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ORIGINAL ARTICLE

Thombosis, major bleeding, and survival in COVID-19 supported by veno-venous extracorporeal membrane oxygenation in the first vs second wave: a multicenter observational study in the United Kingdom

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Abstract

Background: Bleeding and thrombosis are major complications of veno-venous (VV) extracorporeal membrane oxygenation (ECMO).

Objectives: To assess thrombosis, major bleeding (MB), and 180-day survival in patients supported by VV-ECMO between the first (March 1 to May 31, 2020) and second (June 1, 2020, to June 30, 2021) waves of the COVID-19 pandemic.

Methods: An observational study of 309 consecutive patients (aged ≥18years) with severe COVID-19 supported by VV-ECMO was performed in 4 nationally commissioned ECMO centers in the United Kingdom.

Results: Median age was 48 (19-75) years, and 70.6% were male. Probabilities of survival, thrombosis, and MB at 180 days in the overall cohort were 62.5% (193/309), 39.8% (123/309), and 30% (93/309), respectively. In multivariate analysis, an age of >55 years (hazard ratio [HR], 2.29; 95% CI, 1.33-3.93; P = .003) and an elevated creatinine level (HR, 1.91; 95% CI, 1.19-3.08; P = .008) were associated with increased mortality. Correction for duration of VV-ECMO support, arterial thrombosis alone (HR, 3.0; 95% CI, 1.5-5.9; P = .002) or circuit thrombosis alone (HR, 3.9; 95% CI, 2.4-6.3; P < .001) but not venous thrombosis increased mortality. MB during ECMO had a 3-fold risk (95% CI, 2.6-5.8, P < .001) of mortality. The first wave cohort had more males (76.7% vs 64%; P = .014), higher 180-day survival (71.1% vs 53.3%; P = .003), more venous thrombosis alone (46.4% vs 29.2%; P = .02), and lower circuit thrombosis (9.2% vs 28.1%; P < .001). The second wave cohort received more steroids (121/150 [80.6%] vs 86/159 [54.1%]; P < .0001) and tocilizumab (20/150 [13.3%] vs 4/159 [2.5%]; P = .005).

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Alain Vuylsteke and Hakeem Yusuff contributed equally to this study.

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Conclusion: MB and thrombosis are frequent complications in patients on VV-ECMO and significantly increase mortality. Arterial thrombosis alone or circuit thrombosis alone increased mortality, while venous thrombosis alone had no effect. MB during ECMO support increased mortality by 3.9-fold.

KEYWORDS
COVID-19, extracorporeal membrane oxygenation, hemorrhage, mortality, thrombosis

1 | INTRODUCTION

Veno-venous (VV) extracorporeal membrane oxygenation (ECMO) should be considered for patients with acute respiratory failure due to SARS-CoV-2 infection refractory to optimal conventional management, including mechanical ventilation [1–4].

Severe COVID-19 carries a higher risk of thrombosis compared to other viral pneumonias, such as influenza [5,6]. The use of VV-ECMO is associated with high rates of thrombosis and hemorrhage, which vary between centers. Based on Extracorporeal Life Support Organization registry data, rates of thrombosis and bleeding in patients supported with VV-ECMO for non–COVID-19 were approximately 25.3% and 23.4%, respectively [7]. This is due to a myriad of factors that may include contact activation, disease-related endothelial dysfunction, sepsis-induced coagulopathy, acquired von Willebrand syndrome, platelet dysregulation, consumption of coagulation factors, and anticoagulation [7–11].

COVID-19 infection progressed through several waves, each with distinct transmission and virulence characteristics. With accumulating evidence from multiplatform clinical studies, such as the Randomised Evaluation of COVID-19 Therapy (RECOVERY) trial [12,13] and Randomised, Embedded, Multifactorial, Adaptive Platform Trial for Community Acquired Pneumonia (REMAP-CAP) [14,15], an increasing number of hospitalized patients with COVID-19 received immunomodulatory therapy such as corticosteroid and tocilizumab and early anticoagulation, particularly after the first wave of the pandemic [12,13]. More importantly, with the introduction of mass vaccination against COVID-19 in early 2021, the severity of disease reduced in those who received vaccination [16].

No multicenter study has yet examined the impact of thrombosis and hemorrhage on 180-day mortality in patients with COVID-19 supported by VV-ECMO during the first and second waves of the pandemic, defined as March 1, 2020, to May 31, 2020, and June 1, 2020, to June 30, 2021, respectively. The 180-day follow-up of the last patient included into the study was on December 31, 2021. Previous studies assessing outcomes (including thrombosis and bleeding) of patients with COVID-19 supported by ECMO had a significantly shorter follow-up duration (90days) [17,18] than the follow-up duration of the present study (180 days).

This remains important because of the ongoing clinical need and lack of international consensus on optimal anticoagulation and monitoring strategies for this patient group. The primary aim of this study was to compare the 180-day probability of thrombosis, major bleeding, and mortality in patients supported by VV-ECMO between the first and second waves of the COVID-19 pandemic in the United Kingdom.

Essentials

- Veno-venous extracorporeal membrane oxygenation can be lifesaving in patients with severe COVID-19.
- Outcomes of veno-venous extracorporeal membrane oxygenation–supported patients were compared between the first and second waves of the COVID-19 pandemic.
- The second wave had higher mortality, circuit thrombosis, and major bleeding but lower venous thrombosis.
- Major bleeding and arterial and circuit thrombosis were associated with increased mortality.

Therefore, in the 2 waves, we assessed the following:

1. Overall mortality, thrombosis, and major bleeding.
2. Factors affecting survival, thrombosis, and major bleeding.
3. The effect of thrombosis and bleeding on survival.
4. Differences in these outcomes between the first and second wave cohorts.

2 | METHODS

2.1 | Study design

This was a multicenter observational study that used data collected from 4 of the 6 UK centers (Appendix S1) nationally commissioned to provide ECMO for adult patients with acute respiratory failure (Supplementary Table S1). A total of 309 consecutive adult patients were supported by VV-ECMO for at least 48 hours between March 1, 2020, and December 31, 2021 (spanning the first and second waves of the pandemic) (Appendix S2). Patients were assigned to the first wave cohort (cohort 1) if ECMO was initiated between March 1, 2020, and May 31, 2020, and to the second wave cohort (cohort 2) if ECMO was initiated between June 1, 2020, and June 30, 2021, inclusive. All

patients had SARS-CoV-2 infection confirmed by RT-PCR positive nasal swabs or nasopharyngeal or lower respiratory tract aspirates.

The study was approved by the Human Research Authority, Health and Care Research Wales, and the local Caldicott Guardian in Scotland (20/HRA/1785). All patients lacked capacity and the need for informed consent was waived because of the observational nature of the study.

2.2 | Data collection

Data containing demographics, medical history, treatment, and clinical course were collected retrospectively from prospectively acquired databases by clinicians involved in patient care using a standardized case record form, which was submitted to a central electronic database (REDcap v100.10; Vanderbilt University) hosted by Imperial College London (Coagulopathy in COVID-19—A Multi-Centre Observational Study in UK; full text view; ClinicalTrials.gov NCT04405232). CA-COVID-19 is a UK multicenter study set up to assess the natural history of COVID-19 from hospital admission to 180 days thereafter. Patients with veno-arterial (VA) ECMO are managed differently in relation to anticoagulation intensity (higher intensity compared to VV-ECMO), and some patients may receive antiplatelet treatment in addition to anticoagulation. To include a uniform population of patients, this study included only those patients supported with VV-ECMO. Patients supported with VA-ECMO or a combination of VV-ECMO and VA-ECMO were excluded. All study patients had ended VV-ECMO support and completed the follow-up up to 180 days after VV-ECMO.

2.3 | Anticoagulation

In the absence of robust evidence for intensification of anticoagulation during VV-ECMO in the context of COVID-19, ECMO centers in the United Kingdom maintained anticoagulation protocols that were in use prior to the pandemic. First-line anticoagulation was intravenous unfractionated heparin. Argatroban was used in the context of heparin-induced thrombocytopenia (HIT) or when target anti-Xa levels were difficult to achieve despite appropriate dose titration. Precise anticoagulation protocols were not specified as part of the study design, but in general, heparin anti-Xa levels of 0.2 to 0.3 IU/mL or equivalent activated thromboplastin time (APTT) were targeted in the absence of significant bleeding. In the context of thrombosis identified at initiation or during ECMO, therapeutic heparin anti-Xa levels of up to 0.3 to 0.7 IU/mL or equivalent APTT were targeted according to local clinical discretion. Target APTT was based on the local reference range corresponding to heparin anti–factor Xa chromogenic assay and established for specific APTT reagents. Diagnosis of HIT, transfusion, and hemostatic support are described in Appendices S3 and S4, respectively. Patients who developed HIT were managed with argatroban. Although it is not ideal to monitor argatroban using APTT, argatroban level was not widely available. Therefore, in general, APTT was used to monitor the anticoagulant effect of argatroban.

2.4 | Definitions of clinical outcomes

Bleeding was defined according to the International Society on Thrombosis and Haemostasis Scientific and Standardization Committee criteria for major or clinically relevant nonmajor bleeding (CRNMB) in nonsurgical patients [19,20]. Thrombotic events were defined as image-confirmed pulmonary embolism (PE), deep vein thrombosis (DVT), arterial thrombosis, or thrombosis of the ECMO circuit. Circuit thrombosis is defined as thrombosis in the oxygenator signified by high transmembrane pressure or thrombosis in other parts requiring a change in the circuit or clinical intervention. HIT was defined and diagnosed as detailed in Appendix S3.

Routine whole body computed tomography (CT) was performed within 24 hours of admission for VV-ECMO. Thereafter, imaging for bleeding or thrombosis was performed when clinically indicated. If acute neurologic injury was suspected, noncontrast CT of the brain was used in the first instance to identify intracranial hemorrhage (ICH). Pulmonary haemorrhage was managed as described in Appendix S5.

2.5 | Statistical analysis

Standard descriptive parameters were calculated for categorical and quantitative variables and presented as frequencies with percentages, or medians with a range. Survival probabilities were calculated using the Kaplan–Meier method, and groups were compared using the log-rank test. Variables identified from univariate analyses with P values <.2 were entered into a backward stepping Cox regression analysis to find independent prognostic factors significant at $P < .05$.

To assess the influence of complications after initiation of VV-ECMO on the risk of mortality, each complication was independently entered as a time-dependent variable. Identification of significant independent prognostic factors for the thrombosis and major bleeding required the use of the cumulative incidence procedure with Gray's test to compare groups and the Fine and Gray model for the multivariate setting. Death in the absence of thrombosis or major bleeding was considered the competing event.

Multiple imputation was used to account for missing laboratory values (<10%) but not for comorbidities or clinical outcomes. The multiple imputation by chained equation technique with its regression imputation model was used for this imputation with 10 iterative cycles. Once imputation was done, results were reviewed for each imputed feature to make sure that the imputation has generated plausible data. All tests were 2-sided, and P values <.05 were deemed statistically significant. Analyses were performed using either SPSS version 27 (SPSS v27; IBM), R (v4.0.3, open-source software), or Stata (v17, StataCorp LLC) and open-source software programming languages and libraries (Python [v3.7, open-source software], panda [v1.3.3, open-source software], NumPy [v1.21.2, open-source software], and scikit-learn [v0.22.1, open-source software]).

3 | RESULTS

3.1 | Study population, ECMO duration, and immunomodulatory therapy

A total of 309 consecutive adult patients were included, 159 and 150 of whom were admitted during the first and second waves, respectively. The median age of the overall study population was 48 (range, 19-75) years, and the majority were male (70.6%), with a larger male majority in the first wave cohort (76.7% vs 64%; $P = .014$) (Table 1). There were no differences in body mass index, ethnicity, or comorbidities between the first and the second wave cohorts. The first wave cohort had a higher percentage of ex- or current smokers (17% vs 5.4%; $P = .001$). Multiple differences were observed in blood results at the time of initiation of VV-ECMO between the 2 cohorts (Table 2) but were not associated with the study outcomes in multivariate analysis.

The median duration of VV-ECMO in the overall study population was 17 (range, 2-153) days. Patients in the second cohort had a significantly longer duration of VV-ECMO support compared to the first cohort (19.5 [range, 2-127] days vs 14 [range, 2-153] days; $P = .016$). The emergence of data supporting immunomodulatory therapy for COVID-19 [12,13] meant that more patients in the second cohort received steroids (121/150 [80.6%] vs 86/159 [54.1%]; $P < .0001$) as well as tocilizumab (20/150 [13.3%] vs 4/159 [2.5%]; $P = .005$) (Supplementary Table S3).

3.2 | Transfusion and hemostatic support

Across the whole study population, 268 (87%) patients received at least 1 transfusion of blood products: 250 (80.9%) received red cells, 26 (8.4%) received platelets, 14 (4.5%) received fresh frozen plasma (FFP), and 10 (3.2%) received cryoprecipitate. Thirty-four (11.0%) patients received tranexamic acid.

3.3 | One hundred eighty–day survival and factors contributing to mortality

Overall, the 180-day survival rate was 62.5% (95% CI, 57.3-68.1) (Figure A). Table 2 shows univariate and multivariate analyses of the baseline characteristics that were associated with survival. Increasing age was associated with reduced survival; an age of >55 years on admission was associated with a 2.29-fold (1.33-3.93; $P = .003$) increased probability of mortality at 180 days from the initiation of VV-ECMO. A creatinine level higher than normal was associated with 1.91-fold (95% CI, 1.19-3.08; $P = .008$) increased 180-day probability of mortality. Although thrombocytopenia at the time of initiation of VV-ECMO was associated with reduced survival on univariate analysis, this was not significant on multivariate analysis (Supplementary Table S2).

3.4 | Thrombosis and HIT

Arterial and/or venous thrombotic events were identified in 123 (39.8%) patients (Supplementary Figure SA). One hundred eighty–day probability of arterial or venous thrombosis was 43.5% (95% CI, 37.2%-49.2%). Twenty-eight (9.1%) patients developed arterial thrombosis, of whom 14 (50.0%) developed strokes, 4 (14.3%) developed peripheral arterial disease, and 10 (35.7%) developed arterial thrombosis elsewhere, such as mesenteric ischemia or myocardial infarction. One hundred eighteen (38.1%) patients developed venous thromboembolism (VTE), of whom 91 (77.1%) developed PE/pulmonary thrombosis, 8 (6.8%) developed solitary lower limb DVT, 10 (8.5%) developed DVT elsewhere, and 9 (7.6%) developed both DVT and PE. Forty-six (14.9%) of 309 patients likely had oxygenator failure due to thrombosis. Both arterial and venous thrombotic events were diagnosed in 15 (4.9%) patients. Ten percent (31/309) of patients developed HIT with a 180-day probability of 11.4% (95% CI, 7.5%-15.1%). All patients who developed HIT were treated with argatroban and none of these patients developed major bleeding. Probabilities of 180-day overall thrombotic events; venous, arterial, and circuit thrombosis; and HIT are presented in Table 3.

Supplementary Table S4 shows that baseline troponin I, hemoglobin, and D-dimer levels higher than the normal reference values were associated with increased risk of arterial and/or venous thrombosis (hazard ratio [HR], 2.08 [95% CI, 1.17-3.70], 6.77 [95% CI, 1.87-24.5], and 2.04 [95% CI, 1.12-3.71], respectively).

3.5 | Major and minor hemorrhage

The overall cumulative incidence of major bleeding at 180 days was 32.8% (95% CI, 38.1%-27.0%) (Table 3 and Figure B). Major bleeding was identified in 93 (30.1%) patients, of whom 30 (32.3%) developed ICH, 23 (24.7%) developed pulmonary hemorrhage, 14 (4.5%) developed gastrointestinal hemorrhage, and 26 (8.4%) developed major hemorrhage elsewhere. Platelet count below normal was the only baseline blood result associated with major bleeding on multivariate analysis (Supplementary Table S5). Baseline heparin anti-Xa level was not associated with major bleeding on univariate or multivariate analysis. CRNMB was identified in 108 (35.0%) patients, and 29 patients suffered both major and nonmajor hemorrhagic events. Overall, the 180-day probability of CRNMB was 38.8% (95% CI, 32.6%-44.3%).

3.6 | Impact of thrombosis and major bleeding on 180-day survival

Table 4 shows the association of thrombotic and hemorrhagic events with 180-day survival, both adjusted and unadjusted for age and creatinine at the time of admission.

Arterial and circuit thrombosis were associated with significantly increased mortality, with (adjusted for age and increased creatinine)

TABLE 1 Baseline clinical characteristics of the whole cohort and comparison of the first and the second wave cohorts

Characteristic	Both cohorts (*N* = 309)	Cohort 1 (*N* = 159)	Cohort 2 (*N* = 150)	*P* value
Sex				**.014**
Female	91 (29.5%)	37 (23.3%)	54 (36%)	
Male	218 (70.6%)	122 (76.7%)	96 (64%)	
Age (y)				.91
<42	83 (26.9%)	41 (25.8%)	42 (28.0%)	
42-48	86 (27.8%)	43 (27.0%)	43 (28.7%)	
49-55	76 (24.6%)	40 (25.2%)	36 (24.0%)	
>55	64 (20.7%)	35 (22.0%)	29 (19.3%)	
Ethnicity				.18
White	116 (37.5%)	57 (35.8%)	59 (39.3%)	
Mixed/multiple ethnic groups	6 (1.9%)	3 (1.9%)	3 (2.0%)	
Asian/Asian British	72 (23.3%)	39 (24.5%)	33 (22.0%)	
Black/African/Caribbean/Black British	19 (6.1%)	12 (7.5%)	7 (4.7%)	
Other ethnic groups	9 (2.9%)	8 (5.0%)	1 (0.7%)	
Unknown	87 (28.2%)	40 (25.2%)	47 (31.3%)	
BMI (kg/m^2)				.75
18.6-24.9	45 (14.6%)	29 (18.2%)	16 (10.7%)	
25-29.9	97 (31.4%)	52 (32.7%)	45 (30.0%)	
30-34.9	78 (25.2%)	41 (25.8%)	37 (24.7%)	
34.9-39.9	43 (13.9%)	21 (13.2%)	22 (14.7%)	
>39.9	46 (14.9%)	16 (10.1%)	30 (20.0%)	
Smoking				**<.001**
Current smoker	3 (1.3%)	2 (1.3%)	1 (0.7%)	
Ex-smoker	32 (13.7%)	25 (15.7%)	7 (4.7%)	
No history of smoking	199 (85.0%)	82 (51.8%)	117 (78%)	
Missing	65	50	25	
History of lung disease				.15
No	252 (81.8%)	135 (84.9%)	117 (78.5.0%)	
Yes	56 (18.2%)	24 (15.1%)	32 (21.5%)	
Missing	1		1	
History of diabetes				.99
No	234 (76.5%)	120 (75.4%)	114 (76.5%)	
Yes	72 (23.5%)	37 (23.6%)	35 (23.5%)	
Missing	3	2	1	
Hypercholesterolemia				.72
No	272 (88.0%)	141 (88.7%)	131 (87.3%)	
Yes	37 (12.0%)	18 (11.3%)	19 (12.7%)	
Hypertension				.15
No	212 (69.1%)	115 (72.8%)	97 (65.1%)	
Yes	95 (30.9%)	43 (27.2%)	52 (34.9%)	
Missing	2	1		

P values <.05 are shown in bold.

BMI, body mass index.

TABLE 2 Baseline (at the time of initiation of veno-venous extracorporeal membrane oxygenation) laboratory and observational characteristics of the whole cohort and comparison of the first and the second wave cohorts

Laboratory parameter	*N* = 309, median (IQR)	Cohort 1, median (IQR)	Cohort 2, median (IQR)	*P* value
Hemoglobin (g/L)	105 (94-121)	106 (92-121)	103 (95-120)	.31
White blood cells (10^9/L)	11.7 (8.20-15.8)	11.0 (7.80-14.3)	12.4 (9.10-19.4)	**.002**
Neutrophils (10^9/L)	10.2 (7.10-14.1)	9.25 (6.38-12.6)	11.3 (8.54-17.8)	**<.001**
Lymphocytes (10^9/L)	0.70 (0.50-1.10)	0.70 (0.50-1.10)	0.68 (0.45-1.05)	.070
Platelets (10^9/L)	246 (182-324)	260 (194-333)	232 (170-304)	**.016**
Prothrombin time (s)	14.4 (13.2-16.0)	14.3 (13.3-15.7)	14.5 (13.1-16.5)	.14
APTT (s)	40.1 (29.9-66.3)	39.2 (29.9-66.1)	41.8 (30.0-68.3)	.087
APTT ratio	1.45 (1.10-2.93)	1.30 (1.10-2.20)	2.00 (1.25-3.85)	**.003**
D-dimer (ng/mL)	1700 (340-3450)	3070 (1320-5170)	693 (5.60-2700)	**.008**
Fibrinogen (g/L)	5.80 (4.30-7.40)	6.40 (4.90-7.60)	5.00 (3.60-6.90)	**<.001**
Ferritin (μg/L)	1120 (528-1990)	1290 (725-2210)	945 (421-1690)	.28
Alanine aminotransferase (IU/L)	48 (32-82)	45 (32-73)	53 (34-93)	.17
Bilirubin (μmol/L)	12 (9-21)	14 (9-23)	12 (8-20)	.061
Creatinine (μmol/L)	71 (51-126)	76 (54-138)	69 (49-115)	.049
C-reactive protein (mg/L)	183 (92-272)	231 (156-294)	115 (58-218)	**<.001**
Lactate dehydrogenase (IU/L)	833 (579-1110)	886 (571-1180)	815 (602-1030)	.60
Troponin I (ng/L)	50.0 (14.5-169.0)	54.3 (17.7-131)	47.3 (12.0-202.5)	**.016**
Fraction of inspired oxygen (FiO_2)	60 (43-70)	60 (40-71)	60 (50-70)	.94
Oxygen saturation (SaO_2)	96 (93-97)	95 (93-97)	96 (92-98)	.59
Heparin anti-Xa[a] (U/mL)	0.43 (0.20-0.79)	0.33 (0.16-0.55)	0.55 (0.30-0.87)	**<.001**
Average fraction of inspired oxygen (FiO_2) (%)	50 (40-65)	50 (40-65)	50 (40-69)	.97
Pao_2 (kPa)	9.7 (8.3-12.0)	9.5 (8.2-12.0)	9.7 (8.4-12.2)	.41
$Paco_2$ (kPa)	6.8 (5.9-7.9)	7.0 (5.9-7.9)	6.5 (5.4-7.6)	.13
Lactate (mmol/L)	1.5 (1.1-2.0)	1.4 (1.1-1.9)	1.7 (1.2-2.4)	.030
Bicarbonate (mmol/L)	27.3 (23.0-31.8)	27.2 (23.9-31.9)	27,7 (22.7-31.5)	.54

P values <.05 are shown in bold.

APTT, activated partial thromboplastin time.

[a] Median heparin anti-Xa levels presented here were at the time of initiation of extracorporeal membrane oxygenation (ECMO) and therefore reflect higher intensity anticoagulation prior to the start of veno-venous ECMO in patients in the second cohort. Once ECMO was initiated, all patients in both cohorts received same intensity of anticoagulation with unfractionated heparin.

HRs of 3.0 (95% CI, 1.5-5.9; *P* = .002) and 3.9 (95% CI, 2.4-6.3; *P* < .001), respectively. Nine of 14 patients (64.3%) who developed ischemic stroke subsequently died. While 13 (41.9%) of the 31 patients who developed HIT later died, neither HIT nor VTE was associated with mortality on multivariate analysis.

Major bleeding was strongly associated with mortality, with an adjusted HR of 3.9 (95% CI, 2.6-5.8; *P* < .001). Of 116 patients who died, 49.1% (57/116) had major bleeding, and of these, major bleeding was recorded as the cause of death in 42.1% (24/57). Nineteen (63.3%) patients with ICH, 15 (65.2%) patients with pulmonary hemorrhage, and 9 (64.3%) patients with gastrointestinal hemorrhage subsequently died, with significant adjusted HRs of 2.4 (95% CI, 1.3-4.4), 3.7 (95% CI, 2.0-6.7), and 3.3 (95% CI, 1.6-6.7), respectively, for these complications (Table 4). CRNMB was not associated with mortality. ECMO duration was not associated with mortality.

3.7 | Comparison of outcomes between the 2 cohorts

The 180-day survival probability was greater in the first wave cohort (cohort 1) than the second wave cohort (cohort 2) (71.1% vs 53.3%; *P* = .003) (Table 3 and Figure C). The 180-day probability of circuit thrombosis was significantly higher in cohort 2 (28.1% vs 9.2%; *P* < .001). The 180-day probability of venous thrombosis was significantly greater in cohort 1 (46.4% vs 29.2%; *P* = .002) (Supplementary

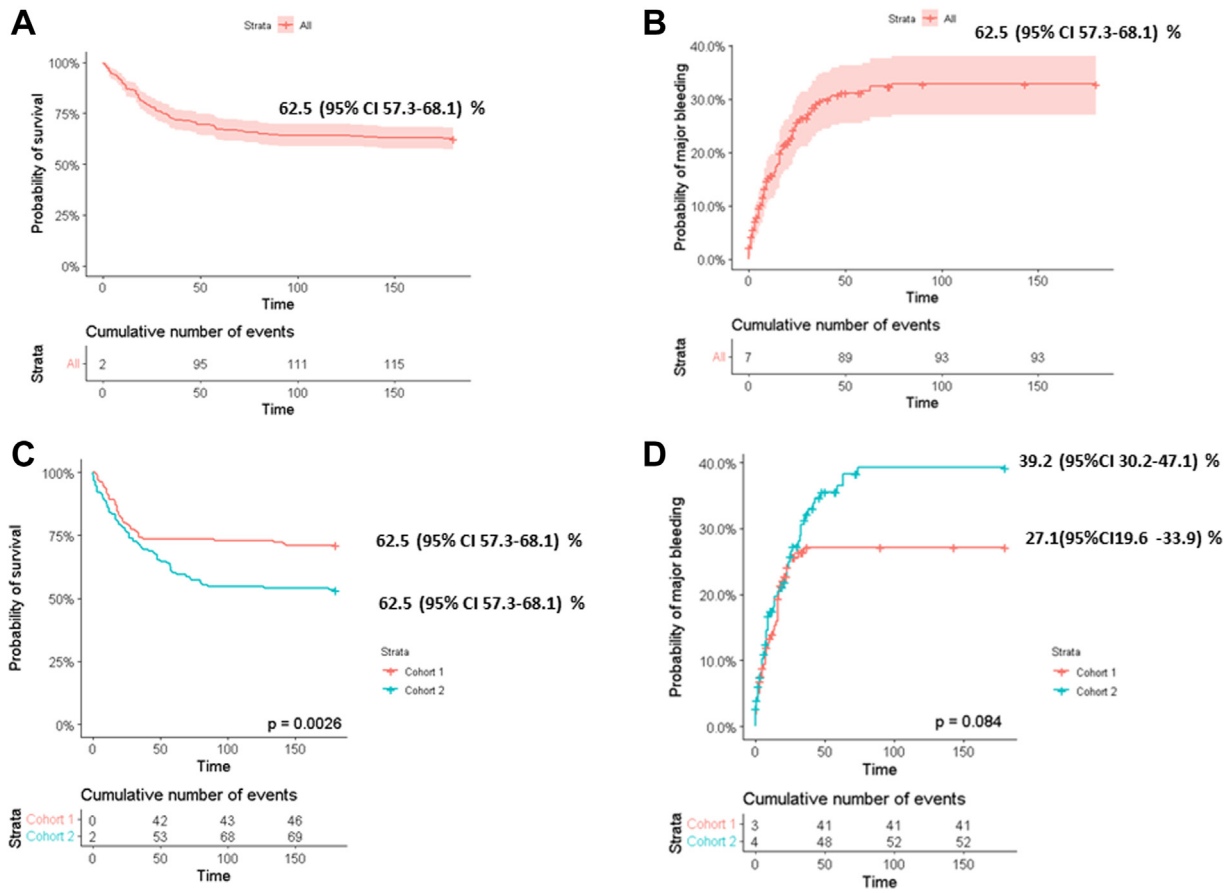

FIGURE Probability of (A) 180-day survival and (B) major bleeding in the overall cohort and comparison between (C) the survival and the (D) major bleeding between the first and second wave cohorts supported with veno-venous extracorporeal membrane oxygenation.

Figure SB), and the difference in the 180-day probabilities of arterial thrombosis was not significant. There was a trend toward a higher 180-day probability of major bleeding in cohort 2 (39.2% vs 27.1%; P = .084) (Figure D). This coincides with the survival curve (Figure C).

3.8 | Transfusion and hemostatic support between the 2 cohorts

A significantly higher proportion of patients in cohort 2 received platelet transfusion compared to cohort 1 (P = .007). However, there were no differences in the number of red cell units or the proportions of patients who received FFP, cryoprecipitate, fibrinogen concentrate, or tranexamic acid between the 2 cohorts. Comparison of the transfusion and hemostatic support is presented in Table 5.

4 | DISCUSSION

In this multicenter observational study comparing thrombosis, major bleeding, and mortality in patients with severe COVID-19 supported by VV-ECMO between first and second waves in the United Kingdom, there was a lower 180-day survival probability in the second wave cohort. There was a trend toward higher major bleeding rate in cohort 2, especially after day 50 on VV-ECMO, which coincides with the divergence of survival curves. Cohort 2 also had a higher risk of developing circuit thrombosis, which was strongly associated with mortality. These occurred despite consistent anticoagulation protocols and no difference in the type of VV-ECMO circuits used between the 2 waves. There was a higher rate of VTE in cohort 1, and cohort 2 was more frequently treated with steroids and tocilizumab. There were no differences in body mass index, ethnicity, or comorbidities between the first and second cohorts. Although there were multiple differences in blood results at the time of initiation of VV-ECMO between the cohorts, none of these were associated with the study outcomes in multivariate analysis. Duration of VV-ECMO support was significantly longer for cohort 2 than for cohort 1, but VV-ECMO duration was not associated with mortality.

Overall, there were high rates of thrombosis and major bleeding. Arterial thrombosis, circuit thrombosis, and major hemorrhage were significant predictors of reduced survival at 180 days, independent of age and renal impairment at baseline, which were also associated with reduced survival.

The overall mortality (37.5%) in this study was comparable to that found in large studies of patients receiving VV-ECMO support both

TABLE 3 Outcome probabilities in the overall cohort and the comparison between the 2 cohorts

Outcome	No. of events	Overall probability at 180 d, % (95% CI)	Cohort 1 probability at 180 d, % (95% CI)	Cohort 2 probability at 180 d, % (95% CI)	*P* value
Survival	193 (62.5%)	62.5 (57.3%-68.1%)	71.1 (64.4%-78.5%)	53.3 (45.9%-61.9%)	**.003**
Arterial thrombosis	28 (9.1%)	10.9 (6.9%-14.7%)	8.1 (3.3%-12.6%)	14.1 (7.5%-20.3%)	.12
Venous thrombosis	110 (35.6%)	38.1 (32.1%-43.6%)	46.4 (37.6%-53.9%)	29.2 (21.0%-36.6%)	**.002**
Arterial or venous thrombosis	123 (39.8%)	43.5 (37.2%-49.2%)	49.2 (40.2%-56.8%)	37.4 (28.3%-45.4%)	**.035**
Major bleeding	93 (30.1%)	32.8 (27.0%-38.1%)	27.1 (19.6%-33.9%)	39.2 (30.2%-47.1%)	.084
Heparin-induced thrombocytopenia	31 (10.0%)	11.4 (7.5%-15.1%)	10.6 (5.3%-15.5%)	12.3 (6.5%-17.8%)	.57
Circuit thrombosis	46 (14.9%)	18.1 (13.2%-22.8%)	9.2 (4.3%-13.9%)	28.1 (19.4%-35.8%)	**<.001**
Arterial or venous or circuit thrombosis	147 (47.6%)	52.2 (45.5%-57.9%)	52.5 (43.5%-60.1%)	52.0 (42.3%-60.0%)	.49
Nonmajor bleeding	108 (35.0%)	38.8 (32.6%-44.3%)	35.1 (26.7%-42.6%)	42.9 (33.6%-51.0%)	.25

P values <.05 are shown in bold.

for COVID-19 (37.4%) and for other indications before the COVID-19 pandemic (34.9%) [7,21].

Other studies of patients with COVID-19 supported by ECMO found high rates of bleeding but reported a lower thrombosis rate than that identified here [22–24]. The higher rate of thrombosis in this study could be due to differences in imaging or anticoagulation protocols or the longer follow-up period of 180 days. A nationwide cohort study (the ECMOSARS registry, France) included 620 patients with COVID-19 supported by ECMO (568 VV-ECMO and 52 VA-ECMO) and reported that 29% experienced ≥1 bleeding events, 16% experienced ≥1 thrombotic events, and 20% experienced both bleeding and thrombosis. ICH was detected in 8% of patients. The presence of major bleeding was associated with a 2.91-fold risk of in-hospital mortality [95% CI, 1.94-4.4]), with presence of ICH having the highest risk (odds ratio, 13.5 [95% CI, 4.4-41.5]), but thrombosis had no effect on mortality. However, the study assessed these outcomes only until 90 days after the initiation of ECMO [22]. Our study found only arterial and circuit thrombosis to be significantly predictive of mortality with HRs of 3.0 (95% CI, 1.5-5.9) and 3.9 (95% CI, 2.4-6.3), respectively. One recent large study of patients without COVID-19 supported with VV-ECMO did find ischemic stroke to be highly predictive of mortality with an adjusted HR of 4.5 [7].

This study presents an adjusted 180-day probability of arterial thrombosis of 10.9% (95% CI, 6.9%-14.7%), with ischemic stroke being the most frequent arterial event (14/28). Arterial thrombosis is a feature of severe COVID-19 outside the context of ECMO; it has been reported to occur in 3% of cases in the intensive care unit [25,26]. This study suggests that both venous thrombosis and arterial thrombosis

TABLE 4 Time-dependent effects of different outcomes on survival of the overall cohort

Clinical outcome	No. of events	Unadjusted hazard ratio (95% CI)	*P* value	Adjusted[a] hazard ratio (95% CI)	*P* value
Arterial thrombosis	28	2.5 (1.3-5.0)	.008	3.0 (1.5-5.9)	.002
Venous thrombosis	110	1.1 (0.8-1.7)	.57	1.1 (0.7-1.6)	.72
Pulmonary embolism	90	1.2 (0.8-1.8)	.43	1.1 (0.7-1.7)	.64
Arterial or venous thrombosis	123	1.1 (0.8-1.7)	.53	1.2 (0.8-1.8)	.37
Major bleeding	93	4.4 (3.0-6.5)	<.001	3.9 (2.6-5.8)	**<.001**
Intracranial bleed	30	3.1 (1.7-5.5)	<.001	2.4 (1.3-4.4)	**<.001**
Gastrointestinal bleed	14	4.0 (1.9-8.2)	<.001	3.3 (1.6-6.7)	**<.001**
Pulmonary bleed	23	3.4 (1.9-6.0)	<.001	3.7 (2.0-6.7)	**<.001**
Heparin-induced thrombocytopenia	31	1.5 (0.8-2.8)	.19	1.4 (0.8-2.6)	.26
Circuit thrombosis	46	3.4 (2.1-5.5)	<.001	3.9 (2.4-6.3)	**<.001**
Multiorgan failure	116	2.1 (1.5-3.1)	<.001	1.7 (1.1-2.5)	**.011**
Arterial or venous or circuit thrombosis	147	1.6 (1.1-2.3)	.02	1.6 (1.1-2.3)	**.017**
Nonmajor bleeding	108	1.2 (0.8-1.9)	.32	1.2 (0.8-1.9)	.35

P values <.05 are shown in bold.

[a] Adjusted models contained the factors patient age and creatinine at admission.

TABLE 5 Comparison of the transfusion and hemostatic support between the first and second wave cohorts

Transfusion and hemostatic support	Cohort 1	Cohort 2	*P* value
Red cell units, median (range)	1 (0-6)	1 (0-10)	.86
Platelet units			**<.001**
No	154 (97%)	129 (86%)	
Yes	5 (3%)	21 (14%)	
Fresh frozen plasma			.51
No	153 (96%)	142 (95%)	
Yes	6 (4%)	8 (5%)	
Cryoprecipitate			.17
No	156 (98%)	143 (95%)	
Yes	3 (2%)	7 (5%)	
Fibrinogen concentrates			.67
No	157 (98.7%)	147 (95.0%)	
Yes	2 (1.3%)	3 (2%)	
Tranexamic acid			.10
No	146 (92%)	129 (86%)	
Yes	13 (8%)	21 (14%)	

P values <.05 are shown in bold.

are major concerns in patients supported with VV-ECMO for severe COVID-19.

A much lower rate of arterial events such as ischemic stroke was reported in patients without COVID-19 supported by VV-ECMO in data derived from the Extracorporeal Life Support Organization registry [7]. However, this registry does not collect data on certain important bleeding and thrombotic complications, including upper respiratory bleeding, DVT, and PE, and there is also a possibility of underdetected and underreported arterial events if CT scans were not performed systematically in some centers [27–29].

The adjusted 180-day probability of circuit thrombosis was 18.1% (95% CI, 13.2%-22.8%), which is similar to incidence rates reported in recent large studies of patients with and without COVID-19 supported by ECMO [7,22]. However, this study uniquely found circuit thrombosis to be an independent indicator of mortality on multivariate analysis (HR, 3.9; 95% CI, 2.4-6.3). Although the reason for this is not clear, circuit thrombosis despite standard intensity anticoagulation for VV-ECMO could be an indicator of a hyperinflammatory response in these patients, and unlike other studies [23], we did not alter the anticoagulation intensity in our cohort.

The 180-day probability of major bleeding was 32.8% (27.0%-38.1%) in this study, which is lower than the rate reported in a previous study by Schmidt et al. [23]. However, Schmidt et al. [23] included both VA- and VV-ECMO in their analysis and had increased the intensity of anticoagulation. Major bleeding also carried a significantly increased risk of death, with HRs of 2.4 (95% CI, 1.3-4.4), 3.3 (95% CI, 1.6-6.7), and 3.7 (95% CI, 2.0-6.7) associated with ICH, gastrointestinal hemorrhage, and pulmonary hemorrhage, respectively. Furthermore, bleeding was a documented cause of death in 20.7% of the overall study population (24/116), and 42.1% (24/57) of the patients who had major bleeding subsequently died. This is consistent with numerous previous studies in the context of VV-ECMO [7,9,22]. As postulated by this and other groups, the strong relationship between major bleeding and mortality in the context of VV-ECMO may be related to the necessary temporary discontinuation of systemic heparin after the detection of hemorrhage and resultant loss of off-target antiviral, anti-inflammatory, and anticomplement effects of the drug [29–31] in addition to the direct effects of bleeding itself.

Of all recorded baseline characteristics, creatinine levels higher than normal and an age of >55 years were the only independent predictors of mortality in multivariate analysis, with significant HRs of 1.91 (95% CI, 1.19-3.08) and 2.29 (95% CI, 1.33-3.93), respectively. These findings are consistent with numerous ECMO studies both in and outside the context of COVID-19 [32–35]. One recent meta-analysis reported older age and renal replacement therapy before ECMO initiation were predictive of in-hospital mortality [36]. However, the meta-analysis also showed chronic lung disease and male sex to be mortality predictors, unlike this study.

The second cohort had a lower probability of 180-day survival than the first cohort (53.5% [95% CI, 45.9%-61.9%] vs 71.1% [95% CI, 64.4%-78.5%]) despite being more heavily treated with steroids and tocilizumab. This is consistent with the findings of other ECMO studies examining mortality rate over the course of the pandemic [17,37,38]. After the adoption of immunomodulatory therapies in the early hospital treatment of severe COVID-19, the patients who progressed to require VV-ECMO despite this treatment may have had more generally refractory disease than those previously accepted for ECMO, which might account for the higher mortality rate during second and subsequent waves. This study was conceived during the first wave, and as a result, no data were collected on COVID-19 strains. However, 1 large study demonstrated no crude difference between 90-day mortality rates in patients infected with the wild-type, Alpha, or Delta variants of COVID-19, and the wild-type variant was dominant during the period associated with the greatest mortality [18]. This study showed a trend toward more major bleeding events in cohort 2 (P = .084) compared to cohort 1, which could have contributed to higher mortality in the second cohort in a multifactorial process. Greater steroid use and longer duration on VV-ECMO are likely to be contributory. Furthermore, there is a striking difference in the bleeding events after 50 days (which was parallel until day 50) on ECMO between the 2 cohorts: cohort 2 continued to have bleeding events until day 100 while cohort 1 events plateaued. This coincides with the survival curve (Figure B). This could be due to the longer duration of ECMO in cohort 2 (19.5 [range, 2-127] days vs 14 [range, 2-153] days in cohort 1, P = .016) causing platelet dysfunction, including acquired von Willebrand disease [39]. Interestingly, a significantly higher proportion of patients in cohort 2 received platelet transfusion compared to cohort 1 (P = .007), with no difference in the number of red cell units or proportion of patients who received FFP,

cryoprecipitate, fibrinogen concentrate, or tranexamic acids between the 2 cohorts.

Other causes for the higher mortality rate in cohort 2 in this study could be the higher circuit thrombosis (28.1% vs 9.2%), which was strongly associated with mortality in multivariate analysis, though not a risk factor identified elsewhere [7,22]. The reason why there was a higher rate of circuit thrombosis in the second cohort was not clear. Longer duration on VV-ECMO, unaltered anticoagulation, and hyperinflammation (increased white cells and neutrophils) are likely contributory. Although there were several differences in the baseline laboratory parameters between the 2 cohorts, none of these parameters were associated with mortality in the multivariate analysis, suggesting that the higher mortality in the second cohort is multifactorial (Table 2). Reduced venous and overall thrombosis rate in the second cohort is most likely related to early initiation of thromboprophylaxis, including high intensity, early in the course of the disease prior to initiation of VV-ECMO, in accordance with evidence from the REMAP-CAP study [14,15]. This also may have been a contributing factor for the higher major bleeding rate in cohort 2. Both bleeding and thrombotic events were assessed within 24 hours of initiation of VV-ECMO by performing CT scans, especially of the brain.

The strengths of this study include its multicenter setting, large patient cohort, consistent treatment protocols, 180-day follow-up period, detailed data set generated using a predefined case record form, systematic imaging, and documenting the bleeding and thrombotic events with robust statistical analysis. Its main limitations include the retrospective design and the lack of documented information regarding vaccination status and SARS-CoV-2 variant in the second cohort. Additionally, this study did not have information on Simplified Acute Physiology Score II (SAPS II), Sequential Organ Failure Assessment (SOFA) score at the initiation of VV-ECMO, time from first symptoms to intensive care unit admission, time from first symptoms to intubation, time from intensive care unit admission to initiation of VV-ECMO, duration of noninvasive ventilation prior to intubation, and ventilation parameters. However, patients were selected for VV-ECMO according to the agreed national criteria in the United Kingdom. Furthermore, because we used Hemosisl AcuStar HIT-immunoglobulin G (Instrumentation Laboratory) rather than a functional assay, such as serotonin release assay, for the diagnosis of HIT, it is possible that we may have overestimated the incidence of HIT.

5 | CONCLUSION

This multicenter study of 309 consecutive patients with COVID-19 supported by VV-ECMO reports high incidence of thrombosis and major bleeding. Older age, renal impairment at the time initiation of VV-ECMO, arterial thrombosis, circuit thrombosis, and major bleeding were independently associated with 180-day reduced survival. The cohort treated on or after June 1, 2020, had higher 180-day mortality, reflecting a concerning trend toward increasing mortality rates in patients with COVID-19 supported by VV-ECMO over time (although this may be an artifact of improvements in early COVID-19 treatment preventing the need for VV-ECMO in responsive patients). Reduced overall thrombotic events are most likely due to early initiation of thromboprophylaxis prior to initiation of VV-ECMO in the second wave of the pandemic. This study further characterizes the complex competing risks that affect long-term outcome in patients with COVID-19 supported by VV-ECMO. Prospective studies are required to determine optimal anticoagulant and hemostatic management of this patient group.

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AUTHOR CONTRIBUTIONS

D.J.A. conceived the study; acquired the funding; and was involved in data collection, data verification, data analysis, preparation of figures, data interpretation, writing of the original draft, and reviewing and editing of the manuscript. A.W. contributed to the original draft of the manuscript. I.R., Z.O., and R.S. were involved in data verification, data analysis, preparation of figures, data interpretation, and reviewing and editing of the manuscript. M.G., G.I., L.C., L.F., S.L., R.J., A.V., and H.Y. were involved in data collection, data interpretation, and reviewing and editing of the manuscript. M.L. interpreted the data and reviewed and edited the manuscript. D.J.A. is responsible for the study design, had full access to all the data in the study, and had final responsibility for the decision to submit for publication. All authors interpreted the results, reviewed the manuscript, approved the final work, and agree to be accountable for the accuracy and integrity of the work.

DECLARATION OF COMPETING INTERESTS

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SUPPLEMENTARY MATERIAL

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