

ORIGINAL ARTICLE

Use of rotational thromboelastometry to predict hemostatic complications in pediatric patients undergoing extracorporeal membrane oxygenation: A retrospective cohort study

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Handling Editor: Neil Zakai

Abstract

Background: The incidence of hemostatic complications in pediatric patients undergoing extracorporeal membrane oxygenation (ECMO) is high. The optimal anticoagulation strategy in children undergoing ECMO is unknown.

Objectives: To study the association between hemostatic complications, coagulation tests, and clinical parameters in pediatric patients undergoing ECMO and their effect on survival.

Methods: We performed a retrospective cohort study of pediatric patients undergoing centrifugal pump ECMO. Collected data included patient characteristics, risk factors, and coagulation test results. Statistical analysis was done using logistic regression analysis for repeated measurements. Dependent variables were thrombosis and bleeding, independent variables were rotational thromboelastometry (ROTEM), activated partial thromboplastin time (aPTT) and antifactor-Xa assay (aXa) results, ECMO duration, age <29 days, sepsis and surgery.

Results: Seventy-three patients with 623 ECMO days were included. Cumulative incidences of thrombosis and bleeding were 43.5% (95% confidence interval [CI], 26.0%-59.8%) and 25.4% (95% CI, 13.4%-39.3%), respectively. A lower maximum clot firmness of intrinsic ROTEM (INTEM; odds ratio [OR], 0.946; 95% CI, 0.920-0.969), extrinsic ROTEM (OR, 0.945; 95% CI, 0.912-0.973), and INTEM with heparinase (OR, 0.936; 95% CI, 0.896-0.968); higher activated partial thromboplastin time aPTT; OR, 1.020; 95% CI, 1.006-1.024) and age <29 days (OR, 2.900; 95% CI, 1.282-6.694); surgery (OR, 4.426; 95% CI, 1.543-12.694); and longer ECMO duration (OR, 1.149; 95% CI, 1.022-1.292) significantly increased thrombotic risk. Surgery (OR, 2.698; 95% CI, 1.543-12.694) and age <29 days (OR 2.242, 95% CI 1.282-6.694) were significantly associated with major bleeding. Patients with hemostatic complications had significantly decreased survival to hospital discharge ($P = .009$).

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Conclusion: The results of this study help elucidate the role of ROTEM, aPTT, anti-factor Xa, and clinical risk factors in predicting hemostatic complications in pediatric patients undergoing ECMO.

KEYWORDS

blood coagulation test, extracorporeal membrane oxygenation, hemorrhage, pediatrics, thrombosis

Essentials

- The best coagulation protocol in pediatric extracorporeal membrane oxygenation (ECMO) is unknown.
- Our objective was to study the relation between hemostatic complications, coagulation tests, and clinical factors.
- Lower maximum clot firmness, age (neonate), higher activated partial prothrombin time, surgery, and longer ECMO time increase thrombotic risk.
- Major bleeding was associated with surgery and age <29 days.

1 | INTRODUCTION

Extracorporeal membrane oxygenation (ECMO) provides temporary cardiopulmonary support for critically ill children with refractory cardiac and/or respiratory failure. According to the Extracorporeal Life Support Organization (ELSO) registry, neonatal and pediatric ECMO runs account for almost 50% and 25% of the total number of ECMO runs, respectively.¹ Unfortunately, the incidence of hemostatic complications, including bleeding and thrombotic complications, is high, and these complications are associated with an increased mortality in pediatric patients undergoing ECMO.² In the ELSO registry, hemorrhagic complications including intracranial hemorrhage (ICH) were reported in up to 29.1% of neonatal and 28.5% of pediatric patients undergoing ECMO. Thrombotic complications arose in up to 16.7% of neonatal and 12.4% of pediatric patients.¹ The majority of hemostatic complications occurs in the first 2 weeks of the ECMO course.³

The underlying mechanism for hemostatic complications in patients undergoing ECMO is a shift of the hemostatic balance. Activation of the inflammatory and coagulation systems leads to a hypercoagulable state through the exposure of blood to the non-endothelial surface of the extracorporeal circuit.⁴ Systemic anticoagulation is necessary to prevent thrombotic complications and to retain patency of the extracorporeal circuit.⁵ Unfractionated heparin (UFH) is the anticoagulant of choice in pediatric ECMO due to the short half-life and potential for reversal by protamine sulfate.^{6,7} However, an important drawback of anticoagulant use is the risk of bleeding complications. This risk may be even higher in patients with infection, disseminated intravascular coagulation, and during and shortly after surgery. Thus, a delicate balance between bleeding and thrombotic complications exists in patients undergoing ECMO.

Although the majority of ECMO experience is obtained in neonates and children, no optimal method is known for establishing the hemostatic state in pediatric patients undergoing ECMO.⁸ Moreover, no consensus on therapeutic target levels exists and anticoagulation

protocols differ between pediatric ECMO centers, while the level of evidence is low.^{6,9,10} Extrapolation from adult guidelines is limited, as hemostasis develops during the first years of life. For example, adult antithrombin levels are reached at an age of approximately 6 months, possibly contributing to the variable effect of heparin in neonates and infants, as the effect of heparin is mediated through antithrombin.^{5,11}

Coagulation tests most frequently used in pediatric ECMO are standard tests including activated clotting time, activated partial thromboplastin time (aPTT), and anti-factor Xa assays (aXa) or a combination of these tests.^{9,10,12} In contrast to these standard tests, viscoelastic tests such as thromboelastography (TEG) or rotational thromboelastometry (ROTEM) give a representation of the whole clotting process and can be used as bedside tests, providing clinicians with results within 30 minutes. Both methods are based on the same principle.¹³⁻¹⁵ Normal values of ROTEM in children have been described.¹⁶ Viscoelastic tests enable clinicians to analyze the baseline hemostatic state through exclusion of the heparin effect by adding heparinase. The difference between samples with and without heparinase can aid in determining the true effect of heparin.¹⁷ Although it is a promising technique, the use of viscoelastic tests in case of mild coagulation deficiencies and defects of the primary hemostasis (von Willebrand disease and platelet aggregation) is limited.¹⁸ Nevertheless, an international survey showed that 43% of 187 investigated pediatric ECMO centers reported the use of TEG or ROTEM as part of the coagulation monitoring protocol.⁹

Whereas several papers have published results of studies on coagulation management in pediatric ECMO, the association between viscoelastic tests and hemostatic complications in children undergoing ECMO has not often been studied.¹⁹⁻²¹ The aim of this study is to investigate the incidence of hemostatic complications and their association with ROTEM and clinical parameters in a cohort of pediatric patients undergoing ECMO. In addition, we studied the association between hemostatic complications and standard test (aPTT and aXa) results and the effect of these complications on survival.

2 | MATERIALS AND METHODS

2.1 | Study design and patients

This is a retrospective observational cohort study of all pediatric patients undergoing ECMO between January 2011 and May 2018 in the tertiary pediatric intensive care unit of the Erasmus MC–Sophia Children's Hospital, Rotterdam, The Netherlands. The Medical Ethics Committee of the Erasmus MC approved the study design (MEC-2018-1238). Due to the retrospective nature of this study, no informed consent was needed.

All children (<18 years old) supported with centrifugal pump ECMO were eligible for this study. Patients with >50% of ECMO support days without ROTEM data were excluded. Furthermore, second ECMO runs and the days of and after administration of anticoagulants other than UFH, including coagulation factor concentrate, were omitted. Patients with an ECMO run shorter than 72 hours were excluded to decrease the chance of including hemostatic complications caused by the underlying disease. An ECMO run is considered the period from ECMO cannulation until ECMO decannulation. Since 2012, all patients undergoing ECMO have been supported with a centrifugal pump; therefore, patients with roller pump ECMO were excluded. Some of the included patients were previously described in the study of Stiller et al.²²

2.2 | ECMO circuit and anticoagulation management

The ECMO circuit consisted of the iLA-active Dp3 ECMO system (Xenius AG, Heilbronn, Germany) with a centrifugal pump and the Novalung minilung petit (± 1800 g–5 kg), minilung (5–15 kg) or the iLa membrane (>15 kg) (Xenius AG, Heilbronn, Germany). All patients were treated according to the local pediatric ECMO anticoagulation protocol. aPTT was measured four times per day and was used as the primary anticoagulation monitoring tool. aXa levels were obtained four times per day and were used as a safety measure. Once daily, fibrinogen, prothrombin time, factor V, D-dimers, antithrombin, and ROTEM measurements were performed. The aPTT goal was set every day for each patient depending on individual risk factors per patient. Patients with standard risk of bleeding complications (>1 year old, no trauma or surgery <48 hours before cannulation and no preexisting coagulation disorders) were managed with an aPTT goal between 60 and 85 seconds and an aXa level between 0.5 and 1.0. Patients with a high thrombotic risk (<1 year old and/or a preexisting thrombotic risk) had an aPTT goal from 85 to 120 seconds and an aXa level between 0.5 and 1.0. The aimed aPTT values for patients prone to bleeding (trauma or surgery <48 hours before ECMO or surgery during ECMO) ranged from 50 to 70 seconds and an aXa level ranging from 0.3 to 0.7. In case of high-risk surgery or severe bleeding complications, the heparin dose was decreased and infrequently stopped on discretion of the treating ECMO physician. The target value for fibrinogen was >1 g/L, and a platelet count

<100 $\times 10^9$ /L was considered an indication for platelet transfusion. Persistent high D-dimers >50 mg/L fibrinogen equivalent units and low fibrinogen <1 g/L despite correction with high-volume plasma (30 mL/kg) and/or hemolysis (free hemoglobin level) >20 to 50 μ mol/L in at least two samples were considered indications for circuit thrombosis, leading to ECMO circuit change. The protocol did not change during the study period.

2.3 | Data collection

Data were collected from patients' electronic files, including demographic data (age, sex), ECMO configuration, indication for ECMO support (respiratory, cardiac, or ECMO applied during extracorporeal cardiopulmonary resuscitation [ECPR]), duration of ECMO support, and survival to discharge from the hospital. The parameters surgical interventions, presence of sepsis, time and results of coagulation tests, including ROTEM, aPTT, and aXa were collected from each day of ECMO support. The clotting time (CT) and the maximum clot firmness (MCF) of intrinsic (INTEM) and extrinsic (EXTEM) coagulation pathways, INTEM with heparinase (HEPTTEM), and the MCF of fibrin formation (FIBTEM) were included. Since most hemostatic complications occur in the first 14 days of ECMO support,³ the variables used in the generalized estimated equations (GEEs), including hemostatic complications, were collected until the 14th day of ECMO support.

Each patient's ECMO run was divided into 1-day periods. Multiple thrombotic or hemorrhagic events per day were considered a single event. In case of a bleeding and thrombotic event on the same day, the coagulation results were excluded from analysis. When a hemostatic event lasted multiple days, the ROTEM results from the first day were included. As surgical interventions may affect the hemostatic system for a longer period, surgery was considered a period of 72 hours after the surgical intervention. When multiple ROTEM results were available on a single day, the first complete list of ROTEM results of that day was used. On the day of an event, the last ROTEM results before the event were used. All aPTT and aXa results were collected to a maximum of four per day, since aPTT and aXa are measured four times per day according to the local protocol. The minimum aPTT and aXa values in the 24 hours before an event were used in the analysis of thrombosis and the maximum aPTT and aXa values in the 24 hours before an event were used in the analysis of bleeding complications. On days without an event, the minimum and maximum aPTT and aXa values of that day were used.

2.4 | Coagulation tests

Blood was collected in 3.2% trisodium citrate tubes and directly analyzed in the coagulation laboratory of Erasmus MC. The citrate to blood ratio was 1:9. The citrate tubes were centrifuged for 15 minutes at 1700 g. ROTEM results were obtained using the ROTEM delta (Werfen) with reagents from Werfen (Breda, The Netherlands).

aPTT (reagent: Actin FS, Siemens, Munich, Germany) and aXa (reagent: Liquid Anti-Xa, Instrumentation Laboratory, Bedford, MA, USA) were performed using the Sysmex CS5100 coagulation analyzer (Siemens Healthcare Diagnostics B.V., Newark, DE, USA).

2.5 | Definitions

In concurrence with ELSO, major bleeding was defined as clinically overt bleeding associated with a hemoglobin fall of at least 2 g/dL in a 24-hour period, >20 mL/kg over a 24-hour period, or a transfusion requirement of one or more 10-mL/kg packed red blood cell transfusions over that same time period. Moreover, bleeding that was retroperitoneal, pulmonary, or involved the central nervous system, or bleeding that required surgical intervention was defined as major bleeding.²³ Minor bleeding events were defined as a bleeding complication that did not match the major bleeding definition, such as minor bleeding from the puncture site or intravenous line. Thrombotic complications consisted of circuit thrombosis, leading to a change of the ECMO circuit, and patient thrombosis, including cardiac thrombosis, gastrointestinal thrombosis, and stroke. Scoring of outcome was performed by a panel of three members (JD, EW, HO) of the research team, and events were appointed as bleeding or thrombotic complications. ECPR was defined as ECMO applied during cardiopulmonary resuscitation. Surgery was considered an invasive procedure with incision of the skin. Percutaneous procedures were not considered surgical interventions. Sepsis was defined as the systemic inflammatory response syndrome in conjunction with or as a result of a suspected or proven infection.²⁴ Neonates were considered all children <29 days old. Risk factors were assessed until the 14th day of ECMO support.

2.6 | Statistical analysis

Normally distributed variables were expressed as mean (standard deviation). Continuous variables that were not normally distributed were displayed as median (interquartile range). Survival of patients was described using a Kaplan-Meier curve. Survival was compared using the log-rank test between patients with bleeding, thrombotic complications, or both bleeding and thrombotic complications and patients without hemostatic events. The cumulative incidence of bleeding and thrombosis was determined using the Aalen-Johansen estimator for the cumulative incidence accounting for the competing risk of death. The distribution of minimum and maximum aPTT and aXa values was compared between neonates and children using the Mann-Whitney *U* test.

Associations with major bleeding and thrombotic complications were first assessed using a univariate logistic regression analysis. Thereafter, a multivariable logistic regression analysis for repeated measurements based on GEEs was performed. An independent working correlation matrix was used in the GEE models to account for the within-subject clustering of observations. To assess the

association between major bleeding complications and ROTEM results, separate GEE models were generated for each ROTEM variable (CT and MCF of INTEM, EXTEM, and HEPTTEM and the MCF of FIBTEM) with major bleeding as the dependent variable. The relation between thrombotic events and ROTEM results was analyzed similarly, with thrombosis as the dependent variable. The independent variables in these analyses were the results of ROTEM (CT and MCF of INTEM, EXTEM, and HEPTTEM and the MCF of FIBTEM), day of ECMO support (coded as a continuous variable), age <29 days, sepsis, ECMO duration, and surgical interventions. The association between aPTT and aXa and hemostatic complications was investigated in the same manner as ROTEM components.

Statistical analysis was performed using SPSS version 24.0 (IBM, Chicago, IL, USA). A *P* value of .05 was considered the limit of significance in all tests. A Bonferroni correction for multiple testing was conducted for all parameters of coagulation tests resulting in an adjusted significance level of $\alpha_{\text{altered}} = .05/9 = .006$.

3 | RESULTS

3.1 | Patient characteristics

We studied the medical records of 179 pediatric patients undergoing 180 ECMO runs between January 2011 and May 2018, of whom 73 patients were included. Of the 107 excluded ECMO runs, 54 patients had insufficient ROTEM data, 44 patients had an ECMO run <72% hours, 8 patients received alternative anticoagulants, and 1 patient had two ECMO runs, of which only the first was included. The included patients accounted for 623 ECMO support days. The median ECMO support duration during the study period was 5 days, with an interquartile range between 3 and 8 days. A total of 31 surgical interventions were performed in 26 (35.6%) patients. The surgical interventions comprised seven (22.6%) congenital diaphragmatic hernia repairs, four (12.9%) cardiothoracic surgeries, five (16.1%) laparotomies, and four (12.9%) surgical hemostases; six (19.4%) interventions were ECMO cannula repositioning or recannulation, and six (19.4%) surgeries were classified as other. Five patients had multiple surgical interventions. Thirty-one (42.5%) patients met criteria for sepsis on ≥ 1 days. Demographics and clinical characteristics are shown in Table 1.

3.2 | Incidence of hemostatic complications

In the study population, 53 hemostatic complications occurred in 32 patients (43.8%): 29 bleeding and 24 thrombotic events (Table 2). Adjusted for the competing risk of mortality, the cumulative incidence of thrombotic complications was 43.5% (95% CI, 26.0%-59.8%), and the cumulative incidence of bleeding complications was 25.4% (95% CI, 13.4%-39.3%) (Figure 1A, B) Seventeen (23.3%) patients developed 24 thrombotic events, of which the majority (75%) was circuit thrombosis leading to a circuit change. Twenty (27.4%) patients suffered from 22 major bleeding complications. Nine of

TABLE 1 Demographics and details of extracorporeal membrane oxygenation

Patients, n	73
ECMO support days	623
Age at cannulation, mo, median (IQR)	3.3 (0.05-37.2)
Male, n (%)	33 (45.2)
Neonate, n (%)	30 (41.1)
Preterm neonates, n (%)	3 (4.1)
Weight, kg, median (IQR)	4.5 (3.3-14.0)
Sepsis, n (%)	31 (42.5)
Patients with surgical interventions, n (%)	26 (35.6)
ECMO configuration, n (%)	
VV-ECMO	30 (41.1)
VA-ECMO	43 (58.9)
ECMO indication, n (%)	
Cardiac	21 (28.8)
Respiratory	48 (65.8)
ECPR	4 (5.5)
ECMO duration during study period, d, median (IQR)	5 (3-8)
Survival to discharge, n (%)	37 (50.7)
Time between last ROTEM and complication, h, median (IQR)	7.6 (3.0-10.8)

Abbreviations: aPTT, activated partial thromboplastin time; aXa, anti-factor Xa level; ECMO, extracorporeal membrane oxygenation; ECPR, extracorporeal cardiopulmonary resuscitation; IQR, interquartile range; ROTEM, rotational thromboelastometry; VA, venoarterial; VV, venovenous.

these 22 major bleeding events affected the central nervous system, and cardiopulmonary resuscitation (CPR) preceded ECMO initiation in five of these cases. One patient suffered from a thrombotic and hemorrhagic complication on the same day, and five patients suffered from both thrombotic and bleeding complications during the ECMO treatment. Four patients (5.5%) developed seven minor bleeding complications, consisting of bleeding from the puncture site of an intravenous line or ECMO cannulas. The median time between initiation of ECMO support and the first bleeding or thrombotic complication was 124 and 212 hours, respectively.

3.3 | Association between laboratory and clinical parameters and thrombotic events

Results of INTEM MCF, EXTEM MCF, FIBTEM MCF, and HEPTTEM MCF are summarized for patients with and without thrombosis in Figure 2A. (Results of other ROTEM values are available in Supporting Information 1A and 2.) In a univariate analysis, a reduced MCF of all ROTEM components and a higher minimum aPTT in the 24 hours before an event were significantly associated with increased risk of thrombotic events (Supporting Information 3). CT of all ROTEM components was not associated with thrombotic events. In the multivariate analysis, a lower MCF of INTEM, EXTEM, and

HEPTTEM remained significantly associated with increased risk of thrombotic events (Table 3).

The minimum aPTT 24 hours before an event was significantly associated with thrombotic events, but the minimum aXa results did not show this pattern (Table 3). The minimum aPTT in 24 hours before a thrombotic complication was significantly higher than the minimum aPTT of patients without thrombosis. The median aPTT was 81.0 seconds and 67.0 seconds in children with and without thrombotic complications, respectively ($P < .01$). The median aXa value 24 hours before a thrombotic event was 0.37 and 0.49 IU/mL in children with and without thrombosis, respectively ($P = .75$). Age <29 days, surgical interventions, and a longer duration of the ECMO treatment significantly increased the risk of thrombotic events (Table 3).

The minimum and maximum aPTT values were significantly higher in neonates in comparison to children. However, neonates had significantly lower minimum and maximum aXa values compared to children (Table 4).

3.4 | Association between laboratory and clinical parameters and bleeding events

Results of INTEM MCF, EXTEM MCF, FIBTEM MCF, and HEPTTEM MCF are summarized for patients with and without bleeding complications in Figure 2. (Results of other ROTEM values are available in Supporting Information 1B and 2.) No significant association was found between bleeding complications and results of ROTEM, aPTT and aXa in the univariate (Supporting Information 3) and multivariate analysis (Table 3). In the multivariate analysis, surgical interventions and age <29 days significantly increased the risk of major bleeding events (Table 3). The maximum aPTT and aXa 24 hours before a bleed did not significantly differ between children with and without bleeding complications. The median aPTT was 117.0 and 99.0 seconds in children with and without bleeding complications, respectively ($P = .58$). The median aXa value was 0.59 IU/mL and 0.61 IU/mL in children with and without bleeding complications, respectively ($P = .51$).

3.5 | Survival

Overall survival to discharge was 50.7%. After 120 days of follow-up, the cumulative survival to hospital discharge was 33% in patients with bleeding complications, 25% in patients with thrombotic complications, and 40% in patients with bleeding and thrombotic complications, which was significantly decreased compared to children without hemostatic events (73%) ($P = .009$) (Figure 3).

4 | DISCUSSION

Hemostatic complications occurred in almost 50% of pediatric patients undergoing ECMO in this selected cohort: Half suffered from

TABLE 2 Overview of hemostatic complications in (A) patients with one thrombotic complication or major bleeding complication and (B) patients with more than one hemostatic complication with time between events

	First event	Time, h	Second event	Time, h	Third event	Time, h	Fourth event
(A)							
1	Surgical site bleeding	-	Surgical site bleeding	-	Circuit change		
2	Circuit change	9	Surgical site bleeding	106	Surgical site bleeding	15	Circuit change
3	Stroke	48	CNS bleeding	79	Circuit change	40	Portal vein thrombosis
4	Circuit change	13	Circuit change				
5	CNS bleeding	218	Circuit change				
6	GI bleeding	22	Stroke				
7	Cardiac thrombosis	68	Circuit change				
8	Circuit change	111	Circuit change				
9	Circuit change	31	Circuit change				
	Thrombotic complications	n			Major bleeding complications	n	
(B)							
	Circuit change	6			CNS bleeding	7	
	Stroke	1			GI bleeding	2	
	Splenic thrombosis	1			Pulmonary bleeding	2	
					Surgical site	2	
					Cardiac	1	
					ENT bleed	1	

Note: - indicates that the time between complications is unknown.

Abbreviations: CNS, central nervous system; ENT, ear, nose, and throat; GI, gastrointestinal.

major bleeding complications and the other half from thrombotic events. Surgical interventions and age <29 days were significantly associated with an increased probability of bleeding complications. The MCF of all ROTEM variables, age <29 days, surgical interventions, and a longer duration of ECMO treatment were associated with increased probability of thrombotic complications. Moreover, children suffering from a thrombotic complication had a significantly higher minimum aPTT before an event than children without thrombotic complications. A higher incidence of thrombosis in patients age <29 days and a more prolonged aPTT at this young age compared to older children could support these results. Hemostatic complications were associated with a significantly decreased survival at discharge from the hospital.

The incidence of hemostatic complications in this study is comparable to the incidence found in the literature. Similarly as described by Dalton et al and ELSO,^{1,3} the majority of the thrombotic events were circuit clots. In addition, Bembea et al showed that 40% of their ECMO runs were complicated by circuit clots requiring circuit changes, comparable to the incidence in this cohort. In the same study, bleeding events occurred in 33% of the patients.¹² Dalton et al³ revealed a higher incidence of bleeding events (70.2%), with most events occurring at surgical and tube placement sites. Surgical bleeding was scarcely noted in our patient files. Possibly, the prospective study design of Dalton et al allowed a more accurate documentation of these complications. In the current cohort, a considerable part of major bleeding complications were ICH. Intracranial complications emerged as abnormalities on radiographic imaging,

which were all retrospectively accessible to the study team. In five of the nine patients with ICH, CPR preceded the development of ICH, despite lower target ranges for heparin treatment after CPR due to the increased risk of intracranial bleedings.

In this study population, no significant association was found between ROTEM parameters and bleeding complications. However, lower MCF of EXTEM, INTEM, and HEPTM and a higher minimum aPTT 24 hours before the event were significantly associated with a higher probability of thrombosis. This was surprising, since the opposite is expected in a prothrombotic condition, as found in other ECMO studies. The lower MCF of EXTEM, INTEM, and HEPTM in newborns compared to older children could be the result of a higher incidence of thrombosis in patients age <29 days and a more prolonged PT and aPTT at this young age compared to older children. Laine et al²⁵ showed an association between low MCF in EXTEM and FIBTEM and bleeding complications in 15 adults undergoing ECMO support. In a recent study of 40 pediatric patients with heart failure on ECMO, a low maximum amplitude and high reaction time in TEG combined with the fibrinogen concentration, appeared to be useful in prediction of the bleeding risk.²⁶ Since the majority of thrombotic events was due to circuit thrombosis leading to circuit change, we hypothesize that the reduced MCF and higher minimum aPTT in thrombotic events may be explained by consumption of coagulation factors and platelets in the extracorporeal circuit due to the subclinical growth of a thrombus. The nonsignificant difference in minimum aXa values before a thrombotic event is in accordance with this

FIGURE 1 (A) The cumulative incidence of thrombosis and death using the Aalen-Johansen estimator for the cumulative incidence accounting for the competing risk of death. (B) The cumulative incidence of bleeding and death using the Aalen-Johansen estimator for the cumulative incidence accounting for the competing risk of death

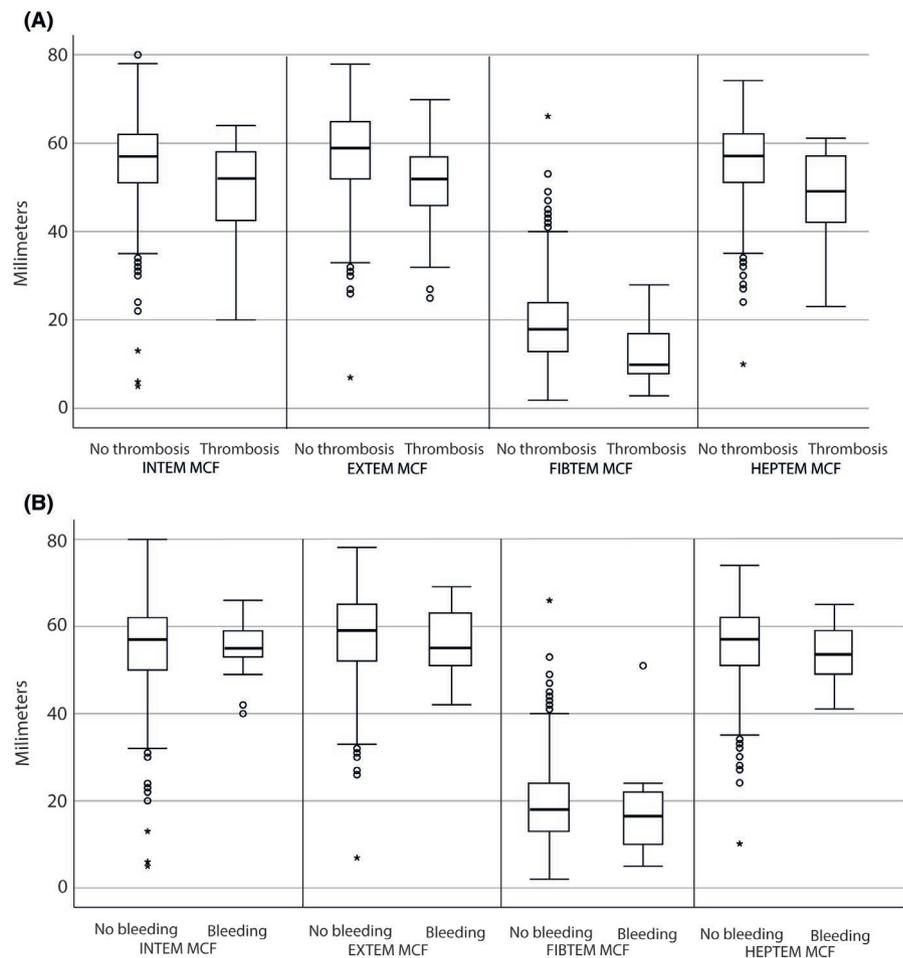
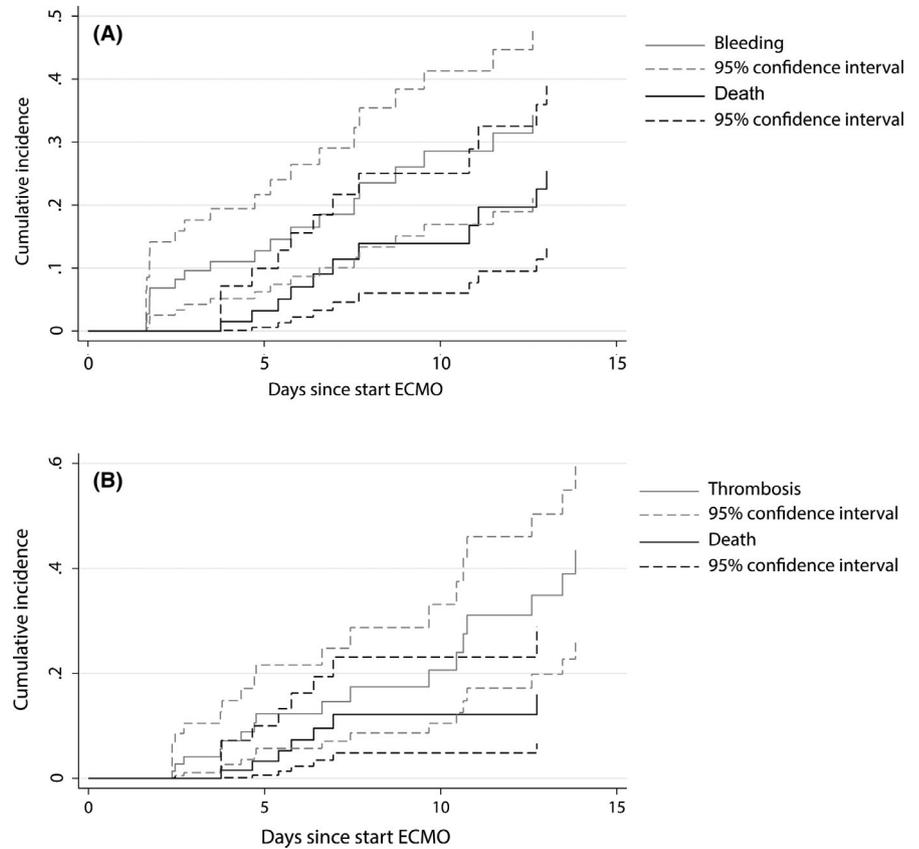


FIGURE 2 Boxplots of maximum clot firmness (MCF) of INTEM, EXTEM, FIBTEM, and HEPTEM of (A) patients with and without thrombosis, and (B) patients with and without bleeding complications. EXTEM, extrinsic rotational thromboelastometry; FIBTEM, rotational thromboelastometry assay for fibrin formation; HEPTEM, intrinsic rotational thromboelastometry with heparinase; INTEM, intrinsic rotational thromboelastometry

TABLE 3 Multivariate analysis^a results of potential predictors for thrombotic complications and major bleeding complications using the generalized estimating equations model

Variable	Thrombosis			Major bleeding		
	OR	95% CI	P value	OR	95% CI	P value
EXTEM CT (s)	0.984	0.957-1.010	.21	1.000	0.995-1.006	.94
EXTEM MCF (mm)	0.945	0.912-0.973	<.01	1.003	0.953-1.055	.92
INTEM CT (s)	1.002	1.000-1.004	.11	1.000	0.997-1.003	.92
INTEM MCF (mm)	0.946	0.920--0.969	<.01	1.010	0.968-1.055	.64
FIBTEM MCF (mm)	0.918	0.848-0.969	.03	0.989	0.928-1.054	.72
HEPTEM CT (s)	1.004	0.998-1.015	.39	1.001	0.993-1.009	.84
HEPTEM MCF (mm)	0.936	0.896-0.968	<.01	0.988	0.942-1.035	.60
aPTT (s) ^b	1.015	1.006-1.024	<.01	0.998	0.990-1.007	.69
aXa (U/mL) ^b	0.764	0.150-3.878	.75	0.608	0.252-1.467	.29
Age <29 d	1.599	0.704-3.630	.26	2.242	1.041-4.829	.04
Sepsis	2.930	1.282-6.694	.01	1.237	0.540-2.830	.62
Surgical interventions	4.426	1.543-12.694	.01	2.698	1.023-7.113	.05
Time since start of ECMO, d	1.149	1.022-1.292	.02	0.965	0.851-1.094	.58

Abbreviations: aPTT, activated partial thromboplastin time; aXa, anti-factor Xa assay; CT, clotting time; ECMO, extracorporeal membrane oxygenation; EXTEM, extrinsic rotational thromboelastometry; FIBTEM, rotational thromboelastometry assay for fibrin formation; HEPTEM, intrinsic rotational thromboelastometry with heparinase; INTEM, intrinsic rotational thromboelastometry; MCF, maximum clot firmness.

^aAge <29 d, sepsis, surgical interventions, and the duration of ECMO support were included in all generalized estimated equations, and the rotational thromboelastometry (ROTEM) components were individually added. Due to the Bonferroni correction, .006 was considered the level of significance for the results of all ROTEM components, aPTT, and aXa.

^bThe minimum aPTT and aXa values 24 h before event were used in the analysis of thrombotic complications and the maximum aPTT and aXa values 24 h before event were used in the analysis of major bleeding complications.

Significant values are indicated in bold.

TABLE 4 Median aPTT and aXa values for neonates and children

	Neonates	Children	P value
Minimum aPTT, s	83	61	<.01
Minimum aXa, IU/mL	0.46	0.52	<.01
Maximum aPTT, s	142	88	<.01
Maximum aXa, IU/mL	0.57	0.64	<.01

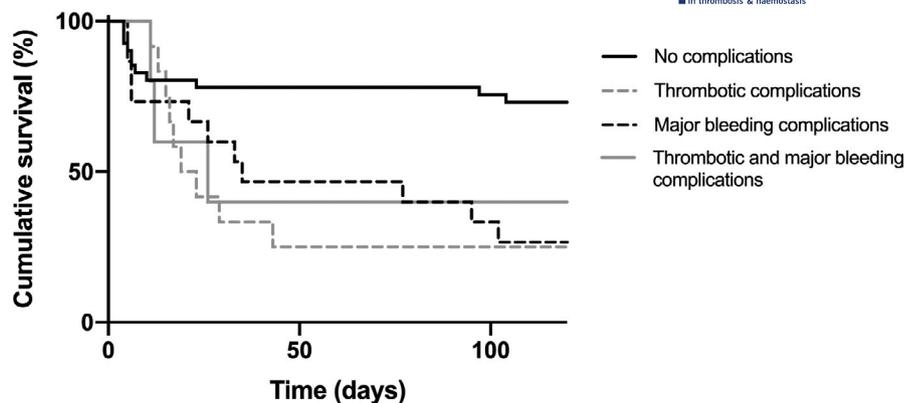
Abbreviations: aPTT, activated partial thromboplastin time; aXa, anti-factor Xa.

hypothesis. Boxplots of the MCFs of all ROTEM parameters show much overlap between children with and without thrombotic complications. Further studies are necessary to determine the value of ROTEM in the prediction of hemostatic complications in pediatric patients undergoing ECMO. In our cohort, standard coagulation tests were not significantly associated with bleeding complications. Conflicting results are described in the literature about the association between standard tests and hemostatic complications. In a univariate analysis of the study of McMichael et al,²¹ aXa and aPTT did not correlate significantly with any bleeding complication, circuit clot, or stroke. However, Irby et al²⁰ performed a retrospective cohort study comparing 17 pediatric patients undergoing ECMO needing a circuit change with a comparable group of 45 patients undergoing ECMO who did not have a revision of their

circuit. The group with circuit change had a significantly decreased aXa levels compared to the group without a circuit change.

In this study, age <29 days at ECMO cannulation significantly increased the probability of thrombotic and bleeding events, emphasizing the delicate hemostatic balance in sick neonates.²⁷ It is known from epidemiological venous thrombosis studies in children that neonates have an increased risk for thrombosis.^{28,29} Thrombotic events occurred despite the higher target ranges for aPTT and aXa for neonates compared with other children in our anticoagulation protocol. Neonates appeared to have significantly ($P < .01$) higher minimum and maximum aPTT levels, but a significantly ($P < .01$) lower minimum and maximum aXa in comparison to children. These higher aPTT levels can partly be explained by the prolonged baseline aPTT levels of neonates compared to children due to lower coagulation factor levels. Furthermore, it confirms the age-related differences in response to unfractionated heparin as shown by Ignjatovic et al³⁰: Compared to adolescents and adults, an increase of aPTT in relation to increasing heparin concentrations is higher in neonates. Children with a longer ECMO run had a significantly increased risk of thrombotic complications, reflecting the results of other studies.³ Surgical interventions significantly increased the probability of thrombotic events as well. In our institution, postsurgical patients are managed with lower aPTT and aXa target ranges perioperatively and during the 72 hours after surgery, potentially leading to more circuit thrombosis and subsequent circuit change, the majority of thrombotic complications in

FIGURE 3 Kaplan-Meier curves of cumulative survival to hospital discharge of pediatric extracorporeal membrane oxygenation (ECMO) patients with thrombotic complications, bleeding complications or both types of complications versus patients without hemostatic complications from start of ECMO through 120 days of follow-up. Log-rank test: $P = .009$



this cohort. Finally, surgical interventions were associated with an increased risk of major bleeding complications. Nardell et al³¹ investigated excessive bleeding in 145 pediatric patients undergoing postcardiotomy ECMO and found an incidence up to 31% patients with excessive bleeding events. Similarly, 7 (26.9%) of 26 postsurgical patients in this cohort suffered from a major bleeding complication. This is the first study to investigate the association between surgical interventions and hemostatic complications in a cohort with noncardiotomy pediatric patients undergoing ECMO support.

In this cohort, the survival was significantly decreased in children undergoing ECMO with bleeding and/or thrombotic complications compared to patients without hemostatic complications, confirming findings from earlier studies.^{1-3,12,32} The exclusion of short ECMO runs may have influenced the mortality rates in our study.

The most important limitation of this study was the retrospective design. As result, this is a selected cohort, as >50% of all runs were excluded, mostly due to missing ROTEM results and short duration of ECMO support. ROTEM was not routinely done initially. As a consequence, 54 patients lacked ROTEM data on >50% of ECMO support days. Therefore, the generalizability of this cohort is limited. Moreover, due to the low number of patients, other confounders, for example, CPR or heparin infusion rates, that may play a role in the interaction between coagulation test results and hemostatic complications, could not be included in the GEEs. Moreover, we could not perform any additional statistical analysis on survival. Additionally, due to the retrospective design, the exact timing of occurrence of complications was difficult to determine. Consequently, ROTEM measurements from thrombotic events could be the result of developing blood clots, rather than the hemostatic state leading to a thrombotic event. Moreover, the true cause of bleeding complications at surgical sites was difficult to verify, since these events could have been caused by a prohemorrhagic hemostatic state or as a direct effect of the surgical intervention. Another limitation was the definition of thrombosis. Thrombosis was defined as circuit change due to circuit thrombosis or patient thrombosis. In some patients, it was difficult to establish whether circuit change was the result of circuit clots, abnormal coagulation parameters, or circuit failure. Circuit clots were not always objectified and the decision to change the circuit was often based on the expertise of the bedside

ECMO expert. Nevertheless, this is one of the first few pediatric ECMO studies investigating the correlation between ROTEM test results and hemostatic complications. A strong point of this study is the inclusion of the last test result of coagulation tests before a hemostatic event. In the existing literature, time between coagulation tests and complications is rarely known, and average values are often noted.

In conclusion, coagulation management in pediatric patients undergoing ECMO remains challenging. Assessing the ability of coagulation tests to predict hemostatic complications is of essence to improve the prevention of these potentially lethal complications. This is the first study investigating bleeding and thrombotic complications and their association with ROTEM, aPTT, and aXa in pediatric patients undergoing ECMO. The hemostatic management of postsurgical patients undergoing ECMO is challenging. Larger prospective studies are needed to elucidate the role of viscoelastic and standard coagulation tests in predicting hemostatic complications in pediatric patients undergoing ECMO and to gain more insight in pathophysiological and surgical processes that lead to bleeding and thrombotic complications in postsurgical patients undergoing ECMO.

RELATIONSHIP DISCLOSURE

The authors declare no conflicts of interest.

AUTHOR CONTRIBUTIONS

JGD: concept and design, analysis and/or interpretation of data; and critical writing and revising the intellectual content. OE: revising the intellectual content. EDW: concept and design, interpretation of data, critical writing and revising the intellectual content, final approval of the version to be published. JvR: analysis and interpretation of data. MPMdM: interpretation of data, revising the intellectual content. J-WK: revising the intellectual content. RJMH: revising the intellectual content. CHvO: concept and design, interpretation of data, critical writing and revising the intellectual content, and final approval of the version to be published.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

How to cite this article: Drop JG, Erdem Ö, Wildschut ED, et al. Use of rotational thromboelastometry to predict hemostatic complications in pediatric patients undergoing extracorporeal membrane oxygenation: A retrospective cohort study. *Res Pract Thromb Haemost*. 2021;5:e12553. <https://doi.org/10.1002/rth2.12553>