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ORIGINAL RESEARCH

Bleeding and Thrombosis in Patients With Out-of-Hospital Ventricular Tachycardia/ Ventricular Fibrillation Arrest Treated With Extracorporeal Cardiopulmonary Resuscitation

Alejandra Gutierrez, MD; Rajat Kalra, MBChB, MS; Kevin Y. Chang, MD; Marie E. Steiner, MD, MS; Alexandra M. Marquez, MD, MSTR; Tamas Alexy, MD, PhD; Andrea M. Elliott, MD; Meagan Nowariak, BA; Demetris Yannopoulos, MD; Jason A. Bartos, MD, PhD

BACKGROUND: Extracorporeal cardiopulmonary resuscitation improves outcomes after out-of-hospital cardiac arrest. However, bleeding and thrombosis are common complications. We aimed to describe the incidence and predictors of bleeding and thrombosis and their association with in-hospital mortality.

METHODS AND RESULTS: Consecutive patients presenting with refractory ventricular tachycardia/ventricular fibrillation out-of-hospital cardiac arrest between December 2015 and March 2022 who met the criteria for extracorporeal cardiopulmonary resuscitation initiation at our center were included. Major bleeding was defined by the Extracorporeal Life Support Organization's criteria. Adjusted analyses were done to seek out risk factors for bleeding and thrombosis and evaluate their association with mortality. Major bleeding occurred in 135 of 200 patients (67.5%), with traumatic bleeding from cardiopulmonary resuscitation in 73 (36.5%). Baseline demographics and arrest characteristics were similar between groups. In multivariable analysis, decreasing levels of fibrinogen were independently associated with bleeding (adjusted hazard ratio [aHR], 0.98 per every 10 mg/dL rise [95% CI, 0.96–0.99]). Patients who died had a higher rate of bleeds per day (0.21 versus 0.03, $P<0.001$) though bleeding was not significantly associated with in-hospital death (aHR, 0.81 [95% CI. 0.55–1.19]). A thrombotic event occurred in 23.5% (47/200) of patients. Venous thromboembolism occurred in 11% (22/200) and arterial thrombi in 15.5% (31/200). Clinical characteristics were comparable between groups. In adjusted analyses, no risk factors for thrombosis were identified. Thrombosis was not associated with in-hospital death (aHR, 0.65 [95% CI, 0.42–1.03]).

CONCLUSIONS: Bleeding is a frequent complication of extracorporeal cardiopulmonary resuscitation that is associated with decreased fibrinogen levels on admission whereas thrombosis is less common. Neither bleeding nor thrombosis was significantly associated with in-hospital mortality.

Key Words: bleeding ■ cardiac arrest ■ coagulopathy ■ ECMO ■ eCPR ■ survival ■ thrombosis

Correspondence to: Alejandra Gutierrez, MD, Cardiovascular Division, University of Minnesota, 420 Delaware Street SE, MMC 508, Minneapolis, MN 55455. Email: agb@umn.edu

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CLINICAL PERSPECTIVE

What Is New?

- In this large single-center study with a protocolized approach to anticoagulation for patients with ventricular tachycardia/ventricular fibrillation out-of-hospital cardiac arrest bleeding as defined by Extracorporeal Life Support Organization, major bleeding was common, occurring in 68% of the cohort, whereas thrombosis was less frequent, occurring in 24%, with more than half of the events being arterial thrombi.
- Bleeding events are multifactorial, including trauma from prolonged cardiopulmonary resuscitation, access site bleeding, and mucosal bleeding.
- Neither bleeding nor thrombosis is associated with overall in-hospital mortality.

What Are the Clinical Implications?

- The high incidence of bleeding and low incidence of thrombosis with the current approach to anticoagulation that often involves antithrombotic therapy reinforces the need for a better method to risk stratify patients to better tailor anticoagulation strategies.
- The lack of association of bleeding and thrombotic events with mortality support a less aggressive anticoagulation strategy to minimize bleeding; larger trials should evaluate anticoagulation strategies.

Nonstandard Abbreviations and Acronyms

ACT	activated coagulation time
DAPT	dual antiplatelet therapy
eCPR	extracorporeal cardiopulmonary resuscitation
OHCA	out-of-hospital cardiac arrest
VA ECMO	venoarterial extracorporeal membrane oxygenation

When performed by experienced operators and institutions with established protocols, extracorporeal cardiopulmonary resuscitation (eCPR) has been shown to improve survival after out-of-hospital cardiac arrest (OHCA).[1–8] The incidence of emergency medical services-assessed OHCA is estimated to be 350 000 in 2015 per the American Hospital Association, with 7% surviving with a good neurologic outcome.[9] Mortality after OHCA has remained poor with further worsening during the COVID-19 pandemic.[9] The ARREST (Advanced Reperfusion Strategies for Patients With Out-Of-Hospital Cardiac Arrest and Refractory Ventricular Fibrillation) trial demonstrated that eCPR, including emergent cannulation with extracorporeal membrane oxygenation (ECMO), improved the absolute survival to hospital discharge by 36% for patients with OHCA due to ventricular tachycardia or ventricular fibrillation (VT/VF) as the presenting rhythm.[1] Anticoagulation management of patients presenting with VT/VF OHCA supported by eCPR is challenging, with competing thrombogenic insults and high bleeding risk due to trauma from prolonged CPR and coagulopathy related to cardiac arrest and the ECMO circuit. Bleeding is the most common complication of eCPR, occurring in 8% to 70% of cases depending on the case series and definition of bleeding used,[2,10,11] whereas thrombotic rates are not well documented in the literature.

The bleeding risk associated with eCPR is multifactorial and its quantification is difficult. The contact of blood with artificial surfaces and the sheer stress of the mechanical circuit lead to an activation of the coagulation cascade and subsequent thrombogenesis. Therefore, patients are anticoagulated to prevent thromboembolic events and oxygenator thrombosis.[12] eCPR in the setting of severe coronary artery disease presents further challenges as patients often require dual antiplatelet therapy (DAPT) to protect the newly placed coronary stents.[11,13] Moreover, the trauma associated with prolonged CPR and the inflammation and coagulopathy associated with ischemia and reperfusion injury that hallmarks the postcardiac arrest syndrome enhances the already heightened risk of bleeding and thrombosis.[14] Data regarding the incidence and predictors of bleeding and thrombosis as well as their impact on outcomes in patients with VT/VF treated with eCPR are lacking.

We aimed to describe the incidence, severity, and predictors of bleeding and thrombosis and their association with in-hospital mortality.

METHODS

Study Population

Consecutive patients enrolled in the University of Minnesota out-of-hospital refractory VT/VF arrest protocol between December 2015 and March 2022 were eligible for inclusion. Procedures were followed in accordance with the ethical standards of the institutional review board and in accordance with the Helsinki Declaration of 1975. The study was reviewed and approved by the institutional review board at the University of Minnesota (IRB #1703M11301). A waiver of informed consent was granted given the research

was retrospective involving no more than minimal risk. The data to support the findings of this study are available from the corresponding author upon reasonable request.

The University of Minnesota protocol has been previously described.[3,11,15–19] Briefly, patients were screened by paramedics (emergency medical services) to include adults 18 to 75 years of age, with a shockable presenting rhythm and no return of spontaneous circulation after 3 shocks or shock-triggered conversion to pulseless electrical activity or asystole, ongoing CPR with a Lund University Cardiac Arrest System (LUCAS), and an estimated transfer time to the closest cannulation site of less than 30 minutes. At the cannulation site, patients were assessed for the presence of the following physiologic criteria: (1) end-tidal CO_2 >10 mm Hg; (2) PaO_2 ≥50 mm Hg; and (3) lactic acid ≤18 mmol/L. Patients meeting the physiologic criteria with ongoing arrest and those who obtained return of spontaneous circulation but were unstable with refractory cardiogenic shock and hypotension despite other interventions such as intra-aortic balloon pump placement (Maquet Cardiovascular, Wayne, NJ), vasopressors or inotropes underwent ultrasound-guided and fluoroscopy assisted percutaneous venoarterial ECMO (VA ECMO) cannulation. Arterial (15–17 Fr) and venous (25 Fr) cannulas were typically inserted in the ipsilateral common femoral artery and femoral vein, though contralateral cannulation was used as needed. An antegrade perfusion cannula was inserted into the superficial femoral artery ipsilateral to the arterial ECMO cannula to perfuse the distal lower extremity. Per protocol, a heparin bolus was administered at the time of cannulation.[20] All patients underwent coronary angiography with percutaneous coronary intervention as indicated following cannulation. An intravascular cooling catheter was placed for targeted temperature management, with a goal temperature of 34 °C for 24 hours unless uncontrolled bleeding necessitated a higher temperature target. The addition of an intra-aortic balloon pump was left to the discretion of the interventional cardiologist to maintain coronary perfusion in the setting of severe coronary artery disease or lack of cardiac pulsatility, defined as an arterial pulse pressure of less than 10 mm Hg after initiation of VA ECMO and percutaneous coronary intervention. All patients had noncontrast computed tomography of their head, chest, abdomen, and pelvis upon admission given the high prevalence of trauma associated with CPR.[2,21]

Patients were admitted to a centralized cardiac intensive care unit. A continuous unfractionated heparin infusion was administered targeting an activated coagulation time (ACT) goal of 180 to 200 seconds. Anticoagulation targets were adjusted by the treating physician in patients with uncontrolled bleeding. A heparin infusion of 2 U/mL in normal saline was administered at 3 mL/hour continuously through the antegrade perfusion cannula to maintain its patency. This infusion continued regardless of the presence of bleeding.

Study Definitions and Outcome Variables

Data were collected by retrospective chart review of medical records. The primary outcome was in-hospital mortality. Secondary outcomes were major bleeding and thrombosis. Major bleeding was defined by the Extracorporeal Life Support Organization (ELSO) criteria, including clinically overt bleeding associated with a decline in hemoglobin of ≥2 g/dL or ≥2 units of red blood cells transfused during a 24 hours period.[20] This included bleeding in a critical area defined as bleeding occurring in the retroperitoneum, pulmonary, central nervous system, or requiring surgical intervention regardless of the decline of hemoglobin or units of blood transfused. Given initial volume expansion, hemolysis, intraprocedural blood loss, and frequent laboratory draws, it is common for patients' hemoglobin values to decline significantly with successful VA ECMO resuscitation after cardiac arrest. Therefore, we scrutinized the medical records to identify clinical signs of bleeding noted by the treatment team or present on imaging associated with transfusions or decrease in hemoglobin to determine major bleeding events. A declining hemoglobin level without clinical bleeding was not considered a bleeding event.

The presence of thrombosis was determined by imaging studies with corresponding clinical correlates of venous or arterial thrombi. This was further classified into (1) arterial thrombi, including stroke as evidenced by imaging, thrombi in the left atrium, left ventricle, aortic valve, or other arterial bed such as the superior mesenteric artery, and oxygenator thrombosis requiring exchange of the oxygenator, and (2) venous thrombi, including deep vein thrombosis and inferior vena cava thrombosis, right atrial thrombi, or pulmonary embolism.

The first arterial blood gas collected just before ECMO cannulation was used to establish the initial hemoglobin level. Other laboratory parameters were obtained from the first complete set of blood work performed on arrival to the centralized cardiac intensive care unit.

Statistical Analysis

Continuous variables were represented as means with SDs and compared using the *t* test or ANOVA tests. Nonnormal continuous variables were represented as medians with interquartile ranges and compared with the Wilcoxon rank-sum test. Categorical variables were represented as counts with proportions and compared with the chi-square test.

We performed multivariable Cox proportional hazards analyses to identify predictors of ELSO major

bleeding events and thromboses. We selected factors for inclusion in multivariable Cox proportional hazards model to determine which factors were associated with these clinical events. For ELSO major bleeding events, we selected age, the use of DAPT during the admission, CPR time, platelet count, antithrombin III, and fibrinogen to evaluate their association with ELSO major bleeding events. For thrombosis events, we selected age, fibrinogen, and antithrombin III to evaluate their association with thrombosis.

Cox multivariable regression analyses were done to account for the effect of clinically important covariates in the association between major bleeding and thrombosis with in-hospital death. Age, sex, CPR time, and use of DAPT were chosen a priori as covariates in Cox multivariable regression analyses. These variables were chosen due to their acknowledged associations with bleeding and thrombotic events. The proportional hazard assumption was checked using Schoenfeld's residuals. For the survival analyses that assessed the association of major bleeding events with in-hospital death, thrombosis was also included as a covariate in the multivariable analyses, due to the tendency of thrombosis to affect clinical anticoagulation management. Similarly, major bleeding events were included as a covariate in the survival analyses that assessed the association of thrombosis with in-hospital death.

In-hospital death may be a competing event for the occurrence of major bleeding events or thrombosis during treatment with VA ECMO. Thus, competing risk analyses were performed to evaluate factors that may be associated with major bleeding events and thrombosis, respectively. In-hospital death from causes other than bleeding events or thrombosis was the competing event. Because this was an analysis to evaluate a causal association rather than a prognostic association,[22] we performed multivariable adjusted Cox proportional hazards regression and reported the results as cause-specific hazard ratios (HRs) with 95% CIs. The level of statistical significance was set at <0.05 for all analyses. The analyses were done with IBM SPSS v28 (Chicago, IL) and StataMP 17.0 (College Station, TX).

RESULTS

Study Population

A total of 260 patients presented with the criteria of a VT/VF cardiac arrest and achieved an organized rhythm at the end of the cardiac catheterization. Of these patients, 23% achieved stable return of spontaneous circulation and did not require VA ECMO to stabilize their cardiogenic shock and were therefore excluded from this analysis. The final study population consisted of 200 patients.

Baseline characteristics are shown in Table 1. The majority of the cohort was male (81%) with a mean age of 57 (12.2) years. Comorbid conditions included coronary artery disease in 26% (52/200), congestive heart failure in 12.5% (25/200), diabetes in 24.5% (49/200), and hypertension in 35.5% (71/200). Before admission, patients' medications included a direct oral anticoagulant in 6 of 200 (3%), a vitamin K antagonist in 4 (2%), aspirin in 29 (14.5%), and a P2Y12 inhibitor in 3 (1.5%). The average CPR time from 911 call or identified arrest by emergency medical services to VA ECMO initiation was 62±19 minutes. An intra-aortic balloon pump was placed in 71% (142/200) of the cohort. Revascularization was performed in 121 of 200 (60.5%) patients, and DAPT was given to 62.0% (124/200) of the cohort.

The hemoglobin on initial presentation to the emergency department or catheterization laboratory was 12.6±2.6 g/dL. Other laboratory parameters were obtained at the time of arrival to the centralized cardiac intensive care unit. Most blood tests were above normal limits (Figure 1), including alanine transaminase (187±199 U/L), aspartate transaminase (372±410 U/L), international normalized ratio (2.0±0.9), ACT (224±63), partial thromboplastin time (195±72 seconds), and D-dimer (16±7 μg/mL). Antithrombin III levels were often below the normal range of our laboratory (>85%), with an average of 59.6±16.9%, whereas the average fibrinogen of our cohort was within normal limits at 234±109 mg/dL.

Predictors of Bleeding

Major bleeding was common, occurring in 135 of 200 patients (67.5%). There was more than 1 site of bleeding in 91 (45.5%) patients. Minor bleeding that did not meet criteria for ELSO major bleeding occurred in 21 of 200 (10.5%) patients, and there was no clinical evidence of bleeding in 44 (22%) patients. Details regarding major bleeding site are shown in Figure 2A. The most common site of major bleeding was access site bleeding. This was present in 106 of 200 patients (53.0%), with 6 patients requiring a surgical intervention to repair this. Intracranial bleeding occurred in 10 of 200 patients (5.0%), including 3 cases of subarachnoid hemorrhage, 2 intraventricular hemorrhages, and 5 intraparenchymal hemorrhages. The median day of diagnosis of intracranial bleeding was 3 (1, 7) days. CPR-related trauma was frequent, occurring in 73 of 200 (36.5%) of the cohort, including mediastinal hematoma in 51 (26%), 14 (7%) with pericardial bleeding, 22 (11%) with a hemothorax, and 14 (7%) with intraperitoneal bleeding. Gastrointestinal bleeding was clinically diagnosed in 33 of 200 (16.5%) patients. Most cases were managed medically, with only 6 of 200 cases (4.7%) undergoing upper endoscopy. The majority of

Table 1. Demographic, Baseline, and Arrest Characteristics of Patients With and Without Major Bleeding and With and Without a Thrombotic Event

	Overall cohort (N=200)	No major bleeding (N=65)	Major bleeding (N=135)	*P* value	No thrombotic events (N=153)	Thrombosis (N=47)	*P* value
Baseline characteristics							
Sex, male	162 (81.0)	54 (83.1)	108 (80.0)	0.74	122 (79.7)	40 (85.1)	0.54
Age, y	57.0 (12.2)	55.5 (12.6)	57.7 (11.9)	0.24	56.8 (12.1)	57.8 (12.5)	0.61
Body mass index, kg/m^2	30.7 (6.2)	30.2 (25.9, 35.4)	29.7 (26.8, 33.8)	0.73	29.7 (26.8, 33.7)	30.6 (25.9, 33.9)	0.99
Comorbidities							
Coronary artery disease	52 (26.0)	14 (21.5)	38 (28.1)	0.41	38 (24.8)	14 (29.8)	0.62
Congestive heart failure	25 (12.5)	6 (9.2)	19 (14.1)	0.48	18 (11.8)	7 (14.9)	0.77
Diabetes	49 (24.5)	14 (21.5)	35 (25.9)	0.62	35 (22.9)	14 (29.8)	0.44
End-stage renal disease	4 (2.0)	1 (1.5)	3 (2.2)	1.00	3 (2.0)	1 (2.1)	1.00
Hyperlipidemia	49 (24.5)	13 (20.0)	36 (26.7)	0.39	35 (22.9)	14 (29.8)	0.44
Hypertension	71 (35.5)	17 (26.2)	54 (40.0)	0.08	49 (32.0)	22 (46.8)	0.09
Arrest characteristics and treatments before ICU admission							
Cardiopulmonary resuscitation time, min	62 (19)	61 (19)	63 (20)	0.84	62 (20)	61 (17)	0.69
Intra-aortic balloon pump	142 (71.0)	42 (64.4)	100 (74.1)	0.23	105 (68.6)	37 (78.7)	0.25
Heparin bolus during cannulation and percutaneous coronary intervention, units	12 578 (4353)	12 585 (5202)	12 575 (3901)	0.99	12 544 (4588)	12 682 (3588)	0.85
Cangrelor	16 (8.0)	3 (4.6)	13 (9.6)	0.34	11 (7.2)	5 (10.6)	0.65
Glycoprotein iib/iiia inhibitor	6 (3.0)	2 (3.1)	4 (3.0)	1.000	3 (2.0)	3 (6.4)	0.29
Dual antiplatelet therapy	124 (62.0)	33 (50.8)	91 (67.4)	0.03	90 (58.8)	34 (72.3)	0.13
Ticagrelor	121 (60.5)	33 (50.8)	88 (65.2)	0.11	87 (56.9)	34 (72.3)	0.08
Clopidogrel	3 (1.5)	0 (0.0)	3 (2.2)	0.55	3 (2.0)	0 (0.0)	0.81

bleeding events (92%) happened while the patients were on VA ECMO. The first major bleeding event was frequently within the first days of hospitalization, with a median time from admission to bleeding of 1 (0, 2) day, with 50% of patients bleeding on day 0 to 1 of admission and 74% of all bleeding events occurring before the third day of the hospitalization (Figure 2B).

Baseline comorbidities were comparable between those who had major bleeding and those without major bleeding (Table 1). In unadjusted analysis, those with a bleeding event had a lower hemoglobin (12.3 versus 13.1 g/dL; *P*=0.05), platelets (179 versus 200×10^3/μL, *P*=0.04), fibrinogen (218 versus 266 mg/dL, *P*=0.004), and antithrombin III levels (57% versus 65%, *P*<0.001) on admission (Figure 1). Our patients had an average D-dimer of 15.9 (7.2) versus 15.2 (7.0) μg/mL for patients with bleeding and no bleeding, respectively, with a normal for our laboratory of 0.0 to 0.5 μg/mL and no significant difference among groups (*P*=0.52). A comparison of presenting laboratory markers of patients who had no thrombotic or bleeding event, thrombosis only, major bleeding only, or both is shown in Figure S1. Only antithrombin III and fibrinogen were statistically significantly lower in those patients who had bleeding only compared with those who had no bleeding or thrombosis.

Use of procedural anticoagulation and antiplatelet medications was not associated with bleeds. The use of glycoprotein iib/iiia inhibitors and cangrelor was uncommon (6/200 [3.0%] and 16/200 [8.0%], respectively). The average dose of heparin given for ECMO cannulation and rate of percutaneous coronary intervention was not significantly different between groups.

In adjusted analyses to evaluate the predictors of ELSO major bleeding events, only fibrinogen was associated with incident major bleeding events. The hazard of ELSO major bleeding events was 0.98 for every 10 unit rise in fibrinogen (adjusted hazard ratio [aHR], 0.98 [95% CI, 0.96–0.99]) (Figure 3). The risk of bleeding seemed to increase with fibrinogen levels below 300 mg/dL (with 47.7% of patients having a major bleed in those with a fibrinogen >300 mg/dL versus 72.8% in those with a fibrinogen <300 mg/dL, *P*=0.003) (Figure 2C).

Outcomes Associated With Bleeding

The hospital course and outcomes are shown in Table 2. In unadjusted analysis, major bleeding was associated with higher transfusion needs, with patients who had a bleeding event receiving a median of 7 (4, 12) units of red

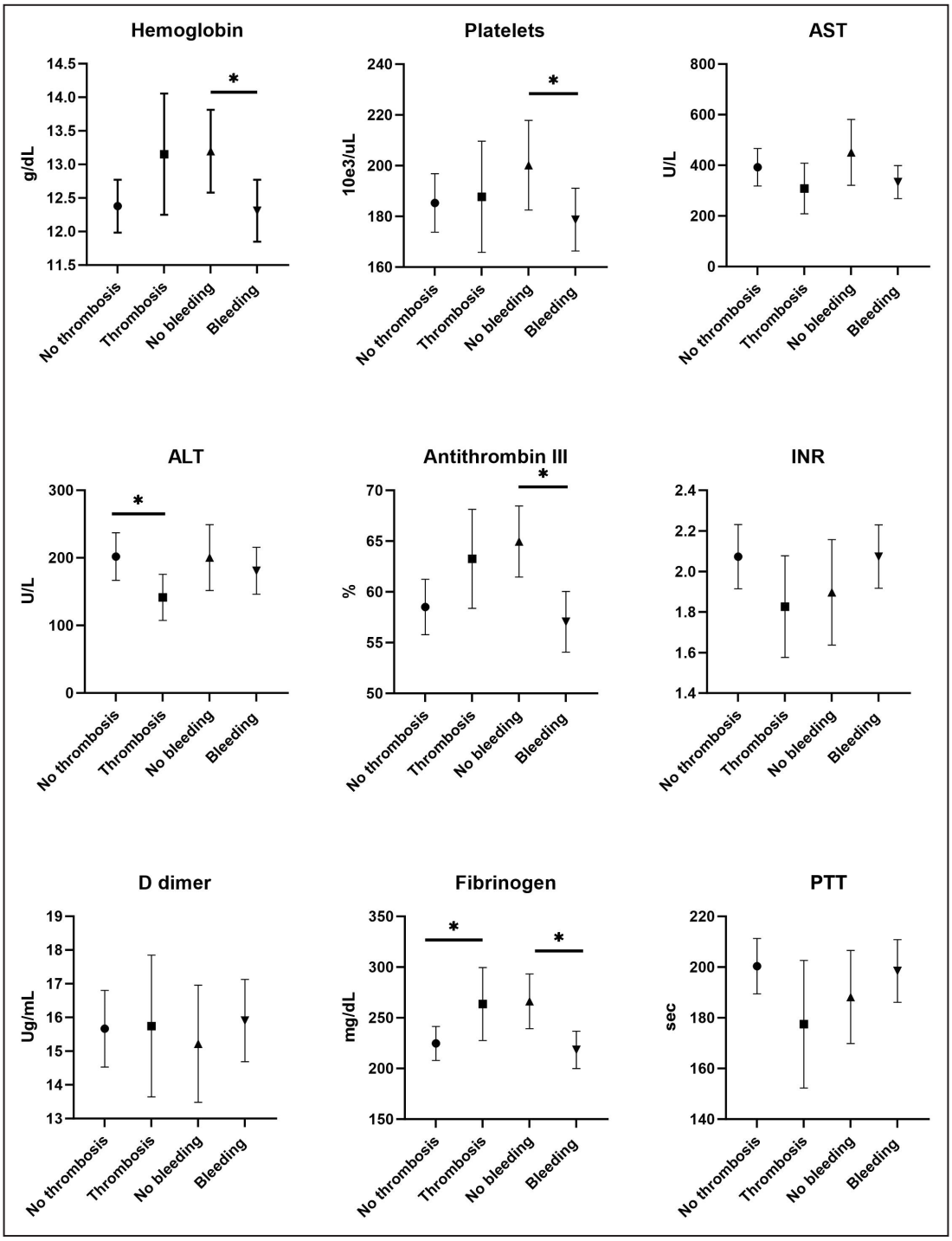

Figure 1. Hematologic markers (displayed as mean [95% CI]) on arrival to the intensive care unit stratified by patients with and without thrombosis and those with and without major bleeding.
ALT indicates alanine transaminase; AST, aspartate transaminase; INR, international normalized ratio; and PTT, partial thromboplastin time. *Denotes a statistically significant difference between thrombosis or no thrombosis and bleeding and no bleeding groups.

blood cells, 2 (0, 5) units of platelets, and 1 (0, 3) unit of fresh frozen plasma. Patients who had a bleeding event had similar rates of renal replacement therapy (30.4% versus 21.5%; *P*=0.25), extubation (29.6% versus 20.0%; *P*=0.20), and successful VA ECMO decannulation (48.1% versus 32.3%; *P*=0.19). For those patients who survived to extubation, the length of mechanical ventilation was longer in patients who had a major bleeding event (9

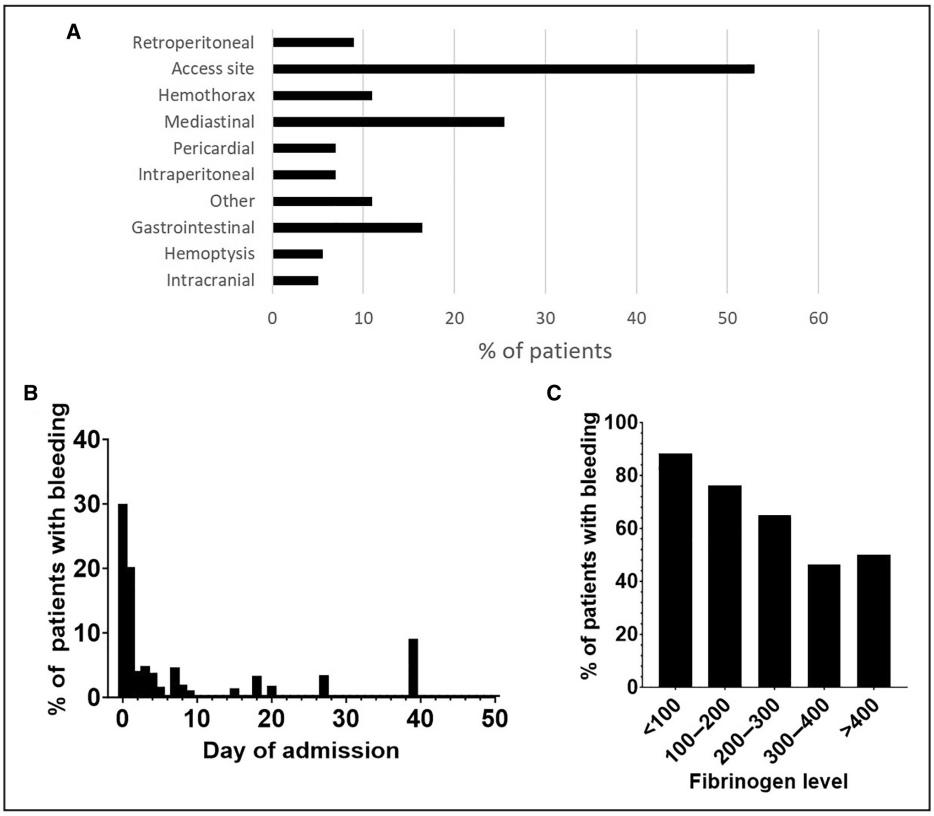

Figure 2. Characteristics of major bleeding events.
A, Sites of major bleeding. **B**, Percentage of admitted patients who had a major bleeding event. **C**, Percentage of patients who had a major bleeding event depending on admission fibrinogen level.

versus 6 days, *P*=0.05). The median length of hospital stay was 8 (2, 21) days. Having a bleeding event was associated with a longer length of hospitalization, with a median of 10 (3, 22) compared with 4 (2, 14) (*P*=0.01) days of admission.

In the adjusted analyses, having an ELSO major bleeding event was not associated with in-hospital death (aHR, 0.81 [95% CI, 0.55–1.19]). In the adjusted competing risks analyses, age (aHR, 1.01 [95% CI, 0.99–1.03]), male sex (aHR, 0.64 [95% CI, 0.36–1.15]), CPR time (aHR, 1.00 [95% CI, 0.99–1.02]), and use of DAPT during the hospitalization (aHR, 0.83 [95% CI, 0.51–1.36]) were not associated with ELSO major bleeding events. Similarly, in the adjusted competing risks analyses with in-hospital mortality as the end point, age (aHR, 0.99 [95% CI, 0.97–1.02]), sex (aHR, 0.66 [95% CI, 0.28–1.53]), CPR time (aHR, 1.00 [95% CI, 0.99–1.02]), and use of DAPT during the hospitalization (aHR, 0.54 [95% CI, 0.28–1.05]) were not associated with in-hospital mortality.

Thrombotic Events

Arterial or venous thrombotic events were identified in 23.5% (47/200) of patients. The sites of thrombi are shown in Figure 4A. Venous thromboembolism, including deep vein thrombosis, right atrial thrombi, and pulmonary embolism, occurred in 22 of 200 (11.0%) patients. Arterial thromboembolism was seen in 31 (15.5%), with 6 patients experiencing both arterial and venous thrombi during their hospitalization. Oxygenator thrombosis requiring exchange of the membrane was uncommon, occurring in 1.5% of the cohort (3/200). Two of these occurred the day of admission soon after cannulation and the other one occurred 12 days after cannulation. Despite continuous anticoagulation infusion through the reperfusion cannula, problems with thrombus formation in the tubing or catheter occurred in 5 patients (2.5%). Two other patients (1%) had lower limb ischemia requiring thrombectomy to salvage the limb. Thrombosis occurred at a median of 5 (1, 12) days from the day of admission. Arterial thrombi presented earlier (2 [1, 6] days) compared with venous thromboembolism (VTE) events (12 days [9, 16]) (Figure 4B).

There were no differences in baseline characteristics, comorbidities, or arrest characteristics in the groups with and without thrombosis (Table 1). Those who had a thrombotic event had a higher fibrinogen level (264 versus 225, *P*=0.03) and a lower alanine transaminase (141 versus 202 U/L, *P*=0.015)

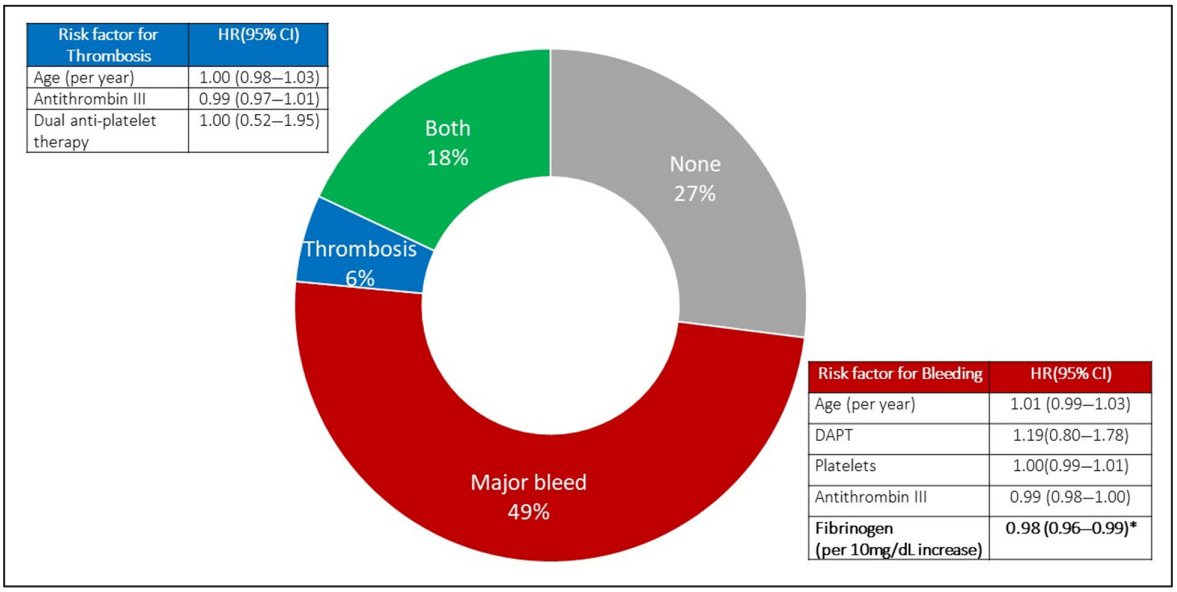

Figure 3. Rates of bleeding and thrombosis. Multivariable model of risks of bleeding and thrombosis.
*Denotes statistical significance. DAPT indicates dual antiplatelet therapy; and HR, hazard ratio.

compared with those who did not have a thrombotic event (Figure 1). Treatment characteristics of patients with and without thrombosis are shown in Table 3. The use of an intra-aortic balloon pump was not associated with increased thrombotic events. A thrombus in the inferior vena cava was detected in 6 of 200 (3.0%), accounting for 6 of 22 (27%) of all the deep venous thromboembolisms. Longer cannulation time was more frequent in patients with arterial thrombi but not in those with VTE (Table 3). In the univariate analyses, age, CPR time, baseline use of anticoagulation, DAPT administration, antithrombin III, and platelet count met the prespecified $P<0.20$ threshold for inclusion in the adjusted model.

In the adjusted analyses to determine predictors of thrombotic events, age, use of DAPT during admission, and antithrombin III were not associated with incident thrombosis (Figure 3).

Table 2. Treatment Characteristics and Hospital Course of Patients Who Had a Bleeding Event and Those Without Bleeding Events

	Overall cohort (N=200)	No bleeding (N=65)	Major bleeding (N=135)	*P* value
Transfusions during the hospitalization				
Red blood cells, units	4.5 (1.0, 10.0)	1.0 (0.0, 2.0)	7.0 (4.0, 12.0)	<0.001‡
Platelets, units	1 (0.0, 4.0)	0.0 (0.0, 1.0)	2.0 (0.0, 5.0)	<0.001‡
Fresh frozen plasma, units	1.0 (0.0, 3.0)	0.0 (0.0, 0.0)	1.0 (0.0, 3.0)	<0.001‡
Hospital course				
Renal replacement therapy, N (%)	55 (27.5)	14 (21.5)	41 (30.4)	0.25
Days on continuous dialysis* (N=14)	6.0 (4.0, 18.0)	3.5 (3.0, 4.0)	8.0 (4.0, 20.0)	0.20
Thrombosis, N (%)	47 (23.5)	11 (16.9)	36 (26.7)	0.16
Extubation, N (%)	53 (26.5)	13 (20.0)	40 (29.6)	0.20
Days on mechanical ventilation† (N=53)	8.0 (6.0, 13.0)	6.0 (5.0, 8.0)	9.0 (6.0, 14.0)	0.05‡
Days on VA ECMO	4.0 (3.0, 5.0)	3.0 (2.0, 4.0)	4.0 (2.0, 5.0)	0.05
VA ECMO decannulation, N (%)	95 (47.5)	21 (32.3)	65 (48.1)	0.19
Length of hospital stay, d	8.0 (2.0, 20.5)	4.0 (2.0, 14.0)	10.0 (3.0, 22.0)	0.01‡
Survival to hospital discharge, N (%)	64 (32.0)	17 (26.2)	47 (34.8)	0.29

VA ECMO indicates venoarterial extracorporeal membrane oxygenation.
*Calculated for patients who survived to discontinuation of continuous dialysis.
†Including patients who survived to liberation from mechanical ventilation.
‡Denotes a statistically significant difference between groups.

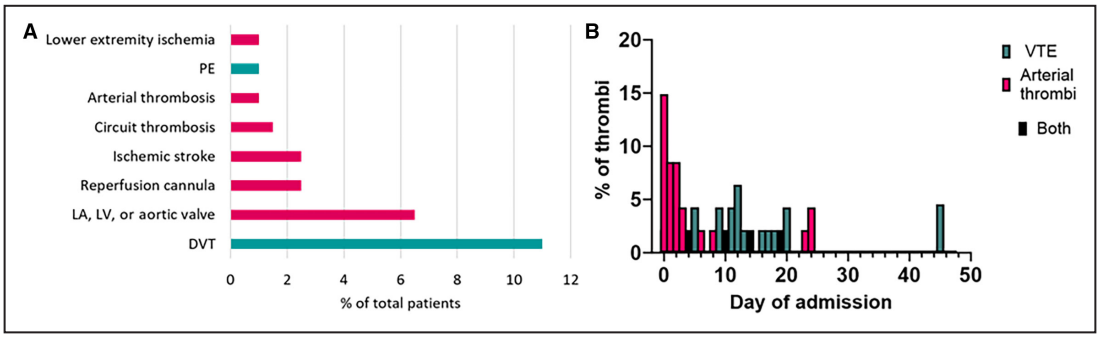

Figure 4. Characteristics of thrombotic events.
A, Percentage of patients with different sites of thrombosis with VTE (green) and arterial thrombosis (pink). **B**, Percentage of admitted patients who present thrombosis per day of admission. Arterial thrombosis refers to aorta or SMA thrombosis. DVT indicates deep vein thrombosis; LA, left artery; LV, left ventricle; PE, pulmonary embolism; SMA, superior mesenteric artery; and VTE, venous thromboembolism.

Outcomes Associated With Thrombosis

Patients who had a thrombotic event had a higher number of transfusions of red blood cells and platelets (7 versus 4 units; *P*=0.01 and 2 versus 1 units; *P*=0.005, respectively) (Table 3). There was no significant difference in terms of renal replacement therapy or rates of extubation. However, the length of stay was significantly longer for those who had a thrombotic event.

After adjustment for age, sex, CPR time, use of DAPT, and the occurrence of ELSO major bleeding events, the occurrence of thrombosis was not associated with in-hospital death (aHR, 0.65 [95% CI, 0.42–1.03]). When stratified by type of thrombosis, VTE

Table 3. Treatment Characteristics and Hospital Course of Patients Who Had a Thrombotic Event Including Arterial Thrombosis and VTE and Those Without Thrombosis

	No thrombosis (N=153)	Any thrombosis (N=47)	*P* value	No arterial thrombi (N=169)	Arterial thrombosis (N=31)	*P* value	No VTE (N=178)	VTE (N=22)	*P* value
Transfusions during the hospitalization									
Red blood cells, units	4 (1, 9)‡	7 (2, 12)‡	0.01‡	4.0 (1.0, 9.0)‡	7.0 (2.0, 12.0)‡	0.05‡	4.0 (1.0, 9.3)	7.0 (2.8, 12.0)	0.07
Platelets, units	1.0 (0.0, 3.0)‡	2.0 (0.0, 5.0)‡	0.005‡	1.0 (0.0, 3.0)	2.0 (0.0, 6.0)	0.06	1.0 (0.0, 4.0)‡	2.0 (1.0, 5.5)‡	0.02‡
Fresh frozen plasma, units	1 (0, 2)	0 (0, 2)	0.50	0 (0, 2)	1 (1.3)	0.39	1 (0, 2)	0 (0, 1)	0.09
Hospital course									
Renal replacement therapy	37 (24.2)	18 (38.3)	0.09	40 (23.7)	15 (48.4)	0.009	49 (27.5)	6 (27.3)	1.00
Days on continuous dialysis* (N=14)	4.5 (2.8, 11.3)	17.0 (6.0, 22.0)	0.12	5.0 (3.0, 18.0)	12.0 (4.0, 12.0)	0.39	5 (3, 12)	22 (13, 22)	0.18
Major bleeding event	99 (64.7)	36 (76.6)	0.18	111 (65.7)	24 (77.4)	0.28	118 (66.3)	17 (77.3)	0.42
Extubation, N (%)	37 (24.2)	16 (34.0)	0.25	48 (28.4)	5 (16.1)	0.23	39 (21.9)‡	14 (63.6)‡	<0.001‡
Days on mechanical ventilation† (N=53), N (%)	7.0 (5.5, 11.0)	11.5 (6.5, 18.5)	0.07	7.5 (6.0, 13.0)	13.0 (8.0, 17.0)	0.17	7.0 (6.0, 11.0)	11.5 (7.5, 15.5)	0.09
VA ECMO decannulation, N (%)	60 (39.2)	26 (55.3)	0.07	73 (43.1)	13 (41.9)	1.00	68 (38.2)‡	18 (81.8)‡	<0.001‡
Length of VA ECMO run, d	3.5 (2.4)‡	4.8 (3.1)‡	0.008	3.6 (2.5)‡	4.9 (3.1)‡	0.04‡	3.7 (2.6)	4.8 (2.9)	0.12
Length of hospital stay, d	6 (2, 18)‡	15 (5, 29)‡	<0.001‡	8 (2, 21)	10 (3, 22)	0.37	6.0 (2.0, 17.3)‡	28.0 (15.0, 37.8)‡	<0.001‡
Survival to hospital discharge, N (%)	46 (30.1)	18 (38.3)	0.38	58 (34.3)	6 (19.4)	0.15	49 (27.5)‡	15 (68.2)‡	<0.001‡y

VA ECMO indicates venoarterial extracorporeal membrane oxygenation; and VTE, venous thrombolembolism.
*Calculated for patients who survived to discontinuation of continuous dialysis.
†Including patients who survived to liberation from mechanical ventilation.
‡Denotes a statistically significant difference between groups.

was associated with in-hospital mortality in unadjusted (Table 3) and adjusted analysis (aHR, 0.22 [95% CI, 0.09–0.60]). The rate of VTE was associated with the length of stay, with a rate of 0.01±0.023 per day for those who survived compared with 0.003±0.015 for those who died (P=0.008). Each additional day of hospitalization was associated with an odds ratio of 1.05 for VTE (95% CI, 1.0–1.1, P<0.001), making it very sensitive to survival bias.

Arterial site thrombosis was not associated with in hospital death in unadjusted (Table 3) or adjusted analysis (aHR, 1.2 [95% CI, 0.73–1.94]).

In the adjusted competing risks analyses, age (aHR, 1.01 [95% CI, 0.98–1.05]), male sex (aHR, 1.47 [95% CI, 0.50–4.34]), CPR time (aHR, 1.00 [95% CI, 0.98–1.02]), and use of DAPT (aHR, 1.44 [95% CI, 0.62–3.34]) were not associated with incident thrombosis. In the adjusted competing risks analyses for in-hospital mortality, CPR time (aHR, 1.02 [95% CI, 1.01–0.103]) was associated with in-hospital mortality, whereas age (aHR, 1.01 [95% CI, 0.99–1.03]), male sex (aHR, 1.09 [95% CI, 0.65–1.83]), and use of DAPT (aHR, 0.67 [95% CI, 0.44–1.02]) were not associated with in-hospital mortality.

DISCUSSION

In this large observational single-center study, we report the incidence and risk factors associated with bleeding and thrombosis and their association with in-hospital mortality. Major bleeding as defined by ELSO is a common complication of eCPR, affecting 67.5% of our cohort. In multivariable analysis, the only risk factor associated with bleeding was decreasing levels of fibrinogen. Thrombosis was less common than bleeding, occurring in 23.5% of patients, with 11.0% of patients having a VTE and 15.5% an arterial thrombus. A higher level of antithrombin III on admission and the administration of DAPT was associated with decreased thrombotic risk. Neither bleeding nor thrombosis was associated with in-hospital mortality when results were adjusted for clinically significant factors.

Reported rates of bleeding in the eCPR population vary widely[5,23–29] but are higher than those of other types of ECMO, including VA ECMO for other cardiac indications[24,28] or venovenous ECMO.[24] The heightened risk of bleeding is thought to be related to trauma from prolonged CPR, hypothermia, and coagulopathy associated with postcardiac arrest syndrome.[5,14,25] In our cohort, we found an incidence of intracranial hemorrhage of 5%, which is similar to that reported in other eCPR cohorts (4.3%–5.6%),[24,26] and 67.5% of patients had major bleeding events. Although elevated, this is concordant with other eCPR cohorts, including the study by Otani et al published in 2018 that reported a 70% (71/233) bleeding rate.[25] In their study, major bleeding was assessed by Bleeding Academic Research Consortium criteria defined as type 3 or higher correlating to overt bleeding plus a decline in hemoglobin of ≥3 g/dL within 24 hours of hospital admission.[25] Similarly, the CHEER (Mechanical CPR, Hypothermia, ECMO, and Early Reperfusion) study had a bleeding rate of 70% (18/26), though they do not specify how they defined this outcome.[5] However, other studies of patients receiving eCPR quote lower bleeding rates, including 38% as defined by the Bleeding Academic Research Consortium type 3 or higher,[23] 39% assessed by type 3b or higher,[27] 26% per ELSO criteria in the ELSO registry,[28] 37% defined as traumatic or bleeding complication without routine employment of computed tomography imaging,[30] and 20% to 24% without a clear definition of major bleeding.[26,29,31,32] The discrepancy is likely due to the various definitions of bleeding, with ELSO-defined major bleeding being a more sensitive criteria including a decline in hemoglobin of ≥2 g/dL/24 hours.[31]

In unadjusted analysis, decreased levels of fibrinogen, antithrombin III, and platelet count were associated with increased risk of major bleeding, though this was negated in the multivariable model. Prior studies on patients who received eCPR suggest that hyperfibrinolysis may increase bleeding risk. In a study including 133 patients, higher D-dimer level on admission (18.8 versus 6.7 μg/mL) was associated with major bleeding.[25] We did not find significant associations between initial D-dimer and bleeding, but the D-dimer levels of our cohort were very elevated (15.7±0.5 μg/mL [normal for our laboratory: 0.0–0.5 μg/mL]) and frequently reported as >20 μg/mL. This may have led to an underestimation of the actual D-dimer levels in patients with bleeding and may explain the disparate findings. However, markers of coagulation factor consumption, including low fibrinogen and low antithrombin III, were associated with bleeding. In adjusted analysis, decreased level of fibrinogen was the only variable associated with increased bleeding risk. Another study including all patients receiving VA ECMO identified fibrinogen among other factors to be predictive of bleeding.[28] Low platelet count, elevated D-dimer, and low fibrinogen has been observed in other populations receiving eCPR, with an elevated disseminated coagulation score score being associated with mortality.[27,33] These studies excluded patients on DAPT, whereas we had a significant proportion of patients on DAPT and found a persistent association with markers of consumption and increased bleeding risk.

Major bleeding increased in-hospital morbidity but was not associated with increased mortality. The lack of association with in-hospital mortality diverges from some published ECMO studies where bleeding has been associated with increased mortality.[12,24,34] In

contrast to our data, these studies included venovenous and VA ECMO support[12,24,34] and pediatric and adult patients.[12,24] Further, it is possible that bleeding as defined by the criteria for ELSO major bleeding is an insensitive marker of major events. However, other studies have reported a lack of association between bleeding and in hospital death. In an unadjusted analysis using Bleeding Academic Research Consortium type 3 or higher by Otani et al, the rates of bleeding were similar in survivors and nonsurvivors treated with eCPR (46% versus 33%, P=0.44). Similarly, in a study by Sahli et al including all comers requiring ECMO support, development of bleeding complications during ECMO was not an independent predictor of mortality, though they did not provide their definition of bleeding.[26] Major bleeding was associated with increased transfusion needs in this study, in agreement with prior reports in the literature,[12,24,26,28] and with longer time on mechanical ventilation.

Thrombotic complications are sparsely reported in the eCPR literature. We found a rate of 22.5%, which is similar to that published in another study including patients receiving eCPR with a rate of thrombosis of 21%,[23] but higher than the 7% reported in a recent meta-analysis.[31] The risk of limb ischemia in the literature is around 16% to 24%,[23,31] whereas we had a much lower rate of 1%. We routinely place antegrade perfusion catheters at the time of cannulation and infuse heparin through that catheter. Further, our patients were uniformly recipients of eCPR with an anticoagulation strategy that used an unfractionated heparin infusion targeting an ACT of 180 to 200 seconds. This is not a universal practice and may account for these differences.[31] In our study, predictors of thrombosis included lower levels of antithrombin III and patients without DAPT administration. Data regarding risk factors for thrombosis are lacking. In a meta-analysis including all types of ECMO, the anticoagulation strategy was not significantly associated with thrombotic risk, though the use of antiplatelet therapy was not reported.[31]

In this cohort, thrombosis was not associated with increased mortality. Consistent with other eCPR[23] and general ECMO[31] literature, we did not find any association between survival and thrombosis.[23] Thrombotic complications of eCPR include arterial and venous thrombi and their pathophysiology differs significantly. Arterial thrombi typically present in the first few days of admission while patients are highly reliant on the ECMO circuit and the ejection fraction is frequently limited.[19] The association of VTE with in-hospital mortality is likely due to immortal time bias, with a rate of thrombosis per day of 0.01±0.02 for those who survived versus 0.003±0.02 for those who died. VTE is highly dependent on length of hospital stay, as has been shown in numerous cohorts including our data, where the risk of VTE increased by 5% per each additional day of hospitalization.[35,36] In a study including routine ultrasound evaluation for VTE after decannulation, deep vein thrombosis was found in 15 of 30 (50%) of those who survived to decannulation where venovenous extracorporeal life support and length of cannulation were the only predictors of VTE.[37] In our cohort, the length of VA ECMO cannulation was not associated with the rate of VTE. Our rate of deep vein thrombosis was significantly lower; however, our cohort did not include venovenous ECMO, and we performed ultrasounds only when clinically indicated. Despite the underreported rate of thrombosis, patients receiving eCPR are anticoagulated aggressively, with more than half of them receiving antiplatelet therapy in addition to heparin given the burden of acute coronary syndrome as the cause of VT/VF arrest. Given the high rate of bleeding and low thrombotic risk in our population receiving eCPR, further research should evaluate anticoagulation strategies to find the optimal approach that minimizes risk of bleeding without increasing thrombotic sequelae.[31]

Given the retrospective nature of the study, some limitations are inevitable. Although this represents one of the largest single-center cohorts published, its small size may limit discrimination of small differences between groups. Despite performing adjusted analyses, we cannot account for potential confounding from variables that were not included in the model. The study was observational, and change in anticoagulation management in response to bleeding, thrombotic events, or laboratory values was not protocolized or mandated and was not included in the analysis. Finally, despite using survival analysis and competing risk analysis, survival bias is unavoidable. Patients who die are no longer able to experience a bleeding or thrombotic event; therefore, our results should be interpreted with caution.

CONCLUSIONS

In this large study of patients receiving eCPR, 67.5% of patients experienced major bleeding as defined by ELSO, and 23% of our cohort experienced thrombosis. Lower fibrinogen was associated with increased bleeding risk whereas the use of DAPT and lower antithrombin III levels on admission was associated with decreased thrombotic risk. Major bleeding was not associated with in-hospital mortality, but both thrombosis and major bleeding were associated with in-hospital morbidity with higher transfusion needs and longer mechanical ventilation days for those who bled. There is a need to assess optimal anticoagulation and antiplatelet regimens that minimize bleeding risk without increasing thrombotic consequences.

ARTICLE INFORMATION

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Affiliations

Cardiovascular Division, Department of Medicine (A.G., R.K., T.A., A.M.E., D.Y., J.A.B.), Center for Resuscitation Medicine (A.G., R.K., A.M.M., T.A., A.M.E., D.Y., J.A.B.), Department of Medicine (K.Y.C.), Division of Hematology and Oncology, Department of Pediatrics (M.E.S.), Division of Pediatric Critical Care Medicine, Department of Pediatrics (M.E.S., A.M.M.), University of Minnesota School of Medicine, Minneapolis, MN and University of Minnesota School of Medicine, Minneapolis, MN (M.N.).

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Supplemental Material

Figure S1

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