Peer Review File

Article information: https://dx.doi.org/10.21037/tp-22-104

Reviewer A

Comment 1: Thank you for reporting on this high-risk and understudied population. Overall the findings are analyzed appropriately. I would appreciate more clinical focus in the discussion particularly relating to the nuances of post CPB ECMO. Perhaps an analysis of early vs late hemostatic complications would truly enhance our understanding of the relationship between post bypass management and routine ECMO maintenance. I also think the conclusions related to low PLT count need to be adjusted against the risk of the reaction of low PLT count which is PLT transfusion. The PLT transfusion seems to be a higher risk than the PLT count. More specific items to consider are below.

Reply 1: Thank you very much for your recognition of our research. We have supplemented data and analysis and completely revised the manuscript according to your suggestion.

To highlight the particularity of coagulopathy in pediatric postcardiotomy VA-ECMO for failure to wean from CPB (CPB-ECMO group, n=96), critically ill children (n=50) required postcardiotomy VA-ECMO support for other indications were assessed (Non-CPB-ECMO group) for comparison. In addition, early hemostatic complications were defined as occurring within the first 48 hours since ECMO initiation; otherwise, they were late hemostatic complications. We found that: (1) Failure to wean from CPB significantly increased the risk of bleeding, especially early bleeding; (2) Patients with early bleeding had a higher volume of chest tube drainage, a greater demand for blood products, and an increased risk of mortality; (3) Systemic heparinization was delayed to avoid early bleeding but increased the risk of early hemolysis in the CPB-ECMO group, and the 9.5-hour heparin start time had good discrimination for early hemolysis. The anticoagulation regimens for patients directly transited from CPB to ECMO were complicated in the peri-CPB phase. Delayed systemic heparinization may be an option for many centers. Our study suggests the risk of hemolysis increased over time with delayed systemic heparinization.

Changes in the text: Page 4, line 80-82; Page 5, line 93-94; Page 8, line 154-158; Page 12, line 244-249; Page 15-16, line 329-334.

Your suggestion about PLT transfusion is necessary. We paid more attention to PLT transfusion and did related analyses. There was no significant difference in the PLT infusion volume between the survivors and non-survivors in the CPB-ECMO group. In the univariate logistic regression analysis, PLT transfusion volume was not significantly associated with in-hospital mortality [OR=1.037 (0.995, 1.080), P=0.082] (Table 4). Thrombocytopenia was associated with a nearly nine-fold increase in in-hospital mortality after adjusting for PLT transfusion volume in the logistic regression analysis examining the association between thrombocytopenia and in-hospital mortality (Table 4).

Changes in the text: Page 10, line 213-214; Table 4.

Abstract:
Comment 2.1. Last sentence of results section; please clearly state the relationship (i.e. increased or decreased hemolysis)
Reply 2.1: Thanks for your suggestion. We have rewritten the results section that delayed systemic heparinization increased the risk of early hemolysis.
Changes in the text: Page 2, line 40-43.

Intro:
Comment 3.1. reference one is very old. please use newer reference if possible.
Reply 3.1: Thanks for the reminder. We have updated the reference (Pediatr Crit Care Med. 2018 Jun;19(6):544-552)
Changes in the text: Page 3, line 55; Page 17, line 357-360.

Comment 3.2. Second sentence needs a reference to support the claim or needs to be re-stated.
Reply 3.2: Thanks for your valuable suggestions. We have rewritten the first paragraph of the introduction to be concise and updated the references.
Changes in the text: Page 3-4, line 55-68.

Comment 3.3. Sentence 3 is awkward and the first paragraph could be written in a more concise manner.
Reply 3.3: We have rewritten the first paragraph of the introduction to be concise. The manuscript was reviewed by someone whose first language is English. Hope you will be satisfied.
Changes in the text: Page 3-4, line 55-68.

Comment 3.4. Aim is to explore the RELATIONSHIP between hemostatic complications and timing of heparin
Reply 3.4: In the revised manuscript, we supplemented the non-CPB-ECMO as a control group. Additionally, we defined early/late hemostatic complications within 48 hours of ECMO implantation as the boundary. Our aim is fully stated below.
The aim of this retrospective observational study, which took place at a Chinese ECMO center, was to assess whether bleeding or thrombosis differ in VA-ECMO patients who were directly transitioned from CPB compared to those who received postcardiotomy VA-ECMO for other indications. The impacts of hemostatic complications in early or late stages on in-hospital patients, as well as the association between the timing of systemic heparinization and hemostatic complications, were assessed in VA-ECMO patients who failed to wean from CPB.
Changes in the text: Page 4, line 69-74.

Methods:
Comment 4.1. is "clinically sig bleeding" a separate category? as written it is a separate category that is not defined. Perhaps you meant to write clinically sig

bleeding which we defined as...
Reply 4.1: "Clinically sig bleeding" is not a separate category nor an observational outcome in this study. Major bleeding is one hemostatic complication that we paid attention to. Major bleeding included re-exploration due to surgical site or cannula site bleeding, gastrointestinal bleeding, pulmonary hemorrhage, and intracranial hemorrhage.
Changes in the text: Page 5, line 89-90.

Comment 4.2. line 134, please spell out units unless journal accepts this abbreviation. (i.e. 100U UFH --> 100 units of UFH).
Reply 4.2: Thank you for the correction. We have made the corresponding changes.
Changes in the text: Page 6, line 120.

Comment 4.3. line 136 please spell our seconds unless journal accepts this abbreviation.
Reply 4.3: Thanks for the correction. We spelled the seconds in full with abbreviations.
Changes in the text: Page 6, line 122.

Comment 4.4. May be worth dividing your descriptions of anticoagulation into sections (i.e. peri-CPB, maintenance)
Reply 4.4: Your advice is valuable. We have divided anticoagulation management during ECMO into two sections: the early stage at ECMO initiation (peri-CPB period in the CPB-ECMO group) and the maintenance phase.
Changes in the text: Page 6, line 117; Page 6-7, line 128-133.

Comment 4.5. line 138-139, would avoid "a relatively loose" and quantify as best you can. Consider "was based on clinician bedside judgement without a protocolized approach".
Reply 4.5: Thanks for your reminder. In the revised manuscript, we adopted your suggestion "was based on clinician bedside judgment without a protocolized approach".
Changes in the text: Page 6, line 124-125.

Comment 4.6. line 150; would remove "was improved" and instead use was altered or something else that does not suggest superiority. If you feel you have references to support superiority please keep "was improved" and add reference.
Reply 4.6: We agree with you. We have rephrased "the monitoring was improved with the addition of" to "was supplemented".
Changes in the text: Page 7, line 139.

Comment 4.7. line 154 "continuously improved" seems nebulous. Perhaps a supp table showing when important content was changed with date/time

stamps.
Reply 4.7: In Supplementary Table 1, we added * to highlight the new items "Xa, ATIII, D-Dimer, FDP" in 2017.
Supplementary Table 1. Coagulation monitoring items and targets

Coagulation Monitor	Target range
Hemoglobin (g/L)	>100
Platelet ($\times 10^9$/L)	>50
Activated clotting time (s)	140-200
Activated partial thromboplastin time (s)	50-80
Anti-factor Xa level* (IU/mL)	0.2-0.4
Antithrombin-III* (%)	>50
Fibrinogen* (g/L)	>1.5
D-Dimer* (ug/mL)	0-0.5
Prothrombin time (s)	11.5-14.5
International normalized ratio (INR)	0.8-1.2
Fibrin/Fibrinogen Degradation Products* (ug/ml)	0-5

*Items were adopted since 2017
Changes in the text: Supplementary Table 1

Comment 4.8. Were there ATIII thresholds?
Reply 4.8: Our current threshold for AT III is >50%, which was added in the revised manuscript.
Changes in the text: Page 7, line 146.

Comment 4.9. line 160, change 'prepared' to administered
Reply 4.9: Thanks for your advice. It has been changed.
Changes in the text: Page 7, line 147.

Comment 4.10. line 163; please spell out first use of all acronyms (pFHB)
Reply 4.10: Thanks for your reminder. We have spelled out the first use of all acronyms [plasma-free hemoglobin (pFHb)].
Changes in the text: Page 5, line 91.

Comment 4.11. line 199; "long duration" not needed since you state the duration
Reply 4.11: Thanks for your suggestion. We have deleted it.
Changes in the text: The original sentence has been deleted from the text.

Comment 5: Results: Well written
Reply 5: Thank you for your recognition. Because we supplemented the control group and staged the hemostatic complications, the "Results" section was significantly changed. We updated the results based on the principles of scientific rigor and conciseness.
Changes in the text: Page 9-11, line 181-240.

Discussion:
Comment 6.1. would remove sentence with the phrase "the battle begins"
Reply 6.1: Thanks for your kind reminder. We have deleted it.
Changes in the text: The original sentence has been deleted from the text.

Comment 6.2. line 274, suggest using "accounted for chest tube, etc. to adjust for bleeding and thrombosis
Reply 6.2: Thanks for your suggestion. We have used "We accounted for chest tube draniage, APTT and ACT to adjust for bleeding and thrombosis" to replace "We weighed chest-tube drainage, APTT, and ACT to balance bleeding and thrombosis".
Changes in the text: Page 13, line 266-267.

Comment 6.3. Line 282, as written could use a reference
Reply 6.3: The original sentence has been deleted in the revised discussion section. In our study, major bleeding was diagnosed in 69.8% of patients, and more than half (52.2%, 35/67) of these cases occurred within 48 hours of ECMO initiation in the CPB-ECMO group. The prevalence of major bleeding, including early bleeding, was significantly lower in the control group. Re-exploration due to surgical or cannulation site bleeding, the main manifestation of major bleeding, was more common in the CPB-ECMO group (Table 2). Furthermore, multivariate logistic regression analysis showed that failure to wean from CPB correlated positively with the level of bleeding during ECMO after adjusting for illness severity (Table 3). Postcardiotomy VA-ECMO was an independent risk factors associated with early major bleeding events (The Annals of thoracic surgery. 2021;111(2):623-8.)
Changes in the text: Page 9, line 192-198; Page 10, line 218-219; Page 13, line 265-266.

Comment 6.4. The second paragraph while true uses a lot of space that could be dedicated more specifically to how these mechanisms are linked or not to your results
Reply 6.4: The original paragraph has been deleted in the revised discussion section. It does not correlate well with the current results.
Changes in the text: The original paragraph has been deleted in the text.

Comment 6.5. line 312, would change the wording "imperfect timing" because it assumes there is a perfect timing which has not been proven
Reply 6.5: We agree with you. We have removed perfect timing and replaced the original sentence with "We found that the timing of systemic heparinization can predict early hemolysis, and the best Youden index is 9.5 hours". Delayed systemic heparinization increased early hemolysis in the CPB-ECMO group.
Changes in the text: Page 13, line 276-277.

Comment 6.6. Please clarify line 319-320, by clearly stating the relationship and direction of relationship found
Reply 6.6: In the reference (Pediatr Crit Care Med 2018;19:1067-76), a lower mean heparin infusion dose was associated with higher daily pFHb. We cite this article to show that insufficient anticoagulation may contribute to increased hemolysis. The reference has been deleted.
Changes in the text: The original sentence has been deleted in the text.

Comment 6.7. Would be careful in drawing a conclusion that low plts are related to mortality particularly given that the relationship with low plt and mortality (3x) is actually much lower than the relationship between PLT transfusions and mortality (9x). Perhaps the transfusions are driving the mortality not the low PLT?
Reply 6.7: Your consideration is necessary. We paid more attention to PLT transfusion and did related analyses. There was no significant difference in the PLT infusion volume between the survivors and non-survivors in the CPB-ECMO group. In the univariate logistic regression analysis, PLT transfusion volume was not significantly associated with in-hospital mortality [OR=1.037 (0.995, 1.080), P=0.082] (Table 4). Thrombocytopenia was associated with a nearly nine-fold increase in in-hospital mortality after adjusting for PLT transfusion volume in the logistic regression analysis examining the association between thrombocytopenia and in-hospital mortality (Table 4).
Changes in the text: Page 10, line 213-214; Table 4.

Comment 6.8. Many of your statements are discussed here...
. 2022 Feb 27;2676591211056562. doi: 10.1177/02676591211056562.
Reply 6.8: Thank you for your recommendation. We have read this article comprehensively and meticulously, and we have gained a lot. We also cited this article in the discussion section. The bleeding and thrombosis on extracorporeal membrane oxygenation (BATE) cohort is a large-scale multicenter prospective study on bleeding and thrombosis in pediatric ECMO. It has guiding significance for our research and clinical management.
Changes in the text: Page 12, line 257-260.

Comment 6.9. Lines 348-354 could be strengthened by including some specific (but tempered) clinically applicable recommendations from your study. I.e. we recommend initiating systemic heparin by hour...and adjusting based on... We discourage using...to modify anticoagulation...etc
Reply 6.9: Anticoagulation management in the peri-CPB phase for patients who directly transition from CPB to ECMO is complicated and delayed systemic heparinization may be an option for many centers. Our study suggests that the risk of hemolysis increases with the extension of starting continuous heparin infusion. The PEP model can help assess the severity of coagulopathy. It is recommended to monitor the early pFHb more frequently to avoid early

hemolysis.
Changes in the text: Page 15, line 310-313.

Comment 6.10. Also consider the effect of specific CHD lesions on aVWD as you mentioned particularly given that STAT category was associated with hemolysis and thrombocytopenia (Ann Thorac Surg. 2014 Oct;98(4):1419-24. doi: 11.1016/j.athoracsur.2014.05.035. Epub 2014 Aug 15.
PMID: 25130078)
Reply 6.10: Thank you very much for the valuable suggestion.
In the multivariate logistic regression analysis of hemostatic complications, the STAT category was an independent risk factor for hemolysis and thrombocytopenia (Supplementary Figure 1). To explore the effect of specific CHD lesions, we counted the main diagnoses of patients with hemolysis and thrombocytopenia, as shown in the table below. DORV (n=11, 23.4%) was the most common diagnosis in patients with hemolysis, and TGA (n=9, 32.1%) was the most common diagnosis in patients with thrombocytopenia. The prevalence was much higher than that in the entire CPB-ECMO cohort.
The patients were diagnosed with highly heterogeneous CHD. Different congenital heart surgeries cause platelet dysfunction and coagulopathy, so we adjusted for this confounding factor with the STAT category in multivariate logistic regression analysis.
Table. Main diagnosis of patients with hemolysis or thrombocytopenia

Main diagnosis	Hemolysis (n=47)	Thrombocytopenia (n=28)	All (n=96)
TGA	8 (17.0)	9 (32.1)	20 (20.8)
DORV	11 (23.4)	4 (14.3)	14 (14.6)
TOF	7 (14.9)	2 (7.1)	15 (15.6)
RVOTO	2 (4.3)	0 (0.0)	6 (6.3)
VSD	4 (8.5)	1 (3.6)	7 (7.3)
PA	3 (6.4)	3 (10.7)	7 (7.3)
SV	2 (4.3)	3 (10.7)	6 (6.3)
TECD	4 (8.5)	0 (0.0)	4 (4.2)
Supra-aortic stenosis	1 (2.1)	1 (3.6)	3 (3.1)
ALCAPA	0 (0.0)	0 (0.0)	4 (4.2)
Ebstein's anomaly	1 (2.1)	0 (0.0)	3 (3.1)
CoA	0 (0.0)	1 (3.6)	2 (2.1)
HRHS	1 (2.1)	1 (3.6)	2 (2.1)
AS+PS	1 (2.1)	1 (3.6)	1 (1.0)
ASD + atrial mass	1 (2.1)	1 (3.6)	1 (1.0)
HLHS	1 (2.1)	1 (3.6)	1 (1.0)

Notes: categorical data are presented as n (percent). TGA, transposition of great arteries; DORV, double outlet right ventricle; TOF, tetralogy of Fallot; ROVTO, right ventricular outflow tract obstruction; VSD, ventricle septal defect; PA,

pulmonary atresia; SV, single ventricle; TECD, total endocardial cushion defect; ALCAPA, anomalous origin of left coronary artery from the pulmonary artery; CoA, coarctation of aorta; HRHS, Hypoplastic right heart syndrome; AS, aortic stenosis; PS, pulmonary stenosis; ASD, atrial septal defect; HLHS, hypoplastic left heart syndrome.
Changes in the text: Page 14, line 305-307.

Comment 6.11. The PEP model was not developed using post CPB patients. This is a novel application of the model and it appears to be predictive. One of the major predictors of this model as pre operative infection. Any additional thoughts?
Reply 6.11: The PEP model showed high discrimination for in-hospital mortality as a risk adjustment tool in the CPB-ECMO group, with an AUROC of 0.679 (95% CI 0.571-0.787). We further explored the association of PEP model with hemostatic complications, blood product transfusion, and other clinical outcomes. Except for early hemolysis [AUROC=0.619 (95% CI 0.507-0.732)], PEP model didn't have predictive values for bleeding, circuit change, and thrombocytopenia. A weak correlation existed between RBC transfusion (P=0.005, r=0.229), hospital length of stay (P=0.003, r=-0.245), ICU stay (P=0.007, r=-0.221) and PEP model.
The score includes PH, APTT, and INR, indicating the severity of coagulopathy. Thus, it has a high degree of discrimination for in-hospital mortality in the CPB-ECMO group with multiple blood disorders at ECMO initiation. Additionally, it is associated with RBC transfusion and early hemolysis. The PEP model can be an effective tool to assist clinicians in assessing and developing individualized anticoagulation regimens in pediatric post-cardiotomy VA-ECMO failed to wean from CPB.
Preoperative infection had no significant effect on mortality and hemostatic complications in our study. Perhaps most notably are the differences in types of organisms classified between our research and the BATE cohort (Perfusion. 2021;36(4):407-14).
Changes in the text: Page 10, line 202-208; Page 14, line 298-305.

Limitations:
Comment 7.1. line 358, first sentence is not needed.
Reply 7.1: Thanks for your reminder. We have changed it to "This study did have some limitations".
Changes in the text: Page 15, line 322.

Comment 7.2. Insufficient sample size to do what? Would you have chosen a different end point? Done a different type of regression? Please be more specific.
Reply 7.2: We have added a control group. For comparison, critically ill children (n=50) who required VA-ECMO support and were not directly transitioned from CPB after cardiac surgery were also assessed (Non-CPB-ECMO group).

The outcomes of our research expanded to three. (1) To compare the prevalence of hemostatic complications in the CPB-ECMO group with the Non-CPB-ECMO group. (2) To assess the impacts of hemostatic complications in different stages on clinical outcomes in the CPB-ECMO group. (3) To explore the association between the timing of systemic heparinization and hemostatic complications at different stages.
Additionally, the impact of hemostatic complications at different stages on in-hospital mortality was assessed using univariate logistic regression.
Changes in the text: Page 4, line 80-82; Page 8, line 154-158; Page 8, line 164-165.

Conclusion
Comment 8.1. First sentence is more of an intro statement than a conclusion of your study
Reply 8.1: Thanks for your reminder. We have deleted it.
Changes in the text: The original sentence has been deleted in the text.

Comment 8.2. Again, I think the impact of low platelets needs to be considered in greater detail. I would suggest a sub analysis of mortality using PLT transfusion and adjusting for PLT count and see if the independent association remains.
Reply 8.2: Your advice is necessary. We have done sub-analyses of mortality using PLT transfusion and adjusting for thrombocytopenia/PLT count and see if the independent association remains. PLT infusion volume was not an independent risk factor for in-hospital mortality in both sub-analyses (as shown in the table below). In the univariate logistic regression analysis, PLT transfusion volume was not significantly associated with in-hospital mortality [OR=1.037 (0.995, 1.080), P=0.082] (Table 4).
Table. Multivariate logistic regression analysis of in-hospital mortality

Variables	OR	(95%CI)	P value
PLT transfusion (ml/kg/d)	1.013	0.958, 1.070	0.653
Thrombocytopenia	8.388	2.361, 29.802	0.001
Age (m)	0.996	0.959, 1.035	0.855
Weight (kg)	1.017	0.852, 1.214	0.851
STAT category	1.121	0.704, 1.786	0.630
PEP model (%)	1.049	1.007, 1.094	0.023

Note: PLT, platelet; STAT, Society of Thoracic Surgeons-European Association for Cardio-Thoracic Surgery; PEP, Pediatric Extracorporeal Membrane Oxygenation Prediction.

Table. Multivariate logistic regression analysis of in-hospital mortality

Variables	OR	(95%CI)	P value
PLT transfusion	1.030	0.980, 1.083	0.246

(ml/kg/d)			
PLT median (×10^9/L)	0.988	0.971, 1.005	0.160
Age (m)	0.997	0.963, 1.034	0.890
Weight (kg)	1.025	0.869, 1.209	0.766
STAT category	1.194	0.771, 1.849	0.426
PEP model (%)	1.051	1.011, 1.092	0.012

Note: PLT, platelet; STAT, Society of Thoracic Surgeons-European Association for Cardio-Thoracic Surgery; CPB, cardiopulmonary bypass; ECPR, extracorporeal cardiopulmonary resuscitation; ICU, intensive care unit; MAP, mean arterial pressure; VIS, vasoactive-inotropic score; PEP, Pediatric Extracorporeal Membrane Oxygenation Prediction.

Changes in the text: Page 10, line 213-214; Table 4.

Reviewer B

Comment: Jin et al have submitted a retrospective review of all patients who required the use of VA ECMO for an inability to wean from CPB following various cardiac surgical procedures. Their cohort is stratified according to hospital mortality (survivors vs. non-survivors) and the primary outcomes of interest appear to be rates of hemostatic complications while on ECMO (major bleed, circuit change, hemolysis, and thrombocytopenia) as well as an evaluation of UFH start time following ECMO implementation. The statistical methods appear sound.

The authors conclude that GI bleeding, need for ECMO circuit change, and the presence of hemolysis and/or thrombocytopenia all increased the risk of in-hospital mortality for this population. Additionally, they identify that UFH start time had an association with the presence of hemolysis.

I believe the major flaw of this study is its clinical applicability. As the authors point out, this is an extremely difficult population of patients to treat. They identify an association between GI bleeding, circuit change, hemolysis, and thrombocytopenia with mortality which is not all that surprising. The patients who were not survivors had a significantly higher PEP model score at ECMO implantation, which suggests they are more critically ill at the time of ECMO initiation and the hemostatic complications seen are, in part, a reflection of their worse clinical course. They note that a delay in UFH start is associated with higher max plasma free haemoglobin levels, which again is not surprising. However if one were to ask how to use the outcomes of this study in a clinical realm, I suspect the answer would be to start UFH as soon as possible, which is already the goal of clinicians who treat these patients. In patients who continue to have a delayed start time of UFH, there is presumably a clinical reason why there has been a delay in starting anticoagulation. Therefore, I am not sure that this study is adding anything unique to the body of literature addressing

anticoagulation use in post-cardiotomy VA ECMO use.

Reply: Thank you for your valuable suggestion. To improve our study's clinical applicability, innovation, and uniqueness, we supplemented data and analysis and made some new findings. On this basis, we almost rewrote the entire manuscript. We hope to have some clinical significance.

To highlight the particularity of coagulopathy in pediatric postcardiotomy VA-ECMO for failure to wean from CPB (CPB-ECMO group, n=96), critically ill children (n=50) required postcardiotomy VA-ECMO support for other indications were assessed (Non-CPB-ECMO group) for comparison. In addition, In addition, early hemostatic complications were defined as occurring within the first 48 hours since ECMO initiation; otherwise, they were late hemostatic complications.We found that: (1) Failure to wean from CPB significantly increased the risk of bleeding, especially early bleeding; (2) Patients with early bleeding had a higher volume of chest tube drainage, a greater demand for blood products, and an increased risk of mortality; (3) Systemic heparinization was delayed to avoid early bleeding but increased the risk of early hemolysis in the CPB-ECMO group, and the 9.5-hour heparin start time had good discrimination for early hemolysis. The anticoagulation regimens for patients directly transited from CPB to ECMO were complicated in the peri-CPB phase. Delayed systemic heparinization may be an option for many centers. Our study suggests the risk of hemolysis increased over time with delayed systemic heparinization.
Changes in the text: Page 4, line 80-82; Page 5, line 93-94; Page 8, line 154-158; Page 12, line 244-249; Page 15-16, line 329-334.

In a previous study, Von et al. (Perfusion. 2020;35(7):626-32) explored delayed systemic heparinization in 15 neonatal post-cardiotomy ECMOs for which the average UFH start time was 18.1±9.3 h. They found that delayed continuous UFH infusion could reduce bleeding and blood product transfusion without increased risk of thrombosis. This seems to be a bit different from our findings. Notably, our number of patients was much larger which thus increases the statistical significance; also, we analyzed the risk of hemolysis and circuit change specifically. In this context, this study found that the timing of systemic heparinization cut-off value of 9.5 h had a good Youden index to predict early hemolysis. This finding can be applied as a reference for planning anticoagulation management in the future.
Changes in the text: Page 14, line 290-297.

The PEP model utilized in this study was developed using prospectively collected data from the bleeding and thrombosis on extracorporeal membrane oxygenation (BATE) study (
Pediatr Crit Care Med. 2019;20(5):426-434) and was externally validated in the data from the ELSO registry (Perfusion. 2021;36(4):407-14). The score included

the PH, APTT, and INR, which can indicate the severity of coagulopathy. Thus, it had a high degree of discrimination for in-hospital mortality in the CPB-ECMO group with multiple blood disorders at ECMO initiation. Additionally, it was associated with RBC transfusion and early hemolysis. The PEP model is an effective tool in assisting clinicians in assessing and developing individualized anticoagulation regimens in pediatric post-cardiotomy VA-ECMO patients who failed to wean from CPB.
Changes in the text: Page 14, line 298-305; Page 15, line 311-313.

This is the largest study aimed at pediatric patients who had directly transitioned from CPB to VA-ECMO after cardiac surgery and uniquely examined the association between timing of systemic heparinization and early/late hemostatic complications. This article compares pediatric post-cardiotomy VA-ECMO patients who failed to wean from CPB while using non-CPB-ECMO as a control to highlight the procedure's high risk for bleeding. In addition, we discuss hemostatic complications by staging to further clarify the reasons and results of the delayed systemic heparinization in the CPB-ECMO group. These findings provided some basis for judging the situation of those special patients and implementing individualized anticoagulation strategies.
Changes in the text: Page 15, line 314-320.