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REVIEW ARTICLE

# Coagulation in pediatric extracorporeal membrane oxygenation: A systematic review of studies shows lack of standardized reporting

Joppe Drop MD[1,2] | Suelyn Van Den Helm BBiomedSciAdvHons[3] | Paul Monagle MD[3,4,5,6] | Enno Wildschut MD[2] | Matthijs de Hoog MD[2] | Sabrina T.G. Gunput PhD[7] | Fiona Newall PhD[3,4,5] | Heidi J. Dalton MD[8,9] | Graeme MacLaren MBBS[3,4,10,11] | Vera Ignjatovic PhD[3,4] | C. Heleen van Ommen MD[1]

[1]Pediatric Hematology, Erasmus University Medical Center – Sophia Children's Hospital, Rotterdam, The Netherlands

[2]Pediatric Intensive Care, Erasmus University Medical Center – Sophia Children's Hospital, Rotterdam, The Netherlands

[3]Hematology, Murdoch Children's Research Institute, Melbourne, Victoria, Australia

[4]Department of Pediatrics, The University of Melbourne, Melbourne, Victoria, Australia

[5]Department of Clinical Hematology, The Royal Children's Hospital, Melbourne, Victoria, Australia

[6]Kids Cancer Centre, Sydney Children's Hospital, Sydney, New South Wales, Australia

[7]Medical Library, Erasmus MC, University Medical Center, Rotterdam, The Netherlands

[8]Department of Pediatrics, INOVA Heart and Vascular Institute, Falls Church, Virginia, USA

[9]Department of Pediatrics, Virginia Commonwealth University, Richmond, Virginia, USA

[10]Department of Paediatric Intensive Care, The Royal Children's Hospital, Melbourne, Victoria, Australia

[11]Cardiothoracic Intensive Care Unit, National University Health System, Singapore City, Singapore

**Correspondence**
Joppe G. Drop, Erasmus MC – Sophia Children's Hospital, Room SP-3506, P.O. Box 2060, 3000 CB, Rotterdam, The Netherlands.
Email: j.drop@erasmusmc.nl

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## Abstract

**Objectives:** Extracorporeal membrane oxygenation (ECMO) involves complex coagulation management and frequent hemostatic complications. ECMO practice between centers is variable. To compare results between coagulation studies, standardized definitions and clear documentation of ECMO practice is essential. We assessed how study population, outcome definitions, and ECMO-, coagulation-, and transfusion-related parameters were described in pediatric ECMO studies.

**Data sources:** Embase, Medline, Web of Science, Cochrane Library and Google Scholar.

**Study selection:** English original studies of pediatric ECMO patients describing hemostatic tests or outcome.

**Data extraction:** Eligibility was assessed following PRISMA guidelines. Study population, outcome and ECMO-, coagulation, and transfusion parameters were summarized.

Joppe Drop and Suelyn Van Den Helm contributed equally.

**Data synthesis:** A total of 107 of 1312 records were included. Study population parameters most frequently included (gestational) age (79%), gender (60%), and (birth) weight (59%). Outcomes, including definitions of bleeding (29%), thrombosis (15%), and survival (43%), were described using various definitions. Description of pump type, oxygenator and cannulation mode occurred in 49%, 45%, and 36% of studies, respectively. The main coagulation test (53%), its reference ranges (49%), and frequency of testing (24%) were the most prevalent reported coagulation parameters. The transfusion thresholds for platelets, red blood cells, and fibrinogen were described in 27%, 18%, and 18% of studies, respectively.

**Conclusions:** This systematic review demonstrates a widespread lack of detail or standardization of several parameters in coagulation research of pediatric ECMO patients. We suggest several parameters that might be included in future coagulation studies. We encourage the ECMO community to adopt and refine this list of parameters and to use standardized definitions in future research.

**KEYWORDS**
blood coagulation, blood coagulation test, critical care outcomes, extracorporeal membrane oxygenation, pediatrics, reference values

**Essentials**

- Extracorporeal membrane oxygenation involves complex coagulation and frequent complications.
- A systematic review of pediatric ECMO studies describing blood tests or outcome.
- A widespread lack of detail and standardization of several parameters was found.
- We suggest parameters for future studies and urge the ECMO community to adopted and refine.

## 1 | INTRODUCTION

Extracorporeal membrane oxygenation (ECMO) is a form of cardiopulmonary bypass in children with severe refractory cardiac and/or pulmonary failure. The use of ECMO has dramatically increased in pediatric patients.[1,2] Many ECMO patients are registered in the Extracorporeal Life Support Organization (ELSO) registry, a comprehensive registry of ECMO patients voluntarily supplied by participating ECMO centers worldwide using a standardized data submission form. In 2020, 133,371 ECMO runs were registered by 463 ECMO centers, with neonatal and pediatric runs representing 32.8% and 21.3% of the total number of ECMO runs, respectively.[1,2]

Although clinical expertise and technology have improved, the incidence of hemostatic complications, including bleeding and thrombosis, remains high in children on ECMO.[1-3] Bleeding occurs 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.[1,2] These hemostatic complications contribute to mortality and morbidity and are therefore important to prevent.[4] Research describing hemostatic tests and/or outcome in ECMO patients has primarily focused on the association between coagulation tests and hemostatic complications, identification of clinically relevant anticoagulation monitoring targets, the efficacy and safety of anticoagulant drugs, and the identification of clinically relevant thresholds for red blood cell and platelet transfusions.[5] In most studies, however, the population size is limited or comprises a specific group of patients. Moreover, there is a large variability in ECMO indications, coagulation protocols, ECMO circuitry, cannulation techniques, and transfusion thresholds.[6-8] To compare results and differences between these studies, clear documentation of the study population, outcome definitions, and ECMO-, coagulation-, and transfusion-related parameters is essential.[9] In the absence of a clear description of these variables, the comparability of research to other studies or the applicability to individual centers remains uncertain. We conducted a systematic review to assess how ECMO-related parameters and complications were described among existing studies to provide a starting point for a standardized ECMO framework to be included in future research.

## 2 | METHODS

This systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[10] Embase.com, Medline ALL via Ovid, Web of Science Core Collection, and the Cochrane Central Register

of Controlled Trials via Wiley were systematically searched on December 11, 2020. Additionally, a search was performed in Google Scholar, from which the 200 most relevant references were downloaded. The search strategy has been attached in Appendix S1.

### 2.1 | Study selection

In this systematic review, published studies in English and evaluating pediatric patients (<18 years old) treated with ECMO and describing hemostatic tests and/or outcome (bleeding, thrombosis, and/or death) were included. Studies published before January 1, 2000; review articles; case reports; editorials; conference abstracts; letters to the editor; and studies without full-text were excluded. Studies with children and adults in which a separate analysis for children was performed were included.

Two independent authors (J.D., S.V.) with research expertise in pediatric ECMO and coagulation screened titles and abstracts to select eligible studies. The same authors scored whether the study population represented the whole pediatric ECMO population or a subpopulation, based on the inclusion and exclusion criteria, and independently performed the risk of bias assessment on all included studies using the Newcastle Ottawa Score.[11] Finally, the evaluation of whether a study had a primary or secondary hemostatic endpoint was performed by the same two authors. Disputes were adjudicated by the senior author.

### 2.2 | Collected data

The study team analyzed five groups of parameters including study population, study outcome, ECMO circuitry, coagulation management, and transfusion management. One author (J.D.) extracted the available data on the elements from these groups from each included article. No automated tools were used.

### 2.3 | Outcomes

The outcomes of this review included the frequency of described elements of Table 1, as well as the various descriptions of outcome definitions and thresholds. The list of proposed parameters was designed during meetings with all authors of this manuscript. One author (J.D.) proposed a draft and during several meetings with all coauthors, the final list was drafted as a result of a consensus process.

## 3 | RESULTS

The PRISMA flowchart of studies is depicted in Appendix S2. A total of 1312 studies were screened on title and abstract (Appendix S2), and 107 studies were included. References of all included studies are shown in Appendix S3, and studies are summarized in Appendix S4. Ninety-six studies (90%) had a retrospective design, and 17 (16%) studies were published using ELSO registry data. Fifty-two (48.6%) studies had a primary hemostatic endpoint and 55 (51.4%) studies described secondary hemostatic endpoints.

### 3.1 | Study population

The most frequently described demographic parameters included the age including gestational age where relevant ($n = 84$ [79%]), gender ($n = 64$ [60%]), and weight of the patient including birth weight where relevant ($n = 63$ [59%]). Race and the ethnic distribution of the study population were mentioned in 18 (17%) studies. ECMO indication groups or primary diagnoses of the study population were described in 38 (36%) and 46 (43%) studies, respectively. APGAR scores at 1 and 5 min were described in five (5%) studies. Eighty-three (78%) studies included neonatal and pediatric patients, 18 (17%) studies studied neonates only, and six (6%) studies investigated pediatric patients only. Seventy-three (68%) studies included a specific subpopulation of the whole pediatric ECMO population. Examples of a subpopulation included neonates after congenital heart surgery and patients with congenital diaphragmatic hernia.

### 3.2 | ECMO circuitry

Most studies ($n = 89$, 83%) described one or more ECMO parameters. The most frequently described ECMO parameters included the type of pump ($n = 52$, 49%), the type of oxygenator ($n = 48$, 45%), mode of cannulation ($n = 39$, 36%), and ECMO flow ($n = 27$, 25%). ECMO circuit parameters are summarized in Table 2.

### 3.3 | Coagulation management

Coagulation management parameters were described in 62 (58%) studies. Frequencies of described coagulation parameters are summarized in Table 3. Most studies used the activated clotting time only (ACT; $n = 38$, 61%) or the ACT in combination with the activated partial thromboplastin time (aPTT; $n = 3$, 5%) or antifactor-Xa essay (AXA; $n = 7$, 11%). Other studies used AXA only ($n = 4$, 6%), aPTT ($n = 3$, 5%) or a combination of these tests ($n = 4$, 6%) to monitor anticoagulation. Three studies (5%) reported the use of thromboelastography or thromboelastometry. Most studies had ACT target ranges between 180 and 200 s, AXA between 0.3 and 0.7 U/ml, and aPTT between 60 and 80 s. Target ranges were adjusted based on bleeding risk including neonatal age or at clinicians discretion.

### 3.4 | Transfusion parameters

Transfusion parameters were described in 39 (36%) studies. The platelet, fibrinogen, and erythrocyte transfusion thresholds were

**TABLE 1** Recommended parameters by the authors and collected data (if available) from each study

| Study population | Outcome | ECMO circuitry | Coagulation management | Transfusion management |
|---|---|---|---|---|
| ECMO indication | Survival term | Type of pump | Main coagulation test | Platelet transfusion threshold |
| Race and ethnicity | Def. neurologic complication | Type of oxygenator | Device main coagulation test | Fibrinogen transfusion threshold |
| Primary diagnosis groups | Def. bleeding complication | Tubing | Frequency of main coagulation testing | RBC transfusion threshold |
| Gender | Def. thrombotic complication | Coating | Therapeutic target ranges | AT transfusion threshold |
| Weight | Def. hemolysis | Heat exchanger | Additional coagulation tests | |
| Age and Gestational age | Def. bloodstream infection | Bridge | Device additional coagulation test | |
| In- and exclusion criteria | Def. sepsis | Venous reservoir | Reference ranges additional coagulation test | |
| APGAR scores at 1 and 5 min | Def. ECPR | Cannula size | Location of blood withdrawals | |
| | Def. of mechanical complications | Number of stops/cocks/circuit access points | Main anticoagulant | |
| | Def. surgical procedures | Mode of cannulation | Dose of anticoagulant | |
| | Duration ECMO | Cannulations sites | Place of anticoagulant administration | |
| | | Inclusion of distal perfusion catheters | Coagulation protocol | |
| | | Prime fluid | Coagulation protocol around cannulation | |
| | | ECMO eligibility criteria | AT target range | |
| | | Decannulation or ECMO stop criteria | | |
| | | Cannulated by | | |
| | | Flow | | |
| | | RPM | | |
| | | Reference range blood pressure | | |

Abbreviations: AT, antithrombin; Def., definition; ECMO, extracorporeal membrane oxygenation; ECPR, extracorporeal cardiopulmonary resuscitation; RBC, red blood cells; RPM, revolutions per minute.

**TABLE 2** Parameters and frequency of description of ECMO parameters in 107 studies

| ECMO parameters | Frequency, *n* (%) |
|---|---|
| Type of pump | 52 (49) |
| Type of oxygenator | 48 (45) |
| Tubing | 18 (17) |
| Coating | 23 (23) |
| Heat exchanger | 14 (13) |
| Bridge | 10 (9) |
| Venous reservoir | 10 (9) |
| Cannula size | 4 (4) |
| Number of stops/cocks/circuit access points | 1 (1) |
| Mode of cannulation | 39 (36) |
| Cannulations sites | 15 (14) |
| Inclusion of distal perfusion catheters | 2 (2) |
| Prime fluid | 16 (15) |
| ECMO eligibility criteria | 8 (8) |
| Decannulation or ECMO stop criteria | 6 (6) |
| Cannulated by | 5 (5) |
| Flow | 27 (25) |
| RPM | 0 (0) |
| Reference range blood pressure | 3 (3) |

Abbreviations: ECMO, extracorporeal membrane oxygenation; RPM, revolutions per minute.

**TABLE 3** Parameters and frequency of description of coagulation parameters in 107 studies

| Coagulation parameters | Frequency, *n* (%) |
|---|---|
| Main coagulation test | 56 (52) |
| Device main coagulation test | 21 (20) |
| Reference ranges main coagulation test | 52 (49) |
| Frequency of main coagulation test | 26 (24) |
| Additional coagulation tests | 22 (21) |
| Device additional coagulation test | 9 (8) |
| Reference ranges additional coagulation test | 5 (5) |
| Location of blood withdrawals | 6 (6) |
| Main anticoagulant | 53 (50) |
| Dose of anticoagulant | 17 (16) |
| Place of anticoagulant administration | 6 (6) |
| Heparin titration based on/coagulation protocol | 15 (14) |
| Coagulation protocol around cannulation | 34 (32) |

described in 28 (26%), 21 (20%), and 19 (18%) studies, respectively (Appendix S5). The majority of platelet transfusion thresholds were >80.000/mm$^3$ (*n* = 7, 24%) and >100.000/mm$^3$ (*n* = 18, 62%). Fibrinogen target ranges were mostly above 100 mg/dl (*n* = 7, 37%) or 150 mg/dl (*n* = 8, 42%). The red blood cell transfusion threshold was described as a target hemoglobin level between 8 and 12 g/dl (*n* = 6, 38%) or a hematocrit above 30%–40% (*n* = 10, 63%). Antithrombin supplementation and the antithrombin supplementation thresholds were described in 21 (20%) and 17 (16%) studies, respectively. The antithrombin threshold differed between 50% and 100% of adult values.

## 3.5 | Outcome

### 3.5.1 | Survival

Survival was described in 46 (43%) studies. Twenty-six (56%) studies included survival to discharge, four (9%) included survival to ECMO decannulation, and seven (15%) included survival to discharge and ECMO decannulation. The survival outcome was unclear in nine (20%) studies (e.g., overall mortality). Five (11%) studies described a specific follow-up time (e.g., 45 months) and two (4%) included survival to orthotopic heart transplantation.

### 3.5.2 | Hemorrhagic complications

Hemorrhagic complications were defined in 31 (29%) studies. The ELSO registry defined hemorrhagic complications as events requiring packed red blood cells (PRBCs) or whole blood transfusion (>20 ml/kg/calendar day of PRBCs or >3 U PRBCs/calendar day in neonates and pediatrics and >3 U PRBCs/calendar day in adults) or other intervention such as surgical or endoscopic intervention.[12] In these 31 studies, we found 29 different definitions. Aspects of bleeding definitions are shown in Table 4.

### 3.5.3 | Thrombotic complications

Thrombotic complications were defined in 16 (15%) studies. The ELSO registry definition of thrombotic complications is not described.[12] Aspects of thrombotic complications are shown in Table 5.

### 3.5.4 | Neurologic complications

Twenty-one studies (20%) described neurologic complication definitions. The ELSO registry definition includes brain death, seizures (clinically determined or confirmed by electroencephalogram), diffuse ischemia of the central nervous system, radiologically proven (ultrasound, computed tomography, or magnetic resonance imaging) infarction and hemorrhage in the central nervous system, and the performance of a neurosurgical procedure.[12] Cerebral hemorrhage is described in 17 (81%) definitions and stroke in 20 (95%) definitions. Various definitions included abnormalities on ultrasound or computed tomography (*n* = 14, 67%), brain death (*n* = 7, 33%), clinical

**TABLE 4** Parameters included in 31 bleeding complication definitions with corresponding frequency

| Parameter | Frequency, *n* (%) |
|---|---|
| GI/retroperitoneal | 21 (66) |
| CNS/intracranial/neurologic bleed | 17 (53) |
| Surgical site | 15 (48) |
| Cannulation site | 14 (45) |
| Bleeding that requires surgical intervention in an operating suite | 13 (42) |
| Pulmonary | 12 (39) |
| Requiring transfusion packed red blood cells in 24 h | 10 (32) |
| Fatal bleed | 3 (10) |
| Bleeding associated with a decrease in Hgb of at least 20 g/L (2 g dl) in 24 h | 6 (19) |
| Blood loss >20 ml/kg/d | 6 (19) |
| DIC requiring transfusion or intervention | 4 (13) |
| Deviance from anticoagulation protocol/required >50% decrease of heparin infusion for ≥12 h or | 2 (6) |
| Sanguineous chest tube output | 2 (6) |
| Genitourinary | 2 (6) |
| A new onset hemorrhage | 1 (3) |
| Bleeding that required circuit change | 1 (3) |
| Hemothorax | 2 (6) |

Abbreviations: CNS, central nervous system; DIC, disseminated intravascular coagulation; GI, gastrointestinal; Hgb, hemoglobin.

**TABLE 5** Parameters included in 16 thrombotic complication definitions with corresponding frequency

| Parameter | Frequency, *n* (%) |
|---|---|
| Circuit change | 12 (67) |
| Intravascular (venous, arterial, intracardiac) | 4 (22) |
| Stroke/infarction of CNS | 7 (39) |
| Pulmonary embolism | 4 (22) |
| Visible thrombi in oxygenator, or tubing affecting circuit pressures or causing hemolysis | 5 (28) |
| Limb ischemia | 3 (17) |
| Shunt thrombosis | 2 (11) |
| Solid organ infarction | 1 (6) |
| Sick circuit syndrome | 1 (6) |
| Disseminated intravascular coagulation | 1 (6) |

Abbreviation: CNS, central nervous system.

neurologic abnormalities ($n = 2$, 10%), clinical seizures ($n = 9$, 43%), or seizure activity on electroencephalogram ($n = 7$, 33) (Appendix S6).

### 3.5.5 | Extracorporeal cardiopulmonary resuscitation

Extracorporeal cardiopulmonary resuscitation (ECPR) was defined in nine (8%) studies. ELSO has defined ECPR as the application of rapid-deployment venoarterial ECMO to provide circulatory support in patients in whom conventional cardiopulmonary resuscitation is unsuccessful in achieving sustained return of spontaneous circulation.[12,13] In five of nine studies (56%), definitions included active chest compressions leading to or during ECMO cannulation. In three (33%) and two (22%) of nine studies, ECPR definitions included refractory cardiopulmonary resuscitation and ECMO applied during a sudden or witnessed cardiac arrest, respectively.

### 3.5.6 | Hemolysis

Hemolysis was defined in six (6%) of the 107 studies. ELSO defined moderate hemolysis as a plasma peak hemoglobin between 50 and 100 mg/dl occurring at least once during ECMO support and defined

severe hemolysis as a plasma hemoglobin > 100 mg/dl occurring at least once during an ECLS run, sustained for at least 2 consecutive days or if the level of hemolysis led to a change in part or all of the circuit.[12] The lower limit of plasma free hemoglobin varies among definitions between 30 and 50 mg/dl. Two (33%) studies classified the severity of hemolysis in subgroups (mild, moderate, severe) but the cutoff levels for those subgroups were different.

### 3.5.7 | Infection

Infection was defined in eight (7%) studies as bloodstream infection and all definitions included a culture-proven infection. Two definitions (22%) included a white blood cell count <1500/mm$^3$ and one (11%) definition included a positive polymerase chain reaction. Two studies (2%) defined sepsis as a positive blood culture in conjunction with clinical signs of sepsis. The ELSO definition of bloodstream infection or sepsis is not described.[12]

### 3.5.8 | Surgery

Surgical interventions were not defined in any study or by ELSO.[12]

## 4 | DISCUSSION

The incidence of hemostatic complications in pediatric ECMO patients is high, and prevention of these complications remains challenging. Many factors influence the risk for hemostatic complications, such as ECMO indications, ECMO circuitry, infections, surgery, underlying diseases, ECMO duration, and anticoagulation and transfusion management.[5] This review shows that the existing pediatric ECMO literature describing hemostatic tests and/or hemostatic outcomes does not clearly describe many essential factors that influence the hemostatic balance and, consequently, patient outcomes. To assess the contribution of individual components on outcome and to define best practice, it is important to be able to compare practices and results internationally. Therefore, a standardized template is required. This may also improve the quality of registry data, which is particularly used to provide epidemiological and outcome data of ECMO patients.

We showed that ECMO studies describing hemostatic tests and/or hemostatic outcome frequently include specific subpopulations instead of the whole pediatric ECMO population. Several population parameters have been found to increase the risk of hemostatic complications.[5] For example, age has been shown to be significantly associated with daily bleeding complications.[4] Moreover, increasing age concurs with quantitative and qualitative differences in coagulation proteins between various age groups, which are reflected in coagulation tests.[14] Hence, a clear description of the study population is indispensable when describing hemostatic tests and/or outcome in ECMO patients. Described population parameters should at least include the age of the patient, including gestational age where relevant, gender, race and ethnicity, weight of the patient including birth weight where relevant, ECMO indication, primary diagnosis groups, and clear inclusion and exclusion criteria.

Few studies included a description of the ECMO circuit design or circuit components in the ECMO circuit. Broman et al. have made a first step toward a standardized approach to defining cannula practices in ECMO patients.[15] Pump type, mode, and location of cannulation have been associated with bleeding and thrombotic complications in several studies and are important to describe.[5] Given the increase in available technology for ECMO support, specific description of circuitry is essential to identify potential variances in technology performance and affect factors such as hemolysis and thrombosis. Matching centers with similar circuitry and practice may limit variability and help provide scientifically valid results that can be extrapolated to the field.

In addition, description of the anticoagulation protocol and transfusion thresholds was lacking in almost 40% and 60% of studies, respectively. Surveys showed large differences among institutions, both in anticoagulation protocols and in transfusion triggers.[6,8,16] These differences are also revealed in our review, which are most likely explained by the lack of evidence for the optimal test and target ranges to monitor and titrate the coagulation status and the lack of evidence to guide transfusion thresholds in pediatric ECMO patients. Standardization of anticoagulation and transfusion management among centers will permit comparison of testing regimens between centers.[17-19] Burrell et al. investigated 46 studies of adult veno-arterial ECMO patients and found a variable and inconsistent description of patient selection, ECMO management, and outcome parameters, including complication definitions. These findings are similar to findings in this study, suggesting a generalized lack of adequate description across ECMO studies.[20] Although all centers use some form of anticoagulation test to adjust anticoagulant dosing, the current lack of association with any of the multiple coagulation monitoring tests available is another obstacle in decreasing bleeding and thrombotic complications. Given the myriad of tests available and variances in applied medications for anticoagulation and parameters to adjust dosing, deriving scientifically valid results highlights the need for specific projects across sites using standardized definitions and limiting variability in practice to help refine practice and help identify what factors are most important in bleeding and thrombotic events.

Finally, our review demonstrates a lack of specific outcome definitions and interstudy variability of definitions. ELSO has provided definitions of several coagulation- and ECMO-related outcome parameters, including mechanical, hemorrhagic, neurologic, renal, cardiovascular, pulmonary, metabolic, and limb complications.[12] Unfortunately, these definitions are infrequently used in individual studies that do not use the ELSO Registry. Standardized definitions of bleeding and thrombosis are crucial in ECMO coagulation studies. Our review shows that bleeding was only defined in 29% of studies using 29 different definitions and deviated from the ELSO definition. Thrombotic complications were defined even less frequently (19%).

Moreover, ELSO has not defined thrombotic complications separately. Both bleeding and thrombotic complications are associated with death in pediatric ECMO patients.[4] This stresses the need for clear descriptions and distinction between thrombotic and bleeding complications. Another important outcome parameter is survival. Various definitions of survival and follow-up were used, and in almost 20% of studies the definition was not clear. Addressing the follow-up time in survival is crucial because patients might die after weaning from ECMO as result of ECMO-related complications, including bleeding and thrombotic complications.

Uniform definitions of risk factors should also be part of the common template. One of the risk factors for hemostatic complications is a surgical procedure before or during ECMO. Recently, we showed in a retrospective cohort study of 73 pediatric ECMO patients that surgical interventions increased the risk of both bleeding and thrombotic complications.[3] To adequately investigate this risk factor in pediatric ECMO patients, a definition for surgical interventions is needed, as is a description of perioperative anticoagulation strategies. An additional important risk factor is hemolysis, which was associated with thrombotic complications in the study of Dalton et al.[4] ELSO adjusted the definition of hemolysis in 2018 and categorized moderate and severe hemolysis.[12] However, studies published before and after this adjustment used different cutoff values for peak plasma hemoglobin, and the severity was classified in different groups (i.e., mild, moderate, and severe).[4,21-24]

A limitation of this systematic review is the exclusion of studies not written in English. However, we do not think that the excluded studies would alter the conclusion of this study because those studies comprise a small proportion of overall studies.

In conclusion, this review highlights a lack of uniform description of several parameters in literature describing hemostatic tests and/or hemostatic outcomes of pediatric ECMO patients. Discrepancies in reporting were observed in both cardiac and noncardiac studies. We compiled a list of parameters that may be useful to interpret coagulation research in pediatric ECMO patients (Table 1). The list was designed to be inclusive while recognizing that not all these parameters are necessarily of critical relevance. This list is not recommended as the gold standard for publications to include going forward. However, we suggest that the broad domains from this study (study population, outcome, ECMO circuitry, coagulation and transfusion protocol) should be described in future studies in pediatric ECMO patients describing hemostatic tests and/or outcomes. There needs to be considerable consensus work done to develop a standardized framework. As a next step, this review could inform a methodologically robust Delphi process that includes all relevant stakeholders in coming up with a clear set of reporting variables for pediatric ECMO research.

We encourage the ECMO community to adopt and refine this list and to standardize definitions, including bleeding and thrombosis definitions. Standardization of parameters and definitions will improve comparability of study results among centers and will allow clinicians to judge the applicability of studies to their own patient population and ECMO practice.

## RELATIONSHIP DISCLOSURE

None of the authors declare a conflict of interest.

## AUTHOR CONTRIBUTIONS

Joppe Drop, Suelyn Van Den Helm, C. Heleen van Ommen, Enno Wildschut, Vera Ignjatovic, Graeme MacLaren, and Paul Monagle conceptualized the study. Suelyn Van Den Helm, and Joppe Drop helped designing the study. Data collection was performed by Joppe Drop, and Suelyn Van Den Helm acted as second reviewer. Joppe Drop and Suelyn Van Den Helm drafted, reviewed, and revised the manuscript. Sabrina T.G. Gunput aided in the systematic search. Joppe Drop, Suelyn Van Den Helm, Paul Monagle, Enno Wildschut, Matthijs de Hoog, Fiona Newall, Heidi J. Dalton, Graeme MacLaren, Vera Ignjatovic, and C. Heleen van Ommen critically reviewed the manuscript for intellectual content. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

## ORCID

*Joppe Drop* https://orcid.org/0000-0001-6898-1595

## TWITTER

*C. Heleen Ommen* @heleenvanommen

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## SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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