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MAIN TEXT ARTICLE

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Cardiopulmonary bypass-induced coagulopathy in pediatric patients: The role of platelets in postoperative bleeding. A preliminary study

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Abstract

Pediatric patients are particularly prone to cardiopulmonary bypass (CPB)-induced coagulopathy mainly due to hemodilution, consumption of coagulation factors and hypothermia. The aim of the present study was to examine the possible role of platelet count and function as it relates to the bleeding risk after CPB in the pediatric population. All consecutive patients (age <13 years) scheduled for elective cardiac surgery between January 2019 and November 2019 were retrospectively considered for the study. We gathered demographic characteristics, perioperative laboratory data (mainly platelet count and function), transfusion requirements, and blood loss for each patient. Patients with a chest tube output during the first 24 hours after surgery >75th percentile were bleeders (cases). Controls were nonbleeders. A total of 31 patients were enrolled [median age 17 (4-57) months]. A significant postoperative reduction in platelet count ($P < .001$) and function either in ADP-test ($P < .001$), TRAP-test ($P < .001$) and ASPI-test ($P < .001$) was found, with positive correlations between chest tube output within the first 24 hours after surgery and postoperative impairment of platelet count ($R = 0.553$, $P = .001$), ADP-test ($R = 0.543$, $P = .001$), TRAP-test ($R = 0.627$, $P < .001$) and ASPI-test ($R = 0.436$, $P = .014$). Eight children (26%) experienced major postoperative bleeding. Bleeders were significantly younger ($P = .015$) and underwent longer CPB duration ($P = .015$). Despite no significant differences in postoperative platelet count and function between cases and controls, the postoperative reduction (Δ) in platelet count ($P = .002$) and function in ADP-test ($P = .007$), TRAP-test ($P = .020$) and ASPI-test ($P = .042$) was significantly greater in bleeders vs. nonbleeders. A ΔPLT >262 500 $\times 10^9$/L, a ΔADP-test >29 U, a ΔTRAP-test >44 U and a ΔASPI-test >26 U showed to be predictive of major postoperative bleeding. Postoperative bleeding in children undergoing cardiac surgery with CPB was linked to younger age, longer CPB duration, and significant postoperative reduction in platelet count and function. Larger studies are needed to

Guido Di Gregorio and Nicolò Sella contributed equally to the work.

confirm our results and define strategies to reduce postoperative bleeding in these patients.

KEYWORDS

aggregometry, cardiopulmonary bypass, coagulopathy, pediatric cardiac surgery, platelets

1 | INTRODUCTION

Cardiopulmonary bypass (CPB) is mandatory for most cardiac surgical procedures and, although it has been routinely used for many decades, it is a remarkably nonphysiologic state with several well-described adverse effects such as hemostatic dysfunctions and perioperative bleeding.[1] Pediatric patients are particularly predisposed to CPB-induced coagulopathy with increased risk of major bleeding, transfusion and poor outcomes.[2] The cause of excessive bleeding after pediatric cardiac surgery is multifactorial. The coagulation cascade is activated when blood comes into contact with the foreign surfaces of the CPB circuit and via the release in the blood stream of tissue factor during surgical procedures, leading to a continuous consumption of coagulation factors.[3] In addition, the initiation of CPB also results in a premature activation and consumption of platelets.[4] In neonates and toddlers, the unfavorable ratio between their low blood volume and the CPB priming volume may cause significant hemodilution resulting in more severe thrombocytopenia and dilution of coagulation factors.[4] Moreover, at least during the first year of life, the human hemostatic system responds to both endogenous and exogenous modulation differently than the adult one.[5] Indeed, quantitative and qualitative differences in fibrinogen function have been reported between neonates and adults: neonatal fibrin lacks the typical three-dimensional structure of adult cross-linked fibrin network, thus the neonatal clot is more porous and less stable.[6] Finally, patients with congenital heart disease have a unique pathophysiology, often with coagulation alterations (especially cyanotic heart disease): they require high-complexity repairs with numerous sutures, long CPB runs and hypothermia, further increasing the risk of perioperative hemorrhage.[4,7]

We have previously investigated CPB-induced coagulopathy in pediatric cardiac surgery patients. In a different setting, we found that younger age and lower postoperative platelet count are significant risk factors for postoperative bleeding.[8] Furthermore, we demonstrated that the preoperative coagulation pattern among children with cyanotic heart disease is significantly associated with higher blood product requirements—in particular, fibrinogen and fresh frozen plasma (FFP)—and that preoperative thromboelastometry is of the utmost importance as it provides a more thorough and exhaustive assessment of a patient's coagulation status than traditional coagulation tests.[9]

The present study aims to further investigate CPB-induced coagulopathy in pediatric patients, to examine the role of platelets as it relates to the complex damages incurred by the entire coagulation system during CPB. The primary objective is to ascertain any possible association between reduced postoperative platelet count and/or abnormal platelet function and major postoperative bleeding.

2 | PATIENTS AND METHODS

2.1 | Study protocol

The study protocol was submitted to the local Ethics Committee (protocol number m17875). The study was conducted in compliance with the Declaration of Helsinki. The retrospective nature of the study waived the need for the written informed consent of the patient. Data were gathered retrospectively on patients aged <13 years old, scheduled for elective cardiac surgery with CPB between January 2019 and November 2019.

Exclusion criteria were: age ≥13 years old, emergency cardiac surgery or re-intervention, known pre-existing coagulopathies or hematological disorders, hepatic failure, and concomitant treatment with antithrombotic or antiplatelet drugs.

At our institution the perioperative management of children undergoing cardiac surgical procedures is highly standardized. The day before surgery, a blood sample is collected from a peripheral vein to measure blood cell count, hemoglobin concentration, hematocrit, prothrombin time (PT), and activated partial thromboplastin time (aPTT). The day of surgery, general anesthesia is initiated and maintained with total intravenous anesthesia (TIVA) standardized technique (midazolam 0.5 mg/kg/h, fentanyl 2 μg/kg/h, and cisatracurium 2 μg/kg/min). Before heparin administration, a blood sample is collected from a central venous line into one BD Vacutainer tube (with sodium citrate 109 mMol/L) and promptly sent for impedance aggregometry analysis via Multiplate analyzer (Multiplate System, Roche Diagnostics International Ltd, Rotkreutz, Switzerland). In each patient ADP-test, TRAP-test and ASPI-test are performed according to the manufacturer's protocols, as previously described.[10] Briefly, 0.3 mL of arachidonic acid (ASPI) or adenosine diphosphate (ADP) or thrombin receptor activating peptide (TRAP) solution is added to 0.3 mL of anticoagulated whole blood. Aggregation—which is assessed via changes in electrical impedance induced by platelet adhesion to the surface of two silver-coated electrodes—is continuously recorded in

arbitrary units (AU) over 6 minutes, and the area under the curve of AU over time (AUC-U) is taken as a measure of platelet residual reactivity. Tranexamic acid 15 mg/kg is systematically administered, and before aortic cannulation the patient is fully anticoagulated with a 300 IU/kg bolus of unfractionated heparin (UFH) to achieve an activated clotting time (ACT) > 400 seconds. In case of initial ACT < 400 seconds, the standard protocol at our institution consists of firstly administering human antithrombin at a dosage based on preoperative antithrombin activity value to achieve a desired activity of 100%. Further 50–100 IU/kg UFH bolus may be considered if the initial approach fails. ACT monitoring is then used to guide additional UFH administration, maintaining a target ACT > 400 seconds. ACT is measured every 20 minutes as suggested by The Society of Thoracic Surgeons, The Society of Cardiovascular Anesthesiologists, and The American Society of ExtraCorporeal Technology: Clinical Practice Guidelines—Anticoagulation During Cardiopulmonary Bypass.[11] CPB priming volume consists of crystalloids (Elettrol Reid III Fresenius) and human-derived albumin 20%; for children weighing <10 kg we also add packed red blood cells (PRBCs) (to achieve a 30% priming solution hematocrit) and sodium bicarbonate 1 mEq/kg. The priming volume varies with the choice of circuit, which in turn is determined by the required maximum flow rate, as calculated by the patient's body surface. In general, neonates need a maximum flow rate of up to 700 mL/min and the appropriate circuit requires 400 mL priming volume; whereas infants and toddlers need a maximum flow rate of 2300 mL/min and the appropriate circuits may require up to 800 mL priming volume; finally, older children need a maximum flow rate of up to 2800 mL/min and require circuits with 1000 mL priming volume. For every mL of priming volume 1 IU of UFH is added in the CPB circuit. At the end of CPB, protamine is administered to reverse heparin: adequate reversal is monitored by ACT. Platelet function test via Multiplate analyzer is repeated after heparin neutralization and CPB weaning. Postoperatively, upon admitting the patient to the Cardiac Surgery Intensive Care Unit, blood samples are collected to measure blood cell count, hemoglobin concentration, hematocrit, PT, aPTT, D-dimer, and fibrinogen plasma concentration. PRBCs were administered if hematocrit <21% during and after surgery; platelets were transfused if platelet count <50 $\times 10^9$/L in case of active bleeding; additional transfusions were based on laboratory test results and evidence of ongoing bleeding as assessed by a cardiac surgeon and/or anesthesiologist.

Bleeding was measured by chest tube output during the first 24 hours after surgery. Patients were divided into two groups: bleeders (cases) if chest tube output >75th percentile,[2] whereas the remaining were classified as nonbleeders (controls).

2.2 | Statistics

Data are reported as median and interquartile range; categorical variables are expressed as number and fraction (%). Nonparametric tests were applied due to the low sample size. Mann–Whitney *U* test was used to examine differences between the two groups. Spearman's rank analysis was applied to test the correlation between platelet count or Multiplate results, and perioperative bleeding. ROC curves analyses for the bleeding risk were performed and Youden J index was applied to choose the best cutoff values.

A P value <.05 was considered significant.

A post hoc power analysis considering an alpha of 0.05 showed that the power of our trial to detect a difference between cases and controls in the postoperative changes in platelet count and ADP test was 99% and 84%, respectively.

All statistical analyses were performed using GraphPad Prism for Windows (version 6.0, GraphPad Software Inc., San Diego, CA, USA, www.graphpad.com).

3 | RESULTS

Overall, 31 consecutive children were included in the analysis. Baseline demographic and surgical characteristics are listed in Table 1.

A total of 21 (68%) patients received blood product transfusions during the procedure versus 18 (58%) patients during the first 24 hours after surgery. Notably, none required platelet transfusion.

Considering the whole study population, we observed a significant postoperative reduction in median platelet count [preoperative 346 (257-423) $\times 10^9$/L versus postoperative 147 (107-210) $\times 10^9$/L, $P < .001$]. Similarly, we observed a postoperative platelet function impairment in ADP-test [preoperative 35 (27-50) U vs. postoperative 11 (8-14) U, $P < .001$], TRAP-test [preoperative 63 (50-79) U vs. postoperative 22 (16-35) U, $P < .001$] and ASPI-test [preoperative 44 (27-53) U vs. postoperative 8 (4-13) U, $P < .001$].

Significant positive correlations were found between chest tube output within the first 24 hours after surgery and postoperative reduction in platelet count ($R = 0.553$, $P = .001$), ADP-test ($R = 0.543$, $P = .001$), TRAP-test ($R = 0.627$, $P < .001$) and ASPI-test ($R = 0.436$, $P = .014$) as compared to preoperative values (Figure 1).

3.1 | Bleeders versus nonbleeders

Eight (26%) patients were classified as bleeders (cases) due to a chest tube output in the first 24 hours post-surgery >75th percentile,[2] while the remaining 23 (74%) patients were classified as nonbleeders (controls).

TABLE 1 Baseline demographic and surgical characteristics

Baseline characteristic	Total
Patients, n	31
Age, months	17 (4-57)
Male, n (%)	18 (58)
Weight, kg	9.0 (5.6-15.4)
Cyanotic heart disease, n (%)	11 (35)
Preoperative SpO_2, %	96 (86-98)
Type of operations, n (%)	
Correction of ventricular septal defect	9 (29)
Correction of tetralogy of Fallot	7 (23)
Correction of atrioventricular canal defect	4 (13)
Correction of subaortic stenosis	4 (13)
Correction of hypoplastic left heart syndrome	3 (10)
Correction of atrial septal defect	2 (6)
Correction of transposition of the great arteries	2 (6)
Aortic clamp duration, minutes	33 (0-83)
CPB duration, minutes	90 (60-120)
CPB body temperature, °C	33 (33-34)
Postoperative bleeding patients, n (%)	8 (26)
Postoperative chest tube output, mL/kg	10.6 (3.4-15.5)

Note: Data are presented as median and interquartile range (IQR), while categorical variables are expressed as number and fraction (%).

Abbreviations: CPB, cardiopulmonary bypass; SpO2, peripheral oxygen saturation.

The preoperative characteristics of the two groups are reported in Table 2A. Bleeders were statistically younger than nonbleeders [5 (4-9) vs. 19 (9-66) months, $P = .015$], despite presenting no significant body weight differences [6.0 (5.1-7.0) vs. 11.0 (7.2-17.4) kg, $P = .873$]. Preoperative traditional coagulation tests and platelet aggregometry results were similar in both groups, while platelet count was significantly higher in bleeders versus nonbleeders [423 (410-445) vs. 321 (256-386) $\times 10^9$/L, $P = .032$].

The intraoperative characteristics of the two groups are reported in Table 2B. Although bleeders underwent a longer CPB duration versus nonbleeders [128 (112-148) vs. 71 (60-97) minutes, $P = .015$], there were no differences between the two groups as it relates to aortic clamp duration and target body temperature during CPB ($P = .095$ and $P = .131$, respectively). During surgery, bleeders received higher amounts of PRBC [44 (35-62) vs. 18 (0-37) mL/kg, $P = .048$], though both groups received similar amounts of FFP and human fibrinogen concentrate ($P = .322$ and $P = .459$, respectively).

The postoperative characteristics of the two groups are described in Table 2C. No significant differences were found between bleeders and nonbleeders as regards postoperative traditional coagulation tests, platelet count and function, and transfusion requirements. Interestingly enough, bleeders showed a significantly greater postoperative reduction in both platelet count (ΔPLT) and function (ΔADP-test, ΔTRAP-test, and ΔASPI-test) than nonbleeders (Table 3).

The ROC curves for the bleeding risk of ΔPLT, ΔADP-test, ΔTRAP-test, and ΔASPI-test are shown in Figure 2. In particular, a ΔPLT > 262 500 $\times 10^9$/L [sensitivity 91.3% (73.2%-98.5%), specificity 75.0% (40.9%-95.6%)], a ΔADP-test > 29 U [sensitivity 73.9% (53.5%-87.5%), specificity 75.0% (40.9%-95.6%)], a ΔTRAP-test > 44 U [sensitivity 78.3% (58.1%-90.3%), specificity 75.0% (40.9%-95.6%)] and a ΔASPI-test > 26 U [sensitivity 52.2% (33.0%-70.8%), specificity 100.0% (67.6%-100.0%)] showed to be significantly predictive of major bleeding within the first 24 hours after surgery.

4 | DISCUSSION

Our findings demonstrate that pediatric patients undergoing cardiac surgery with CPB are more prone to develop postoperative alterations of the hemostasis, with impairment of the platelet plug and clot formation. It is well established that CPB fosters a reduction of platelet count in children due to premature platelet activation and consumption.[4,8,12-14] Our postoperative data revealed that platelet count dropped by almost 60% and platelet function assessed by Multiplate aggregometry was also severely impaired. It is our belief that such a marked alteration of platelet function cannot be attributed to the reduction of the platelet count alone. Although the underlying mechanisms remain a matter of debate, several authors have postulated that platelet activation by the CPB circuit may cause the platelets to become hypo-responsive to agonist stimulation;[15-17] thus, during cardiac surgery it becomes mandatory to chase strategies that aim at preserving platelet integrity and function, such as the minimal invasive extracorporeal circulation technology.[18]

In our study, we corroborated previous findings that major postoperative bleeding—defined as chest tube output within the first 24 hours after surgery >75th percentile[2]—correlates with younger age and longer CPB duration.[14,16] However, it bears noting that there is no consensus on the correlation between platelet function and CPB duration. Ranucci et al found no significant relationship between those two variables,[16] whereas Bønding Andreasen et al reported that CPB duration correlated significantly with a reduced platelet count and function.[14] Notably, though many studies have shown that coagulation is increasingly impaired with decreasing temperatures,[14,19,20] we found no significant differences in body temperature during CPB between bleeders and nonbleeders. This discrepancy may be explained by the fact that our patients experienced a milder hypothermia for a much shorter period of time.

Moreover, we demonstrated that postoperative platelet count and function assessed by Multiplate aggregometry, were similar in both bleeders and nonbleeders. These results

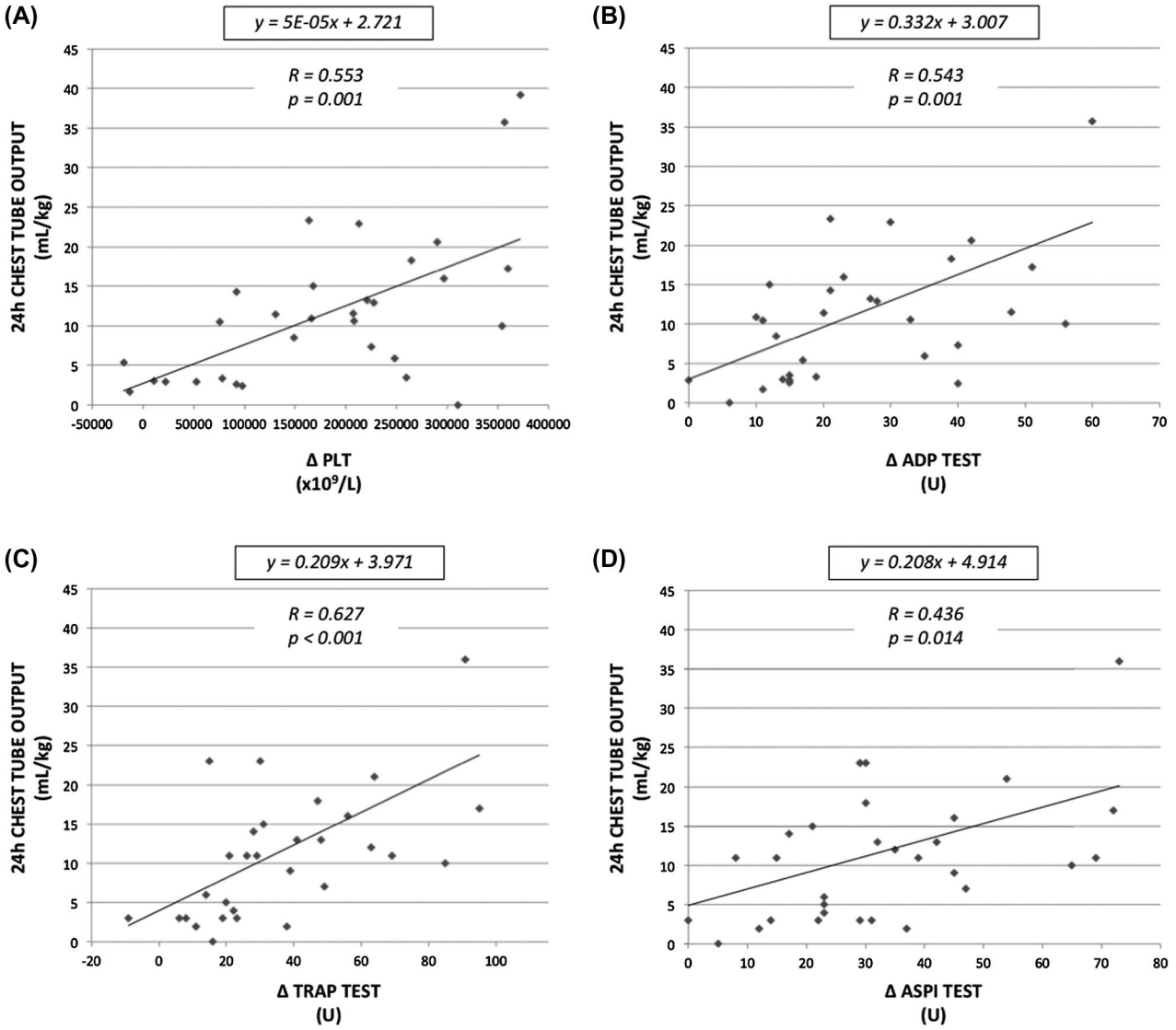


FIGURE 1 Correlation between chest tube output within the first 24 hours after surgery and the postoperative changes in platelet count (ΔPLT;) (A), ADP-test (ΔADP-test) (B), TRAP-test (ΔTRAP-test) (C), and ASPI-test (ΔASPI-test) (D) as compared to preoperative values

are not widely corroborated in the literature; in fact, the association between reduced platelet count and function, and postoperative bleeding has only been recognized by a few authors.[16,21] Gertler et al conducted a study on 110 children aged <1 year and found that platelet function assessed by Multiplate aggregometry was not a reliable predictor of postoperative chest tube output or blood transfusion requirements.[22] A prospective pilot study by Ranucci et al established a clear relationship between reduced platelet count and postoperative bleeding, though no association was found between blood coagulation capability and postoperative bleeding.[16] In contrast, Romlin et al showed that impaired intraoperative platelet function was significantly associated with intraoperative transfusion rate.[23] Finally, Bønding Andreasen et al suggested that increased bleeding tendency might partly stem from decreased platelet count and function,[14] whereas Zwifelhofer et al recently demonstrated that neither thrombocytopenia nor impaired platelet function correlated with excessive postoperative bleeding.[17] These conflicting results may be ascribable to heterogeneity in study design and analyses, but also and more importantly, that of the pediatric population undergoing cardiac surgery (i.e., age, pathologies and comorbidities, and surgical procedures).

Finally, it bears noting that in our series, postoperative bleeding correlated with the extent of postoperative decrease of both platelet count and platelet function assessed by Multiplate aggregometry compared to the preoperative tests. Furthermore, despite no significant differences in the absolute values of postoperative platelet count and function between bleeders and nonbleeders, the sharpest drop was observed in patients who experienced major postoperative bleeding.

We would be remiss not to mention some of the limitations of our study. It is a retrospective monocentric series with a small, albeit homogeneous, study population. Multiplate

TABLE 2 Preoperative (A), intraoperative (B), and postoperative (C) characteristics in bleeders (cases) versus nonbleeders (controls)

	Bleeders (n = 8)	Nonbleeders (n = 23)	*P*
(A) Preoperative characteristics			
Age, months	5 (4-9)	19 (9-66)	.015*
Weight, kg	6.0 (5.1-7.0)	11.0 (7.2-17.4)	.873
PT, %	87 (75-103)	80 (70-90)	.190
INR	1.09 (1.03-1.14)	1.13 (1.07-1.16)	.896
aPTT, seconds	28 (27-30)	27 (26-29)	.352
PLT, $\times 10^9$/L	423 (410-445)	321 (256-386)	.032*
ADP-test, *U*	48 (38-56)	32 (24-46)	.095
TRAP-test, *U*	75 (62-95)	60 (47-74)	.150
ASPI-test, *U*	48 (39-64)	39 (25-51)	.131
(B) Intraoperative characteristics			
CPB duration, minutes	128 (112-148)	71 (60-97)	.015*
Aortic clamp duration, minutes	91 (22-98)	30 (0-45)	.095
CPB body temperature, °C	33 (32-33)	34 (33-34)	.131
PRBC, mL/kg	44 (35-62)	18 (0-37)	.048*
FFP, mL/kg	0 (0-20)	0 (0-0)	.322
HFC, mg/kg	0 (0-53)	0 (0-0)	.459
(C) Postoperative characteristics			
PT, %	60 (46-69)	58 (49-65)	.984
INR	1.38 (1.24-1.60)	1.34 (1.26-1.61)	.952
aPTT, seconds	34 (27-41)	30 (27-33)	.465
Fibrinogen, mg/dL	1.54 (1.34-1.88)	1.60 (1.32-1.95)	.726
D-dimer, ng/L	589 (215-694)	302 (179-541)	.379
PLT, $\times 10^9$/L	141 (74-158)	154 (113-235)	.131
ADP-test, *U*	8 (4-12)	13 (9-18)	.061
TRAP-test, *U*	17 (6-25)	23 (19-36)	.075
ASPI-test, *U*	5 (2-9)	10 (6-13)	.150
PRBC, mL/kg	7 (2-11)	3 (0-10)	.471
FFP, mL/kg	0 (0-22)	0 (0-0)	.298
HFC, mg/kg	0 (0-0)	0 (0-0)	.810

Note: Data are presented as median and interquartile range (IQR). ADP-test normal range: 54-112 U; TRAP-test normal range: 73-143 U; ASPI-test normal range: 71-115 U.[24]

Abbreviations: aPTT, activated partial thromboplastin time; CPB, cardiopulmonary bypass; FFP, fresh frozen plasma; HFC, human fibrinogen concentrate; INR, international normalized ratio; PLT, platelet count; PRBC, packed red blood cells; PT, prothrombin time.

*Statistically significant.

TABLE 3 Changes (Δ) between preoperative and postoperative tests in bleeders versus nonbleeders

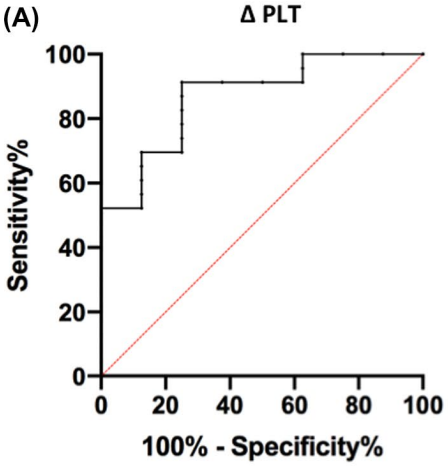
	Bleeders (n = 8)	Nonbleeders (n = 23)	*P*
Δ PLT, $\times 10^9$/L	295 (25-358)	149 (77-223)	.002*
Δ ADP-test, *U*	40 (28-44)	17 (12-30)	.007*
Δ TRAP-test, *U*	57 (43-71)	26 (17-40)	.020*
Δ ASPI-test, *U*	37 (30-58)	23 (16-38)	.042*

Note: Data are presented as median and interquartile range (IQR).

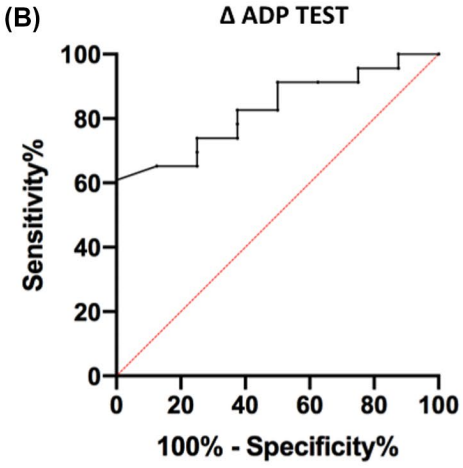
Abbreviation: PLT, platelet count.

*Statistically significant.

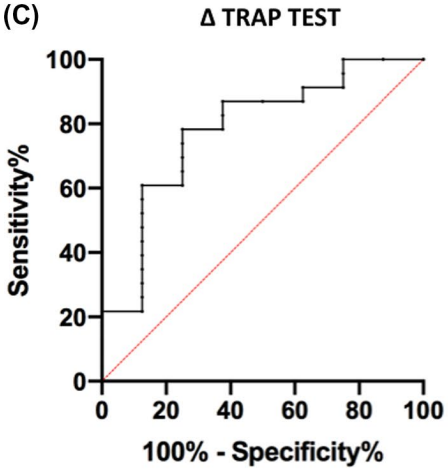
analysis is a poorly sensitive and operator-dependent test that cannot be routinely repeated in pediatric setting due to the relatively large blood volume requirement. Furthermore, the normal value ranges for Multiplate analysis are largely variable according to the age of the patient: infants (0-12 months of age), as were many patients in our series, show lower normal values compared to older children and adolescents.[24] Indeed, a recent report revealed that Multiplate analysis may constitute a less reliable and reproducible tool than light transmission lumi-aggregometry for studying platelet function in pediatric patients.[25] Finally, the bleeding severity was assessed using only one definition (i.e., chest tube output).



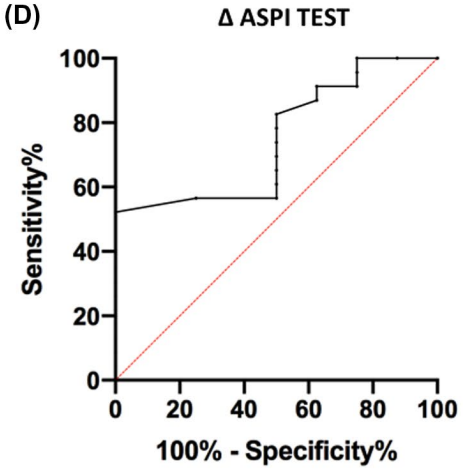
AUC (± SD)	p	CUT-OFF	SE (95% CI)	SP (95% CI)
0.870 (± 0.071)	0.002	>262500 x10^9/L	91.3% (73.2-98.5%)	75.0% (40.9-95.6%)



AUC (± SD)	p	CUT-OFF	SE (95% CI)	SP (95% CI)
0.829 (± 0.074)	0.006	>29 U	73.9% (53.5-87.5%)	75.0% (40.9-95.6%)



AUC (± SD)	p	CUT-OFF	SE (95% CI)	SP (95% CI)
0.783 (± 0.099)	0.019	>44 U	78.3% (58.1-90.3%)	75.0% (40.9-95.6%)



AUC (± SD)	p	CUT-OFF	SE (95% CI)	SP (95% CI)
0.747 (± 0.094)	0.040	>26 U	52.2% (33.0-70.8%)	100.0% (67.6-100.0%)

FIGURE 2 The ROC curves for the bleeding risk within the first 24 hours after surgery of the postoperative changes in platelet count (ΔPLT;) (A), ADP-test (ΔADP-test) (B), TRAP-test (ΔTRAP-test) (C), and ASPI-test (ΔASPI-test) (D) as compared to preoperative values. AUC, area under the curve; SD, standard deviation; SE, sensitivity; SP, specificity; 95% CI, 95% confidence interval [Color figure can be viewed at wileyonlinelibrary.com]

5 | CONCLUSIONS

We found that pediatric patients undergoing elective cardiac surgery with CPB developed a postoperative hypocoagulable state and experienced a concomitant reduction of platelet count and function. Postoperative bleeding is a multifactorial occurrence and may be linked to younger age, longer CPB duration, and greater postoperative decrease in platelet count and function. Further studies are warranted to determine whether our findings are reproducible in a larger group of pediatric cardiac surgery patients and to ascertain the incidence of other relevant clinical outcomes such as ICU length of stay and 30-day mortality which may be affected by CPB-induced coagulopathy.

ETHICAL STATEMENT

The study protocol was notified to the local ethics committee (protocol number m17875), which, given the retrospective nature of the study, waived the need for inform consent. The study was conducted in compliance with the Declaration of Helsinki.

CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest with the contents of this article.

AUTHOR CONTRIBUTIONS

Concept and design: Di Gregorio, Sella, Spiezia
Acquisition, analysis, or interpretation of data: Di Gregorio, Sella, Menin, Spiezia, Pittarello, Vida
Drafting of the manuscript: Sella, Spiezia
Critical revision of the manuscript for important intellectual content: Navalesi, Simioni, Pasin, Boscolo
Supervision: Navalesi, Simioni, Pittarello, Vida

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