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ORIGINAL ARTICLE

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Transfusion-related acute hepatic injury following postoperative platelets administration in pediatric patients undergoing the Fontan procedure

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Abstract

Objective: The final common pathway of single ventricle patients is the Fontan procedure. Among the immediate postoperative complications is acute hepatic injury presented by marked elevation of liver enzymes (alanine transaminase [ALT] and aspartate transaminase [AST]). We aimed to determine the contribution of blood products transfusion to acute hepatic injury.

Design: Single center retrospective cohort study.

Setting: Pediatric Cardiac Intensive Care Unit at a tertiary medical center.

Patients: Ninety-nine pediatric patients undergoing the Fontan procedure between January 2009 and December 2016.

Interventions: None.

Measurements and Main Results: Out of the four types of blood products, transfusion of platelets was found to significantly affect postoperative levels of ALT and AST. Additional factors included postoperative administration of sodium bicarbonate, decreased flow through the Fontan canal and decreased urine output. Preoperative pulmonary artery pressure and pulmonary vascular resistance, cardiopulmonary bypass time, aortic cross-clamp time, amount of postoperative bleeding, and vasoactive-inotropic score did not influence liver enzymes levels

*Uri Pollak and Tatyana Ruderman contributed equally to the performance of this research.

Conclusions: In pediatric Fontan patients, platelets transfusions contribute to an acute hepatic injury. The relation between platelets and transfusion-related acute lung injury (TRALI) has been well described, but this is the first time it is being described in regard to acute hepatic injury (TRAHI). Changing platelet transfusion strategy could decrease morbidity in Fontan patients but further research is needed.

KEYWORDS
acute hepatic injury, congenital heart defect, Fontan, pediatric cardiac surgery, platelets, transfusion-related acute hepatic injury

1 | INTRODUCTION

The Fontan procedure was first introduced in 1968 for the palliation of patients with tricuspid atresia and underdeveloped nonfunctioning right ventricle.[1] Today, the procedure is performed on children born with a variety of congenital heart disease for whom the biventricular repair would not be effective. This procedure results in two separate circulations: the first, where the single ventricle, whether morphologically left or right, is responsible for pumping oxygenated blood to the systemic circulation and the second, a pulmonary circulation, where non-oxygenated venous blood drains from the superior vena cava (SVC) and the inferior vena cava (IVC) straight into the pulmonary arteries.[2] This procedure has transformed the lives of patients born with single ventricle physiology and offered them the potential for survival and good quality of life well into adulthood.[3,4] Since its original description in 1971, many modifications to the procedure have resulted in improved survival, but several long-term complications, among them protein losing enteropathy, plastic bronchitis, and liver fibrosis, are still a major cause of morbidity and mortality.[5]

Hepatic long-term consequences in Fontan patients have been extensively described. Chronic liver failure, which manifests as fibrosis and cirrhosis, and with hepatocarcinoma as a final stage at times, is a common finding among patients with long-standing Fontan circulation.[6] The suspected cause is hepatic venous congestion due to the elevation in venous pressure in both venae cavae. Although liver congestion is more common after the Fontan completion, it has been demonstrated that hepatic stiffness is already increased after the Glenn procedure, where the SVC is being connected straight to the pulmonary artery.[7]

Acute hepatic injury (AHI) can be generally divided into hepatocellular injury and cholestatic injury or a mixed pattern with one type usually being more predominant. The classical finding in hepatocellular injury is elevation in alanine transaminase (ALT) and aspartate transaminase (AST) due to dysfunction of the cellular membrane of the hepatocytes, causing their release into the circulation. AST is less specific as it is found in other tissues such as skeletal and cardiac muscles, kidneys, and brain. Modest elevation of ALT and AST is not specific and may occur with any type of hepatic disorder, whereas marked elevation (few hundreds up to thousands IU/L) usually occurs when the hepatocellular injury is extensive, with etiologies such as viral hepatitis, ischemia, and toxin or drug-induced hepatic injury.[6]

Elevation of ALT and AST during the early postoperative period after the Fontan procedure, is a common finding in our experience, however research in this regard is currently limited. Elevation of transaminases after cardiac surgery in patients with congenital heart disease is not a rare finding, and extreme elevation of ALT, AST and lactate dehydrogenase (LDH) correlate negatively with postoperative survival.[8] Identifying the risk factors for such elevation may improve intra- and postoperative management and consequently improve survival.

In this study, we examined the impact of several factors thought to influence acute hepatic injury after the Fontan procedure, specifically blood products transfusions. We hypothesized that there is a dose-dependent cause and effect relationship between blood products transfusions and elevation of transaminases.

2 | METHODS

The institutional review board (IRB) of the Chaim Sheba medical center, Tel Hashomer, approved this retrospective cohort study protocol.

3 | PATIENTS

All patients who have undergone the Fontan procedure at the Chaim Sheba medical center, Tel-Hashomer, between January 2009 and February 2016 were considered eligible for inclusion. Exclusion criteria included liver disease prior to surgery or lack of information regarding levels of transaminases prior to surgery.

3.1 | Data collection

Data were collected from patient digital records using Microsoft Excel 2016 (Microsoft Corporation, Redmond, WA, USA) spreadsheet application. In order to establish our follow-up period, we first recorded the time to maximal elevation of AST and ALT; other

variables were collected according to this period, with a duration of approximately 120 postoperative hours. Interventions such as blood products and sodium bicarbonate administration were calculated as total amount per kilogram of body weight given until time of maximal levels of transaminases. We collected information regarding four possible types of blood products: packed red blood cells (PRBC), platelets (PLT), cryoprecipitate, and fresh frozen plasma (FFP). Parameters influencing the decision to transfuse; levels of hemoglobin, amount of bleeding, mixed venous saturation, and lactate levels were recorded as maximum (bleeding and lactate) or minimum (hemoglobin and mixed venous saturation) during the first 24 postoperative hours. Unless the purpose of transfusion is urgent volume expansion in the presence of active bleeding, our protocol for blood products transfusion is maximal rate of 10 cc/kg/h and minimal duration of 1 hour.

3.2 | Statistical analysis

The data are presented by frequency distribution for categorical variables and by mean and standard deviations for continuous variables. Due to the maximal levels of ALT and AST being skewed, these outcome variables were transformed into log scale for the regression analysis. Correlation of variables to outcome was calculated using Spearman correlation test. P value < .05 was considered significant.

We used the propensity score[9] in order to correct a possible selection bias in our study, that may result from the possibility that patients who required blood transfusions are also at risk for hepatic injury that may ensue due to their clinical state, regardless of the blood transfusion itself. A propensity score was calculated for each patient as the probability to receive a certain blood product transfusion. In order to calculate the propensity score, the criteria that are used in our unit for administration of blood products need to be determined. These criteria depend on the type of blood product; for transfusion of PRBC, the criteria include amount of bleeding, hemoglobin level, mixed venous saturation, and level of lactate. For transfusion of the remaining products (platelets, FFP, and cryoprecipitate), the main criterion is amount of bleeding. The observational design was treated using a generalized propensity score approach (GPSA) that generalizes the standard two-group approach for multiple group comparisons.[10,11] However, the direct application of the GPSA is impossible due to the following reasons: (a) relatively small sample size (99 patients), (b) A four-dimensional intervention, namely four different types of blood products transfused, and (c) Many of the patients did not receive some or all types of blood products, which means that the distributions are not normal and are a mixture of single-point distribution and skewed continuous distribution. Thus, we have to apply "restricted" GPSA in the following form; each of the four types of blood products was transformed into a binary scale: zero if the patient did not receive this type of blood product, or 1, if the patient did receive this type of blood product. Potentially, this gives 16 combinations. Some of these groups were empty and some included very small[1-4] number of patients. Therefore, we reduced these 16 groups into four types of treatments, due to our small sample size and complex distribution of dose of transfusions: (a) Patient received no transfusions at all, (b) Patient received PRBC and/or FFP, (c)

TABLE 1 Patients Characteristics

Preoperative characteristics		Postoperative characteristics	
Age	64.27 (34.58)	Cardiopulmonary bypass time	71.7 (34.21)
Males	59 (59.6%)	Minimal hemoglobin[a]	12.78 (2.06)
Weight	17.35 (7.77)	Maximal lactate[a]	57.8 (32.1)
Time from Glenn	96, 41.94 (22.71)	Maximal VIS[a]	15.88 (16.25)
Hypoplastic left ventricle	42 (42.5%)	Normal Fontan flow	96, 93 (96.87%)
Hypoplastic right ventricle	57 (57.5%)	Maximal ALT[b]	99, 546.22 (1080.28)
Non-cardiac malformations	94, 20 (20.6%)	Maximal AST[b]	99, 1441.78 (3105.67)
Intra-operative characteristics		Death	99, 5 (5/1%)
Fenestration		Blood products transfusions[c]	
Early fenestration	48 (48.5%)	PRBC	44, 24.34 (19.45)
Late fenestration	6 (6.06%)	PLT	43, 12.13 (9.39)
No fenestration	39 (39.3%)	FFP	64, 53.06 (101.82)
One-step Fontan	6 (6.06%)	Cryopercipitate	27, 7.58 (5.06)
Additional cardiac procedures	99, 33 (33.3%)		

[a]During first 24 postoperative hours, mean (SD).
[b]Measured postoperatively, *n*, mean (SD).
[c]Postoperative transfusions prior to maximal ALT and AST, *n*, mean (cc/kg), (SD). Calculated only for patients who received blood products.

Patient received cryoprecipitate or platelets, and (d) Patient received cryoprecipitate and platelets. Using these groups, we calculated the probability of each patient to belong to each group using multinomial logistic regressions with the possible confounders. The weight of each observation was calculated as the inverse probability of belonging to the group of his/her actual treatment. The relationships between the different transfusions and the maximum level of transaminases were analyzed using backward-weighted linear regression of the logarithm of maximal transaminases' levels on the potential confounders. We present two models for each outcome (ALT and AST). First included all four transfusions and significantly correlated confounders, and the second, concise model, includes only significant predictors. All tests were two sided. *P* value ($P>|t|$) < .05 was considered as significant. All calculations were done using STATA SE software (StataCorp LLC, College Station, TX, USA).

4 | RESULTS

A total of 99 patients were included in the study, none were excluded based on exclusion criteria. The pre, intra, and postoperative characteristics are summarized in Table 1. 44 patients (44.4%) received PRBC transfusions, 43 patients (43.4%) received PLT transfusions, 64 patients (64.6%) received FFP transfusions, and 27 patients (27.3%) received cryoprecipitate transfusions. As Spearman correlation for ALT and AST had a rho of .936, in order to simplify the report of the results, we will address results for ALT unless otherwise stated. Of note, alkaline phosphatase (ALP) and gamma-glutamyl transpeptidase (GGT) levels were not significantly elevated in most of our patients. There were four patients with plasma GGT levels of twice the normal value but without correlation with neither ALT nor AST.

The following variables were found to be statistically significantly correlated ($P < .05$) with maximal elevation in ALT and AST in the early postoperative period after the Fontan procedure (rho and *P* values included are for correlation with ALT, a correlation is stronger the closer it is to |1|). PLT and cryoprecipitate were found to correlate moderately (PLT [rho = .547, *P* = .000]), (cryoprecipitate [rho = .408, *P* = .000]), while FFP and PRBC were found to be weakly correlated (FFP [rho = .348, *P* = .001], PRBC [rho = .246, *P* = .017]).

Among our presumed confounders, only postoperative parameters were found to correlate with our outcomes. These parameters include (in order of declining strength of correlation): (a) Moderate correlation with postoperative administration of sodium bicarbonate (rho = .547, *P* = .000). (b) Weak correlation with urine output during first 8 postoperative hours (rho = −.364, *P* = .000). (c). Weak correlation with maximal vasoactive-inotropic score (VIS) calculated until time of maximal levels of transaminases (rho = .353, *P* = .001). (d). Weak correlation with ventricular function on echocardiogram after the Fontan procedure (rho = .237, *P* = .021).

The preoperative cardiac catheterization parameters (pulmonary artery pressure [PAP] and pulmonary vascular resistance [PVR]) were found not to be correlated with outcomes (with rho coefficient of .025 and .06, respectively). The intra-operative parameters, time on cardiopulmonary bypass (CPB) and time of aortic cross clamp during surgery, were found not to be correlated with outcomes either (with rho coefficient of .05 and .03, respectively). Of note, the amount of bleeding during first 8 postoperative hours (measured as

TABLE 2 Correlation between blood products transfusions, presumed confounders, and maximal levels of ALT and AST

Parameter	ALT (rho)	*P* value	AST (rho)	*P* value
Blood products transfusions				
PRBC[a]	.246	.017	.297	.004
FFP[a]	.348	.001	.402	.000
Cryopercipitate[a]	.408	.000	.410	.000
PLT[a]	.547	.000	.609	.000
Pre-perative parameters				
Time from Glenn to Fontan	.010	.927	−.069	.508
Pre-operative ALT	.060	.564	−.004	.970
Intra-operative parameters				
Cardiopulmonary bypass time	.050	.631	.134	.197
Aortic cross clamp time	.033	.749	.063	.550
Postoperative parameters				
Urine output[b]	−.364	.000	−.345	.001
Sodium bicarbonate administration[a]	.547	.000	.601	.000
Amount of bleeding[b]	.085	.418	.196	.059
Maximal VIS[a]	.353	.001	.431	.000
Ventricular function after Fontan	.237	.021	.217	.036
Flow through the Fontan canal	.189	.069	.186	.072

[a]Postoperative treatment until time of maximal level of ALT and AST.
[b]During first eight postoperative hours.

cc/kg) and abnormal levels of ALT prior to surgery (denoted as normal or abnormal) were also found not to be correlated with outcome (rho coefficient of .085 and .06, respectively) (Table 2).

Four patients (4%) had elevated levels of ALT and AST prior to surgery. In order to address this, we collected the levels of ALT and AST before and after surgery. Only one such patient showed a significant postoperative elevation in transaminases. As mentioned, elevated preoperative levels of liver enzymes did not correlate with outcome.

4.1 | Relation of blood product transfusions to elevation in transaminases

Using multinomial logistic regression, we calculated the probability of each patient to belong to one of the four groups that we have defined (Table 3). The results of our initial weighted linear regression for the four types of blood products, together with our originally presumed confounders are presented in Table 4. In this multivariate regression, blood products that were found to influence log (ALT), yet not significantly, are PLT (coefficient = .053, t = 1.390, $P>|t|$ = .170) and cryoprecipitate (coefficient = .053, t = 0.820, $P>|t|$ = .855). PBC and FFP were not found to influence ALT (coefficient = −.002, t = −0.180, $P>|t|$ = .855, and coefficient = .000, t = 0.260, $P>|t|$ = .792, respectively). The influence of PLT on AST was more significant than on ALT (coefficient = .057, t = 1.960, $P>|t|$ = .054).

Confounders that independently correlated with outcome and remained significant following initial regression are postoperative administration of sodium bicarbonate (coefficient = .612, t = 3.930, $P>|t|$ = .000) and urine output during first 8 postoperative hours (coefficient = −.006, t = −2.040, $P>|t|$ = .045). Flow through the Fontan canal on echocardiogram was significant only for elevation in ALT (coefficient = 2.089, t = 3.680, $P>|t|$ = .000). Ventricular function on echocardiography after the Fontan procedure and maximal VIS were no longer significant.

After employing a backward-weighted linear regression with a stepwise exclusion of insignificant variables, we were left with a concise model (Table 5). Transfusion of PLT was the only blood product found to have a significant influence on elevation of liver enzymes (coefficient = .071, t = 5.310, $P>|t|$ = .000) (Figure 1). The most significant confounders were administration of sodium bicarbonate (coefficient = .560, t = 7.000, $P>|t|$ = .000), and Fontan flow on echocardiography yet with a wide confidence interval (coefficient = 1.968, t = 3.16, $P>|t|$ = .002, 95% CI [0.729, 3.207]). Urine output during 8 postoperative hours had a very low but statistically significant impact (coefficient = −.007, t = −3.700, $P>|t|$ = .000).

5 | DISCUSSION

This study evaluated the relationship between blood products transfusion in the immediate postoperative period after the Fontan procedure and the development of acute hepatic injury characterized by significant elevation of ALT and AST.

Platelets transfusion was found to be significantly correlated with acute hepatic injury in a dose response relation. Transfusion of PRBC, FFP, and cryoprecipitate were not significantly correlated with elevation of transaminases.

Our findings relate to previous studies showing that among different types of blood products, platelets are the most common blood product to cause transfusion-associated adverse events. Most of these adverse events are inflammatory, including transfusion-related acute lung injury (TRALI).[12] In recent years, platelets have emerged as having functions other than hemostasis, and some influence on the liver in particular, arises from the field of liver transplantation. Patients suffering from cirrhosis tend toward thrombocytopenia due to sequestration of platelets in the spleen as a result of portal hypertension, and decreased levels of thrombopoietin (megakaryocytic growth factor), which is partly produced by the liver. Perioperative platelets transfusions have been attributed adverse roles in liver transplantation, such as key involvement in inflammation and ischemia-reperfusion injury. Ischemia-reperfusion occurs as a result of the donated liver experiencing cold ischemia (during harvesting and surgery) followed by rewarming, causing activation of endothelium. After transplantation, platelets become sequestered in the transplanted liver; they adhere to endothelium, and undergo activation, promoting their injurious activities. It has been demonstrated that the level of activation of platelets due to the activated endothelium, correlates with organ function. In addition, platelets may have the ability to induce apoptosis of the sinusoidal endothelial cells, especially after reperfusion, recruit CD4+ cells and participate in graft rejection. A cooperation has been described between platelets, leukocytes, and Kupffer cells, the resident macrophages in the liver, that undergo activation after reperfusion.[13,14] In addition, complexes of platelets-neutrophils are known to be present in many types of inflammation such as sepsis, inflammatory bowel

TABLE 3 Groups of blood products transfusions for propensity score calculation

Group	Frequency	Percent	Cum
Did not receive any transfusion	26	26.26	26.26
Received packed blood cells and/or fresh frozen plasma	26	26.26	52.53
Received only platelets or cryoprecipitate	24	24.24	76.77
Received both platelets and cryoprecipitate	23	23.23	100

Abbreviation: Cum, cumulative percentage.

TABLE 4 Weighted linear regression using blood products and presumed confounders with ALT and AST in log scale

	ALT					AST				
Confounder	**Coeff**	**Std err**	***t***	***P*>|*t*|**	**CI**	**Coeff**	**Std err**	***t***	***P*>|*t*|**	**CI**
Blood product transfusions										
PRBC[a]	−.002	0.011	−.180	.855	−0.025–0.021	−.004	0.008	−.520	.607	−0.021–0.012
FFP[a]	.000	0.001	.260	.792	−0.003–0.003	.000	0.001	.100	.922	−0.002–0.003
Cryopercipitate[a]	.053	0.054	.820	.413	−0.076–0.183	.032	0.054	.600	.549	−0.074–0.139
PLT[a]	.053	0.038	1.390	.170	−0.230–0.128	.057	0.029	1.960	.054	−0.001–0.115
Preoperative parameters										
Time from Glenn to Fontan	−.004	0.009	−.430	.668	−0.021–0.013	−.006	0.006	−.990	.324	−0.020–0.006
Preoperative ALT	−.687	0.600	−1.140	.256	−1.882–0.508	−1.105	0.540	−2.050	.044	−2.180–−0.030
Gender	−.181	0.390	−.460	.644	−0.867–0.326	−.270	0.300	−.900	.369	−0.867–0.326
Intra-operative parameters										
Cardiopulmonary bypass time	−.003	0.007	−.430	.666	−0.017–0.011	.002	0.005	.460	.647	−0.008–0.013
Aortic cross clamp time	−.004	0.006	−.630	.533	−0.017–0.009	−.004	0.005	−.890	.378	−0.013–0.005
Postoperative parameters										
Urine output[b]	−.006	0.003	−2.040	.045	−0.012–0.000	−.004	0.002	−1.670	.099	−0.009–0.001
Sodium bicarbonate administration[a]	.612	0.156	3.930	.000	0.302–0.923	.603	0.112	5.400	.000	0.381–0.827
Amount of bleeding[b]	.037	0.082	.450	.655	0.000–0.200	.104	0.066	1.570	.121	−0.028–0.237
Maximal VIS[a]	−.004	0.018	−.220	.829	−0.039–0.310	.006	0.014	.420	.677	−0.023–0.035
Ventricular function after Fontan	−.102	0.223	−.460	.649	−0.546–0.342	−.153	0.192	−.800	.427	−0.537–0.229
Flow through the Fontan canal	2.089	0.568	3.680	.000	0.957–3.221	1.802	0.496	3.630	.001	0.815–2.790

Notes: Probability > *F* = .000; R^2 = .4644; root mean squared error (MSE) = 1.387.

Abbreviations: Coeff, coefficient (change in log scale when variable is changed in 1 unit); *P*>|*t*|, *P* value of *t*-test; Std err, standard error; *t*, result of *t*-test.

[a]Postoperative treatment until time of maximal level of ALT and AST.

[b]During first eight postoperative hours.

TABLE 5 Concise model, stepwise weighted linear regression using PLT and significant confounders, with ALT and AST in log scale

	ALT					AST				
Confounder	Coeff	Std err	*t*	*P*>|*t*|	CI	Coeff	Std err	*t*	*P*>|*t*|	CI
PLT[a]	.071	0.013	5.310	.000	0.045–0.098	.078	0.011	7.190	.000	0.056–0.099
Urine output[b]	−.007	0.002	−3.700	.000	−0.011–−0.003	−.005	0.002	−3.360	.001	−0.009–−0.002
Sodium bicarbonate administration[a]	.560	0.080	7.000	.000	0.401–0.718	.500	0.070	7.110	.000	0.360–0.639
Flow through the Fontan canal	1.968	0.624	3.160	.002	0.729–3.207	1.673	0.549	3.050	.003	0.582–2.764

Notes: Probability > F = .000; R^2 = .4308; root mean squared error (MSE) = 1.327.
Abbreviations: Coeff, coefficient (change in log scale when variable is changed in 1 unit); *P*>|*t*|, *P* value of *t*-test; Std err, standard error; *t*, result of *t*-test.
[a]Postoperative treatment until time of maximal level of ALT and AST.
[b]During first eight postoperative hours.

disease, and atherosclerosis. The creation of such complexes, through expression of P-selectin on platelet cell surface, requires activation of platelets. It was found that platelets assist neutrophils in adhering to activated or injured endothelium,[15] and in some circumstances, are important in the release of neutrophil extracellular traps (NETs). NETs are networks of extracellular fibers containing DNA from neutrophils, known for their role in combating bacteria, but they can also cause damage to healthy tissue. NETs were found in ischemia-reperfusion injury of the liver[16] and in lungs of TRALI mice models,[17] and neutrophil aggregates are a common finding in lung microvasculature after TRALI. Depletion of platelets or neutrophils was shown to decrease hepatic injury, for example, due to Paracetamol toxicity, and platelet-neutrophil complexes were suggested as therapeutic targets in sterile tissue injuries.[15] Fontan patients were also found to have endothelial dysfunction.[2] Given the different roles of platelets mentioned above, an inflammatory mechanism of acute hepatic injury could be possible in our patients. Non-pulsatile CPB, which is used during the Fontan procedure, also causes endothelial activation.[18] In addition, CPB has been known to predispose to ischemia-reperfusion injury of vital organs including brain, kidney, lung, and liver. When non-pulsatile CPB was compared to pulsatile CPB, the reperfusion slope for non-pulsatile CPB was significantly different 24 hours postoperative than for pulsatile CPB.[19] Thus, Fontan patients could be afflicted by ischemia-reperfusion injury as well.

To suggest an explanation for the dose-response effect of platelets on elevation of liver enzymes, we may examine the threshold model of TRALI pathophysiology. It suggests that for TRALI to occur, factors in the transfused blood product and in the recipient, need to reach a certain combined level. The combined level causes activation of neutrophils.[20] This suggests that sicker patients, who may already have primed neutrophils and activated endothelium, need lower dosage of donor factors in order to develop TRALI, while healthier individuals whose neutrophils have not been primed could still suffer from TRALI if they receive a sufficient amount of donor factors while transfused.

One of the most common causes for acute hepatic injury in the surgical setting, especially in cardiac patients, is hepatic ischemia (HI). HI involves high mortality rates; it is characterized by a marked elevation of transaminases, with resolution within a few days in survivors. HI can be diagnosed with or without a recorded event of hypotension.[21] As HI was possible in our patients due to preoperative risk factors, surgery on CPB and due to acute changes in hemodynamics: hepatic congestion (over perfusion) or HI (under perfusion), caused by the surgery,[19] our chosen possible confounders were such that reflected tissue perfusion and the hemodynamic state. Even after adjusting for these parameters, transfusion of platelets remained significant. Administration of sodium bicarbonate was found to contribute significantly to elevation of transaminases; this treatment may imply poor systemic perfusion, thus contributing to an ischemic injury. Fontan flow after surgery (was denoted as 0-normal, 1-reduced) was also found to contribute to the hepatic injury, as the Fontan procedure is the connection of the IVC to the pulmonary artery, if flow through the anastomosis is impaired, back flow congestion will ensue, acutely

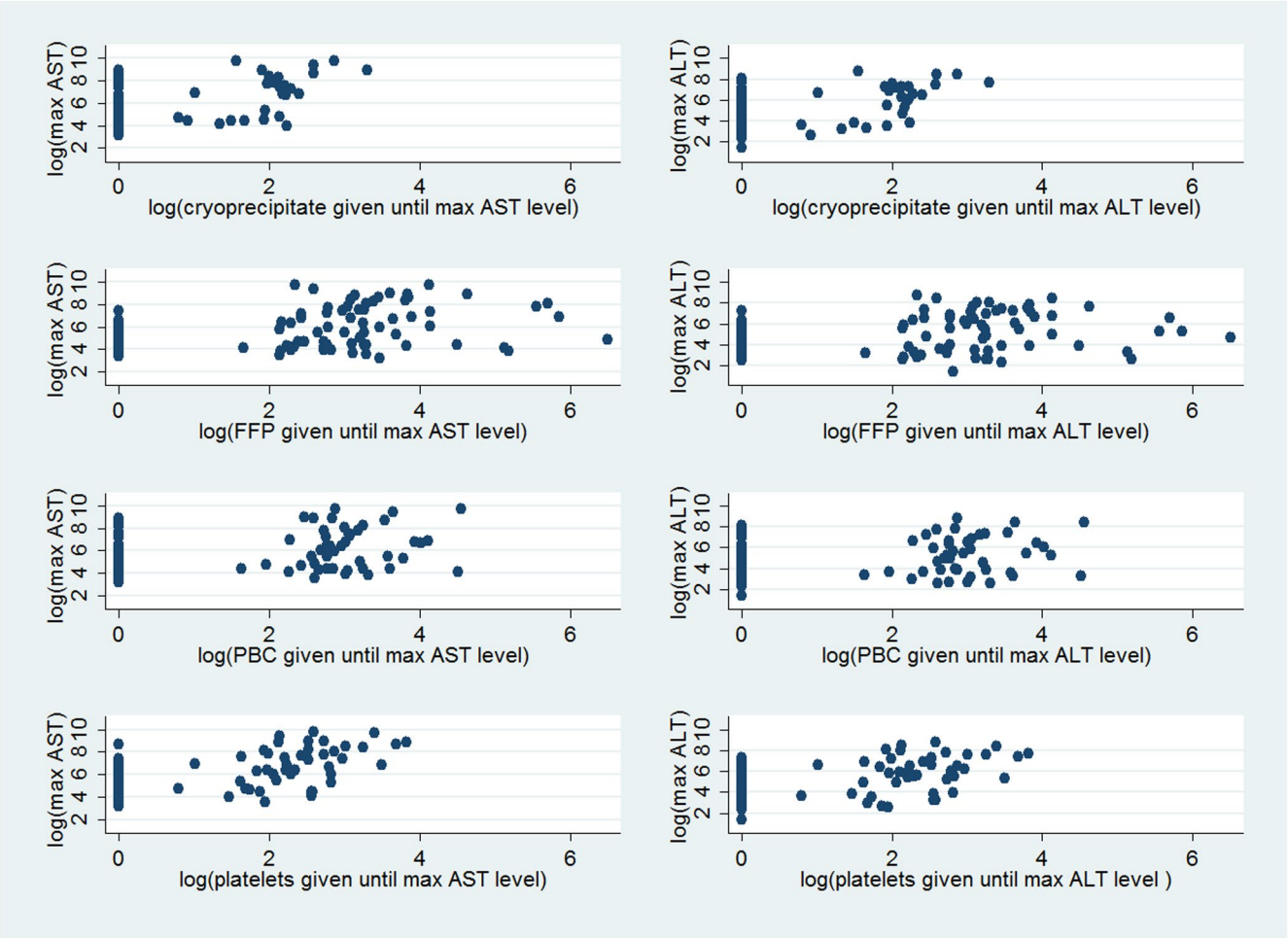

FIGURE 1 Correlation between transfusion of the different blood products (log scale) and maximal levels of ALT and AST (log scale)

injuring hepatocytes. Possible causes for an impaired Fontan flow include stenosis of the anastomosis created during surgery, or elevated PVR that has been shown to occur after CPB due to relative lung hypoperfusion followed by reperfusion, and elevation of thromboxane-A2 (TXA2) levels (synthesized by platelets, endothelial cells, neutrophils, and alveolar type II cells) that result in pulmonary vasoconstriction and increased PVR.[22]

The last factor found to be weakly correlated was urine output during the first 8 postoperative hours, the correlation was negative (the lower the urine output, the higher the transaminases), which could also be explained by a mechanism of under-perfusion, or volume depletion, causing relative ischemia.

However, the correlation of these factors does not necessarily diminish the effect of platelet transfusions. If in fact an ischemia-reperfusion injury is part of the mechanism causing hepatic injury, then sodium bicarbonate administration and decreased urine output could be surrogates for such an injury, which predisposes to hepatic injury by an inflammatory mechanism that involves platelets as previously described. Furthermore, impaired Fontan flow could be a result of increased PVR due to TXA2 secretion, possibly exacerbated by the platelet transfusion itself as TXA2 is synthesized by platelets. Furthermore, factors that were found to be significant could be part of the pathophysiology of the acute hepatic injury mediated by platelets. Administration of platelets in the case of Fontan patients may not necessarily indicate a sicker patient, but may be associated with the use of CPB, which has been found to cause thrombocytopenia, platelet dysfunction, and their exhaustion due to degranulation of alpha and dense granules, which may cause excessive bleeding and subsequent transfusions.[23]

Suspected factors that were not found to correlate with outcome include preoperative elevation in ALT. This could be explained by the fact that the preoperative elevation were mild (up to 223 IU/L), and non-specific, and probably did not indicate a pre-disposition to hepatic injury. Duration of CPB and aortic cross clamp did not correlate with outcome as well, despite our hypothesis that a longer duration may predispose the patients to hypo perfusion and coagulopathy thus contributing to hepatic injury. This could be due to the homogeneity of our study population, where the CPB duration was within a narrow range, which was rather short. In addition, fenestration of the Fontan canal did not have significant impact on transaminases (results not shown, was eliminated during regressions), possibly because in our institution, the creation of a fenestration does not depend on the patient's clinical state, but depends solely on the surgeon's preference. Amount of bleeding was also not correlated with outcome, possibly due to the

patients' close monitoring and administration of volume expansions (either fluids or blood products as indicated) to supplement for volume loss. The maximal VIS lost its significance in the multivariate analysis; this might suggest that an event of under-perfusion by means of low blood pressure may not be the main contributor to the hepatic injury.

Strategies to decrease adverse events caused by transfusions, and specifically transfusion of platelets have been employed around the world, resulting in decreased incidence of adverse events. For example, it has been found that transfusion-related adverse events such as TRALI are associated with plasma-containing products, and are more prevalent with female donors, that contain a greater amount of antibodies. Use of blood products from male-only and naive donors has significantly decreased the incidence of TRALI.[24,25] Other strategies include using platelet-additive solutions in order to decrease the volume of plasma transfused with platelets, and avoiding prolonged storage time of products.[26]

6 | LIMITATIONS

This is a retrospective observational study and as such, the data collected from the PDR may be incomplete. However, most of the relevant data were collected (data not shown). Due to the retrospective nature of our study, no specific clotting factors were taken for specific evaluation of liver function and we had to identify hepatic injury based on elevation of ALT and AST. In addition, as per our unit's protocol, all Fontan patients are initially treated with unfractionated heparin followed by warfarin so coagulation tests are not indicative of hepatic injury either. Another limitation is the relatively small sample size. This may lead to some data loss as we selected only 4/16 options for blood products transfusions due to the small size of the remaining options. The small sample may also intervene with the cause and effect relations of the factors we have chosen. PLT transfusion could in fact be a surrogate for another cause for the hepatic injury. We managed to overcome this limitation by calculating the different contribution of all other confounders, especially those who can be markers of low cardiac output and severity of illness leading to acute hepatic injury. In addition, as described above, most factors that are associated with more severe clinical states were found insignificant in our multivariate regressions.

7 | CONCLUSIONS

There is a clear relationship between postoperative PLT transfusion and the development of acute hepatic injury in pediatric patients undergoing the Fontan procedure. This relationship demonstrate a dose-response pattern. Our results may call for a more judicious use of platelet transfusions in Fontan patients, and possibly other children undergoing cardiac surgery, as has been recommended for different reasons during the last few years. To conclude, we would like to suggest the term TRAHI, transfusion-related acute hepatic injury, in Fontan patients. Further larger prospective randomized controlled trials regarding TRAHI and its relationship with platelets specifically are warranted to elucidate the causality and mechanism of this phenomenon.

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CONFLICT OF INTEREST

The authors declare that they do not have any conflicts of interest or ethical adherence regarding this manuscript and no financial support was obtained for its preparation.

AUTHORS CONTRIBUTIONS

All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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