic events were less frequent and were not associated with mortality. Length of ECMO support was associated with a higher risk of both bleeding and thrombosis, supporting the development and use of strategies to minimize ECMO duration. Our results highlight the need for harmonization of practices across centers regarding hemostasis management on ECMO and for prospective studies to evaluate anticoagulation strategies during ECMO support.

Supplementary Information

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Declarations

Conflicts of interest

AM received payments made to his institution from i-SEP for consulting fees, and LFB for lecture fees. EF declares no competing interests. MS received consultancy fees from Getinge, Xenios FMC and Drager. BR declares no competing interests. IG-T declares no competing interests. ME declares no competing interests. CF declares no competing interests. BL received personal fees from Abiomed, Gettinge, Baxter, Novartis, Sanofi, Amomed, and Orion. AP declares no competing interests. JTR declares no competing interests. MP declares no competing interests. SM declares no competing interests. GL reports lecture fees from Livanova and Abiomed. AV declares no competing interests. NN declares no competing interests.

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