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Hemostatic Outcome Definitions in Pediatric Extracorporeal Membrane Oxygenation: Challenges in Cohorts From Rotterdam (2019–2023) and Melbourne (2016–2022)

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OBJECTIVES: To determine if a priori standardization of outcome hemostatic definitions alone was adequate to enable useful comparison between two cohorts of pediatric extracorporeal membrane oxygenation (ECMO) patients, managed according to local practice and protocol.

DESIGN: Comparison of two separate prospective cohort studies performed at different centers with standardized outcome definitions agreed upon a priori.

SETTING: General and cardiac PICUs at the Royal Children's Hospital (RCH) in Melbourne, Australia, and the Sophia Children's Hospital (SCH) in Rotterdam, The Netherlands.

PATIENTS: Children (0–18 yr old) undergoing ECMO.

INTERVENTIONS: None.

MEASUREMENTS AND MAIN RESULTS: Although outcome definitions were standardized a priori, the interpretation of surgical interventions varied. The SCH study included 47 ECMO runs (September 2019 to April 2023), and the RCH study included 97 ECMO runs (September 2016 to Jan 2022). Significant differences in patient populations were noted. RCH patients biased toward frequent cardiac ECMO indications, central cannulation, and cardiopulmonary bypass before ECMO. The frequency of outcome ascertainment was not standardized.

CONCLUSIONS: This international comparison shows that standardizing hemostatic outcome definitions alone is insufficient for sensible comparison. Uniform interpretation of definitions, consistent frequency of outcome ascertainment, and stratification based on patient populations and ECMO practices are required. Our results highlight the granularity of detail needed for cross-center comparison of hemostatic outcomes in pediatric ECMO. Further work is needed as we move toward potential multicenter trials of pediatric ECMO.

KEYWORDS: extracorporeal membrane oxygenation; hemorrhage; infants; thrombosis

Extracorporeal membrane oxygenation (ECMO) is used to provide (cardio)pulmonary support in children with severe refractory cardiac and/or pulmonary failure. The use of ECMO has increased in pediatric patients over the years (1). From 2009 to 2022, a total of 154,568 ECMO runs were registered, of which 25,739 (16.6%) pediatric and 20,564 (13.3%) neonatal (1). Worldwide, many ECMO patients are registered in the Extracorporeal Life Support Organization (ELSO) registry using a standardized data submission form. Although clinical expertise and technology have improved, the prevalence of hemostatic complications, including bleeding and thrombosis, remains high in children on ECMO (1, 2). In datasets from 2005 to 2018, bleeding

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RESEARCH IN CONTEXT

- The majority of coagulation studies in pediatric extracorporeal membrane oxygenation (ECMO) are retrospective and comprise of small groups.
- Comparison of hemostatic outcomes between pediatric ECMO studies is challenging.
- In this study, we aimed to highlight some of the difficulties in comparing such outcomes using two contemporary pediatric ECMO cohorts.

occurred in up to 29.1% of neonatal and 28.5% of pediatric ECMO patients and thrombotic events occur in up 16.7% of neonatal and 12.4% of pediatric ECMO patients (2, 3). In addition, in these datasets, hemostatic complications were associated with increased mortality and morbidity (3, 4).

A systematic review of literature up to 2020 described hemostatic tests and outcomes in ECMO patients and focused on the association between coagulation test results and the following: hemostatic complications; identification of clinically relevant anticoagulation monitoring targets; the efficacy and safety of anticoagulant drugs; and the identification of clinically relevant thresholds for RBC and platelet transfusions (5). The majority of these studies were retrospective and comprised of small groups of pediatric ECMO patients (5). Furthermore, the literature lacked universally accepted definitions in basics such as: description of study population; characteristics of coagulation and transfusion management; type of ECMO circuit; and outcomes (6). Therefore, to address these problems, we have taken the unique opportunity of comparing two cohort studies with a priori agreed outcome definitions and to determine whether this enabled accurate comparison without also standardizing patient selection and subgroup considerations.

METHODS

In this comparative study, we have used pediatric ECMO data from two studies: one in Melbourne, Australia, and the other in Rotterdam, The Netherlands.

The cohort from Melbourne, Australia, included neonatal and pediatric ECMO patients (age 1 d to 18 yr) had been recruited in an observational study at The Royal Children's Hospital (RCH) PICU from September 2016 to January 2022. The study was approved by the RCH Human Research Ethics Committee (HREC number 35252: "Understanding the mechanisms of bleeding and clotting complications for children on extracorporeal circuits"; approved January 29, 2016). Written informed consent was obtained from legal guardians of all enrolled participants. In this work, all procedures followed the ethical guidelines determined by the RCH HREC and the Helsinki Declaration.

The cohort from the Sophia Children's Hospital (SCH) covered the period from September 2019 to April 2023. The data comes from an observational study recruiting pediatric patients to the Coagulation monitoring to prevent Hemostatic complications in KIDs on ECMO (CHECKID) study (MEC 2019-0085, approved March 07, 2019). The aim of CHECKID was to investigate the association between standard and alternative coagulation tests and hemostatic complications and to study changes in the hemostatic system during ECMO. CHECKID included patients from the PICU of the Erasmus Medical Centre (Rotterdam, The Netherlands) and the neonatal ICU of the Radboud University Medical Centre (Nijmegen, The Netherlands), but for the purpose of this report we only include data from SCH to minimize any variations in ECMO practice and coagulation management. At SCH, CHECKID patients were included after informed consent had been gained from legal guardians within 24 hours of starting ECMO. In this work, all procedures followed the ethical guidelines determined by the RCH HREC and the Helsinki Declaration.

ECMO Circuits and Coagulation Protocols

At the RCH, the ECMO circuit consisted of a Medos Deltastream DP3 centrifugal pump and a Medos HiLite oxygenator (Xenios, Heilbronn, Germany). Anticoagulation was monitored by activated clotting time (ACT) and activated partial thromboplastin time (aPTT) as previously described in the 2016–2019 protocol (7). In SCH, the ECMO circuit consisted of the DP3 integrated ECMO system with a centrifugal pump and a Novalung oxygenator. Treating physicians based their anticoagulation strategy on the aPTT, anti-Xa, and rotational thromboelastometry. The ECMO circuit, coagulation, and transfusion protocols have not changed since the previous retrospective analysis of

2011–2018 SCH data (2). Major differences between both protocols include the use of the ACT or aPTT as primary coagulation test and the use of epoprostenol and nitric oxide in RCH.

Data Collection

At the time of data collection at each center, all information was collected and curated prospectively. In SCH, data were collected from the first 14 ECMO treatment days; in the RCH, data from the whole period of ECMO support was available. The following clinical data were included: age, sex, weight, primary diagnosis, ECMO indication, ECMO mode, cannulation type, use of cardiopulmonary bypass (CPB) before ECMO, and duration of ECMO support. In addition, the occurrence and location of major bleeding and thrombosis, and survival to hospital discharge were collected.

Definitions

Before initiation of the CHECKID study, hemostatic outcome definitions were discussed and harmonized with the RCH study outcome definitions. The definitions of outcomes are shown in **Table 1** (8, 9). Extracorporeal cardiopulmonary resuscitation (ECPR) was defined as ECMO applied during cardiopulmonary resuscitation.

Statistical Analysis

The difference in age, duration of ECMO, and patient weight between centers was calculated using the Mann-Whitney *U* test. A Pearson chi-square test was used to determine the difference in sex, ECMO configuration, cannulation location and indication, use of CPB before ECMO, number of ECMO runs with major bleeding, and thrombosis and survival between centers.

RESULTS

In this two-center, international analysis, we have included 47 and 97 ECMO runs from SCH and the RCH. In SCH, all patients underwent a single uninterrupted ECMO run. In the RCH cohort: four patients had two separate ECMO runs; another four patients were switched from venoarterial to venovenous ECMO; and peripheral cannulation was converted to central cannulation in one patient. Demographic parameters of the whole study are described in **Table 2**. The demographic parameters of patients without CPB before ECMO is shown in **Table 3**; demographics of postcardiotomy and peripherally cannulated ECMO patients are shown in the **Supplementary material 1** and **Supplementary file 2** (http://links.lww.com/PCC/C575), respectively.

Outcome in both cohorts are summarized in **Table 4**. The prevalence of major bleeding complications differed between the centers: (SCH 8/47 [17%] vs. RCH 41/97 [44%]; mean difference, 27%; 95% CI, 10.8–39.8%; $p = 0.0015$). Despite our a priori discussions, in SCH, surgical interventions were interpreted as invasive procedures when skin was incised. In RCH, surgical interventions were interpreted as all interventions by a surgeon or cardiac surgeon. The majority of these complications occurred at cannulation and

TABLE 1.
Definitions of Outcomes

Parameter	Definition
Major bleeding	Bleeding > 4 mL/kg/hr sustained for over 4 hr, intracranial hemorrhage, gastrointestinal bleeding, or pulmonary bleeding requiring endoscopic or surgical intervention or surgical site bleeding requiring surgical exploration (8)
Minor bleeding	Any bleeding that does not fit the major bleeding definition (10)
Thrombotic complications	Objectively diagnosed clinically relevant venous or arterial thrombosis that requires acute intervention or formal anticoagulation beyond the period of ECMO, radiologically proven CNS embolic stroke on head CT, or head ultrasound and ECMO circuit thrombosis requiring circuit change
Sepsis	The systemic inflammatory response syndrome in conjunction with or as a result of a suspected or proven infection (9)

ECMO = extracorporeal membrane oxygenation.

TABLE 2.
Demographic Parameters of Sophia Children's Hospital and Royal Children's Hospital Cohorts

Parameter	Sophia Children's Hospital	Royal Children's Hospital
Number of patients, *n*	47	93
ECMO runs, *n*		
First ECMO runs	47	93
Second ECMO runs	0	4
ECMO support days during study period (d), *n* (maximum of 14 d)	351	598
ECMO duration during study period, median (IQR), d	6 (4–11)	5 (3–8)
Patients' age at cannulation, median (IQR), mo	0.53 (0.07–28.0)	1.9 (0.2–15.1)
Male, *n* (%)	29 (62)	48 (49)
Weight at ECMO initiation, median (IQR), kg	4.5 (3.3–12.2)	4.2 (3.1–11.6)
ECMO configuration, *n*		
Venoarterial ECMO	37	91
Venovenous ECMO	10	6
ECMO cannulation location, *n*		
Peripheral	38	34
Central	9	63
ECMO indication, *n*		
Cardiac	20	72
Respiratory	26	16
Extracorporeal cardiopulmonary resuscitation/other	1	9
Cardiopulmonary bypass before ECMO initiation, *n* (% out of total first and second ECMO runs)	12 (26)	48 (49)

ECMO = extracorporeal membrane oxygenation, IQR = interquartile range.
Age, sex, and weight have not been double counted for the patients with a second ECMO run.

surgical locations. We failed to identify any association between center and the prevalence of thrombosis or survival to discharge.

In the subgroups of patient runs that did not have CPB before ECMO, the prevalence of major bleeding differed by center and was: (SCH 3/35 [9%] vs. RCH 22/49 [45%]; mean difference, 36%; 95% CI, 16.9–51%; $p < 0.001$). We failed to identify any association between center and the prevalence of thrombosis or survival to discharge (**Table 5**). In an additional analysis of postcardiotomy patients, we failed to identify any association between center and the prevalence of hemostatic complications (**Supplementary material 3**, http://links.lww.com/PCC/C575). However, there was an association between center and the prevalence of bleeding complications in peripherally cannulated patients: (SCH 3/35 [9%] vs. RCH 12/31 [39%]; mean difference, 30%; 95% CI, 9.5–48.4%; $p = 0.004$) (**Supplementary file 4**, http://links.lww.com/PCC/C575). We failed to identify any association between center and the prevalence of thrombosis or survival to discharge between the cohorts in the sub analyses.

DISCUSSION

In this international comparison between two pediatric ECMO centers, we have used prospectively curated datasets—each applying strict monitoring protocols (2, 7)—and demonstrated the following. First, we highlight the difficulties in making comparisons across centers. Second, we have reiterated the need for standardized outcome definitions. Last, we illustrate

WHAT THIS STUDY MEANS

- This two-center international study of pediatric ECMO cohorts highlights three major issues when comparing hemostatic outcomes in such cases, and each may impact future clinical trials.
- Standardization of ECMO hemostatic outcome definitions alone is insufficient to allow cross-center comparison of outcomes.
- Hemostatic definitions need to be explicit so that local interpretations of definitions do not influence comparisons. Frequency and method of event ascertainment should be standardized as well.
- The study population, coagulation, and ECMO practice and ECMO circuit components in pediatric ECMO studies need to be described in detail.

the granularity of detail required to compare outcomes in future ECMO studies.

We found that there was an association between center and prevalence of major bleeding, with significantly higher proportion in the RCH cohort. On inspection of the two cohorts, it is possible that the proportion of post-cardiac surgical cases may have been a factor. However, the numbers in the current study do not permit any more than speculation. Here, cardiac surgical interventions are a known risk factor for bleeding complications during ECMO (5). Second, site of cannulation may be a related factor, with central ECMO cannulation usually being more used in post-cardiac surgical cases. Previous studies in pediatric and adult ECMO patients showed that central ECMO cannulation is associated with an increased risk of bleeding complications (8, 9). However, neonatal noncardiac patients are cannulated centrally at the RCH, whereas neonates in SCH are predominantly cannulated peripherally by a pediatric surgeon, reflecting an important difference in practice. Third, although outcome definitions were standardized, we found that both centers had different interpretations of the definition of surgical interventions. In including the need for surgical intervention for bleeding at specific sites as part of the definition for major bleeding, we had not anticipated a difference in interpretation of this aspect. In RCH, surgical interventions were considered all interventions performed by a pediatric or cardiac surgeon and ranged from surgical reexploration in the operating room to an additional surgical suture at the cannulation site. In SCH, surgical interventions were considered as all surgical procedures with an incision of the skin. Consequently, bleeding at cannulation sites requiring surgical sutures were not considered as a major bleeding complication. In our systematic review of the literature up to 2020 (6), we found that the majority of previously published studies do not incorporate enough detail (i.e., population, ECMO, coagulation, and transfusion management), which, in our view, hampers multicenter analyses (6). The difference in interpretation of surgical interventions illustrates that, besides uniform definitions, a clear description of these definitions is needed. For example, if we applied the SCH interpretation of surgical interventions to results of RCH, the prevalence of bleeding would have decreased from 41 of 97 (42%) to 34 of 97 (35%) ECMO runs, but remained significantly different between centers (p = 0.026). The remaining difference may be explained by the higher prevalence of pre-ECMO cardiac surgery and central ECMO cannulation in the RCH study, differences in coagulation management or by unmeasured confounders.

We failed to identify any association between center and prevalence of thrombotic complications. The largest group of thrombotic complications were thrombosis in the circuit requiring circuit change. The diagnosis of circuit clot burden is subjective and different units may have different thresholds for changing circuits. If we were to exclude circuit changes in our data, then the rates of documented thrombosis were two of 97 (2%) in the RCH cohort vs. three of 47 (6%) in the SCH cohort. Whether early circuit changes prevent subsequent embolic events is unknown, but a 1988–2011 cohort of pneumonia cases supported with ECMO shows an association between the need for circuit change and greater odds of mortality (11). In terms of thrombosis, further work is required to optimize a standard definition that is applicable to ECMO patients.

Previous studies report an association between major bleeding complications and survival (2, 3); this

TABLE 3.
Demographic Parameters of Patients Without Cardiopulmonary Bypass Before Extracorporeal Membrane Oxygenation From Sophia Children's Hospital and Royal Children's Hospital Cohorts

Without Cardiopulmonary Bypass Only	Sophia Children's Hospital	Royal Children's Hospital
Number of patients, *n*	35	49
ECMO runs, *n*		
First ECMO runs	35	48
Second ECMO runs	0	1
ECMO support days during study period (d), *n* (maximum of 14 d)	270	337
ECMO duration during study period (d), median (IQR)	7 (4–14)	6 (4–10)
Age at cannulation, median (IQR), mo	2.4 (0.03–34.9)	12 (0.2–22.5)
Male, *n* (%)	19 (54)	25 (51)
Weight at ECMO initiation, median (IQR), kg	5.2 (3.3–14)	8.6 (3.0–21.5)
ECMO configuration, *n*		
Venoarterial ECMO	25	43
Venovenous ECMO	10	6
ECMO cannulation location, *n* (%)		
Peripheral	35	31
Central	0	18
ECMO indication, *n*		
Cardiac	8	25
Respiratory	26	16
Extracorporeal cardiopulmonary resuscitation /other	1	8

ECMO = extracorporeal membrane oxygenation, IQR = interquartile range.
Age, sex, and weight have not been double counted for the patients with a second ECMO run.

was not the case in the current study, but numbers are small and there is likely lack of power to detect any difference.

Our study is unique in its comparison of bleeding outcome parameters across two hemostasis-focused studies in pediatric ECMO patients. However, whether these definitions were optimal remains to be determined. Conceptually, one can define bleeding in terms of: 1) observed blood loss, for example, mL/kg visualized loss or reduction in hemoglobin over time; or 2) physiological impact of blood loss, for example, lactic acidosis, hypoxic injury; or 3) responses to blood loss, for example, transfusion requirements, or use of hemostatic products, changes to anticoagulant regimen or surgical intervention; or 4) site-specific bleeding, for example, CNS, gastrointestinal, and surgical site. In this study, we elected to keep the definition simple, and tried to align with the 2018 ELSO definitions of major bleeding (12). Measuring blood loss or physiological response to blood loss has substantial variability in measurement, and significant potential for other illness or ECMO related factors to cause change. Responses to therapy can also be highly variable. Thus, incorporating objective and quantitative measures in definitions might be the way forward. A limitation of our study is that only two pediatric ECMO cohorts were compared. As a consequence, the generalizability of current findings to other pediatric ECMO cohorts is unknown. In addition, sample sizes were small, limiting multiple comparisons between two centers. Furthermore, no data is reported on the anticoagulation medication delivered, the anticoagulation tests and their targets achieved, or the transfusion therapy delivered, with the assumption that each site adhered to their protocol. Finally, another

TABLE 4.
Outcome Parameters of Sophia Children's Hospital and Royal Children's Hospital Cohorts

Parameter	Sophia Children's Hospital	Royal Children's Hospital
ECMO runs with major bleeding complications, *n* (%)	8 (17)	41 (44)
Cannulation site, *n*	0	13
Surgical site, *n*	5	19
Intracranial	2	5
Pulmonary	0	2
Gastrointestinal	1	0
Other	0	2
ECMO runs with thrombosis, *n* (%)	11 (23)	20 (22)
Circuit change	8	18
Intracranial, *n*	1	1
Peripheral arteries	0	1
Deep venous thrombosis	1	0
Cardiac	1	0
Survival to discharge, *n* (%)	31 (66)	67 (72)

ECMO = extracorporeal membrane oxygenation.

TABLE 5.
Outcome Parameters of Patients Without Cardiopulmonary Bypass Before Extracorporeal Membrane Oxygenation From Rotterdam and Melbourne Cohorts

No Cardiopulmonary Bypass	Sophia Children's Hospital	Royal Children's Hospital
ECMO runs with major bleeding complications, *n*	3 (9)	22 (45)
Cannulation site, *n*	0	13
Surgical site, *n*	1	3
Intracranial	1	3
Pulmonary	0	2
Gastrointestinal	1	0
Other	0	1
ECMO runs with thrombosis, *n*	10 (28)	11 (21)
Circuit change	7	10
Intracranial, *n*	1	1
Peripheral arteries	0	0
Deep venous thrombosis	1	0
Cardiac	1	0
Survival to discharge, *n* (%)	24 (69)	36 (68)

ECMO = extracorporeal membrane oxygenation.

limitation of this study is that long-term morbidity was not studied.

There is a great deal of interest in standardizing pediatric ECMO care in order to facilitate multicenter randomized trials, as evidenced by the recent Pediatric ECMO Anticoagulation CollaborativE initiative publications (10,13–19). Further, the ECMO Core Elements Needed for Trials Regulation And

quality of Life collaboration (in conjunction with the U.S. Food and Drug Administration Center for Devices and Radiological Health) is currently developing consensus outcome measures across multiple domains for use in multicenter trials and use in regulatory approval of pediatric ECMO (20). The results of the current study may further inform such efforts, by emphasizing the need not just for uniform definitions but detailed interpretation of definitions, and ascertainment of frequency and methods. Regardless, differences in pediatric ECMO populations can still complicate the interpretation of results. This issue can be addressed by subgroup analysis but will require larger studies and clear standardized descriptions of patient populations and ECMO methodology.

CONCLUSIONS

In this two center, international ECMO report we highlight the challenges in the comparing outcomes. This study demonstrates that, in addition to uniform outcome definitions, factors such as the method and frequency of outcome ascertainment, interpretation of definitions, and patient populations must also be standardized for valid cohort comparisons between different centers. Definitions need to be explicit so that local interpretations do not influence the comparisons. Future efforts should therefore focus on finding universally and uniformly applicable definitions of outcomes in pediatric ECMO studies (6). Finally, as we move toward potential multicenter trials of pediatric ECMO, these consideration will be critically important.

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