

ORIGINAL RESEARCH

Transfusion Medicine

TRANSFUSION

Impact of platelet characteristics on post-transfusion count response in critically ill children on Extracorporeal Membrane Oxygenation: A secondary analysis of the ECSTATIC trial

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Abstract

Background: Children supported by extracorporeal membrane oxygenation (ECMO) frequently receive platelet transfusions. However, little is known about how characteristics of platelet products affect transfusion effectiveness in ECMO patients. Our objective was to evaluate whether platelet product characteristics were associated with platelet count increment.

Abbreviations: aOR, adjusted odds ratio; CI, confidence interval; ECMO, extracorporeal membrane oxygenation; ECPR, extracorporeal cardiopulmonary resuscitation; GLMM, generalized linear mixed model; ICC, intraclass correlation coefficient; ICU, intensive care unit; IQR, interquartile range; OR, odds ratio; PELOD-2, Pediatric Logistic Organ Dysfunction-2; PR, pathogen-reduction; VA, veno-arterial; VV, veno-venous.

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Study Design and Methods: Secondary analysis of the ECSTATIC randomized controlled trial. Children <18 years on ECMO were randomized to two prophylactic platelet transfusion threshold strategies. In this secondary analysis, the exposure was platelet transfusions characterized by storage duration, ABO compatibility, platelet additive solution, irradiation, and pathogen reduction status. The primary outcome was the platelet count increment after transfusion, dichotomized as higher versus lower based on the median value. Regression models were used to identify associations between product characteristics and platelet count increment, adjusting for clustering.

Results: A total of 161 transfusions among 27 participants met inclusion criteria. The median change in platelet count was 19×10^9 cell/L (IQR 8; 36), and the median time from pre-transfusion to post-transfusion count was 5.9 h (IQR 4.8; 7.1). In univariable analysis, pathogen reduction was associated with a lower platelet count increment (odds ratio = 0.14, $p = .01$). In a multivariable model, higher pre-transfusion platelet count was independently associated with increased platelet count increment (adjusted odds ratio [aOR] = 1.03, $p = .049$), while pathogen reduction was independently associated with decreased count increment (aOR = 0.16, $p = .048$).

Conclusions: Among critically ill children on ECMO, pathogen-reduction and pre-transfusion platelet count may influence the effectiveness of transfusion. These findings support the need for prospective trials that incorporate product-level characteristics into transfusion strategies for pediatric ECMO patients.

KEYWORDS

blood group incompatibility, child, extracorporeal membrane oxygenation, platelet count, platelet transfusion, thrombocytopenia

1 | INTRODUCTION

Children supported by extracorporeal membrane oxygenation (ECMO) are at high risk of thrombocytopenia due to platelet activation,¹ shear force,² circuit hemocompatibility,³ and inflammation.⁴ As a result, they frequently receive prophylactic platelet transfusions, with prior studies indicating transfusion on approximately two-thirds of ECMO days.^{5,6} However, these transfusions are not without risk—associations with increased bleeding, thrombosis, and mortality have been documented,⁷ and data remain limited to guide optimal transfusion practices.

Beyond transfusion thresholds, the characteristics of the platelet products themselves may influence clinical efficacy. Platelets can vary in storage duration, ABO compatibility, and whether they have undergone pathogen-reduction (PR) techniques or are suspended in platelet additive solutions (PASS). They may also be derived from

apheresis or whole blood, and processing differences could impact their post-transfusion effectiveness. Observational data from large pediatric cohorts suggest that such characteristics—particularly longer storage duration, use of PR platelets, and ABO incompatibility—are associated with lower post-transfusion platelet increments and greater transfusion burden, though not with mortality or hospital stay.^{8–10} There are various mechanistic explanations for such observations. For example, platelet storage lesions, including loss of surface glycoproteins, reduced aggregation capacity, and microparticle release, may compromise platelet function and post-transfusion recovery.¹¹ PR or irradiation alter platelet membranes and nucleic acids, potentially also impacting platelet survival and increment.¹² In the context of ECMO, where transfusion needs are already high,^{6,13} reduced platelet increments may necessitate repeated transfusions, increasing donor exposure, risk of

platelet alloimmunization (primarily Human Leukocyte Antigen and, less commonly, Human Platelet Antigen alloimmunization), and overall clinical and resource burden.

Given the frequent use of platelet transfusions in children on ECMO and the potential implications of product variability, we conducted a secondary analysis of the ECSTATIC pilot randomized controlled trial to examine whether platelet product characteristics were associated with the magnitude of post-transfusion platelet count increase.

2 | STUDY DESIGN AND METHODS

We conducted a secondary analysis of the ECSTATIC multicenter pilot randomized controlled trial.¹⁴ ECMO provides extracorporeal support for severe respiratory and/or cardiac failure by draining blood from the patient, circulating it through a pump and an oxygenator for gas exchange, and reinfusing it into the body. Support can be delivered via veno-venous (VV) cannulation for isolated respiratory failure or veno-arterial (VA) cannulation when both cardiac and respiratory support are required. ECMO may also be initiated during active resuscitation, referred to as extracorporeal cardiopulmonary resuscitation (ECPR). In the parent trial, eligible patients were children 0 to <18 years old supported on ECMO who had no or minimal bleeding within 24 h of cannulation, defined according to the Bleeding Assessment Scale in Critically Ill Children. Exclusion criteria included more than minimal bleeding at the time of screening, ECMO support for more than 24 h at screening, post-conception age <37 weeks, and underlying oncologic diagnosis or hematopoietic cell transplant within the prior year. Participants were randomized 1:1 to either a higher platelet transfusion strategy, in which platelets were transfused when the platelet count was $<90 \times 10^9/L$, or a lower platelet transfusion strategy, in which platelets were transfused when the platelet count was $<50 \times 10^9/L$. Participants in both transfusion threshold arms received 10–20 mL/kg of platelets, with platelet counts measured within 12 h before transfusion and again 2–4 h after each transfusion. The study protocol did not mandate specific platelet product characteristics, but instead the product specificities were determined by local blood bank availability and practice.

Patient characteristics included age, sex, race, ethnicity, country, primary reason for ICU admission, severity at intensive care unit (ICU) admission as measured by the Pediatric Logistic Organ Dysfunction-2 (PELOD-2)

score,¹⁵ ECPR status, cannulation mode (VA vs. VV), time from cannulation to randomization, receipt and number of platelet transfusions prior to randomization, and treatment assignment (lower vs. higher threshold).

Platelet characteristics assessed included PR status, ABO compatibility, and storage duration (≤ 4 days vs. > 4 days), as well as product type (apheresis vs. whole blood-derived), use of PAS, and whether the unit was labeled by the blood bank as low-yield, defined as an apheresis-derived platelet unit containing fewer than the minimum standard of 3.0×10^{11} platelets per unit. ABO compatibility was categorized as ABO compatible versus ABO incompatible. ABO-incompatible transfusions were further classified as minor or major mismatch; because minor mismatches were infrequent, minor and major mismatches were combined as incompatible for the analysis. Additional variables included time from pre-transfusion platelet count to transfusion and from transfusion to post-transfusion platelet count.

The primary outcome for this analysis was the platelet count increment, that is, the change in platelet count from the pre- to post-transfusion measurement. Only transfusions that occurred during the study's intervention, outside of temporary protocol suspensions, and for which both a pre-transfusion and post-transfusion platelet count were recorded were included. Per protocol, a platelet transfusion was required within 12 h of a platelet count below the arm threshold, and a post-transfusion platelet count was required 2 to 4 h after the end of each platelet transfusion.

Platelet count increment was dichotomized as “higher” versus “lower” based on the median of the overall distribution.

Simple associations between predictors and platelet count increment category were tested using generalized linear mixed models (GLMMs)—specifically, logistic regression models with a fixed effect for the predictor and a random effect for the patient (to account for within-subject clustering). Based on these results, it was deemed important to also include random effects for site (to account for within-site clustering) in the univariable models. Several variables (e.g., V-A vs. V-V ECMO) exhibited such imbalance or missingness when summarized that they were not included in univariable models. Because the categorized platelet storage duration was frequently missing, univariable modeling was performed while omitting missing values and while categorizing them separately. Variables with $p < .2$ in the univariable GLMMs were entered into a multivariable GLMM to identify independent predictors of a higher platelet count increment.

Analyses were conducted using SAS version 9.4.

3 | RESULTS

3.1 | Population

A total of 161 transfusions among 27 participants met inclusion criteria. Twenty-seven (54%) of the 50 enrolled patients received at least one included transfusion. The 50 enrolled patients were from a total of nine ECMO centers, with eight centers enrolling at least one patient with an included transfusion and eight (mostly overlapping) centers enrolling at

least one patient without any included transfusion. Patient-level characteristics are presented in Table 1 for the overall trial cohort and stratified by whether participants received at least one included platelet transfusion in this secondary analysis. We retained both groups to allow comparison of patients who received platelet transfusions with those who did not. Of the 27 patients who received at least one included platelet transfusion, 15 (56%) were neonates and 12 (44%) were older infants or children, and 96% (26/27) were on V-A ECMO.

TABLE 1 Patient-level characteristics of the overall ECSTATIC trial cohort, stratified by whether participants received at least one included platelet transfusion in this secondary analysis.

	Any included platelet transfusion		Overall (N = 50)
	No (N = 23)	Yes (N = 27)	
Age (years)	0.4 [0.0;6.5]	0.0 [0.0;0.4]	0.2 [0.0;1.7]
Age ≤28 days	8/23 (35%)	15/27 (56%)	23/50 (46%)
Male	7/23 (30%)	15/27 (56%)	22/50 (44%)
Race			
Black or African American	5/17 (29%)	6/22 (27%)	11/39 (28%)
White	11/17 (65%)	16/22 (73%)	27/39 (69%)
Multiracial	1/17 (6%)	0/22 (0%)	1/39 (3%)
Ethnicity			
Hispanic or Latino	8/22 (36%)	3/24 (13%)	11/46 (24%)
Not Hispanic or Latino	14/22 (64%)	21/24 (88%)	35/46 (76%)
Country			
United States of America	23/23 (100%)	24/27 (89%)	47/50 (94%)
Israel	0/23 (0%)	3/27 (11%)	3/50 (6%)
Primary reason for ICU admission			
Acute respiratory failure	14/23 (61%)	12/27 (44%)	26/50 (52%)
Acute cardiac failure	8/23 (35%)	12/27 (44%)	20/50 (40%)
Altered mental status	1/23 (4%)	0/27 (0%)	1/50 (2%)
Sepsis/septic shock	0/23 (0%)	1/27 (4%)	1/50 (2%)
Other surgery	0/23 (0%)	2/27 (7%)	2/50 (4%)
PELOD-2 score on Study Day 1	7.0 [6.0;10.0]	9.0 [6.0;12.0]	8.0 [6.0;11.0]
ECPR	2/23 (9%)	1/27 (4%)	3/50 (6%)
Veno-arterial (VA) cannulation	18/23 (78%)	26/27 (96%)	44/50 (88%)
Time from cannulation to randomization (hours)	17.0 [8.3;23.0]	18.2 [12.5;22.5]	18.1 [10.9;22.8]
Received at least one platelet transfusion prior to randomization	4/23 (17%)	11/27 (41%)	15/50 (30%)
Number of platelet transfusions prior to randomization	1.0 [1.0;1.5]	1.0 [1.0;1.0]	1.0 [1.0;1.0]
Treatment assignment			
Lower threshold	14/23 (61%)	11/27 (41%)	25/50 (50%)
Higher threshold	9/23 (39%)	16/27 (59%)	25/50 (50%)

Note: Results are presented as median and interquartile range, or number and column percentage, as appropriate. The 50 patients were enrolled at a total of nine ECMO centers, with eight centers enrolling at least 1 patient with an included transfusion and a slightly different set of eight centers enrolling at least 1 patient without any included transfusion.

Abbreviations: ECMO, extracorporeal membrane oxygenation; ECPR, extracorporeal membrane oxygen cardiopulmonary resuscitation; PELOD-2, Pediatric Logistic Organ Dysfunction 2.

3.2 | Platelet characteristics

Characteristics of the transfusion are summarized in Table 2 for the 161 included transfusions. The median platelet count prior to transfusion was 68×10^9 cell/L (interquartile range, IQR 46;83), with a median of 1.5 h (IQR 1.1; 2.0) between pre-transfusion count and platelet

transfusion initiation. The median time from pre-transfusion platelet count to post-transfusion platelet count was 5.9 h (IQR 4.8; 7.1).

The median dose was 10.7 mL/kg (IQR 10.0;16.3). Among included transfusions, 74% (119/161) were PR, 62% (100/161) were ABO compatible, 2% (4/161) had minor incompatibility, 35% (57/161) had major

TABLE 2 Transfusion-level characteristics by platelet count increment, and univariable logistic regression models (with random patient and site intercepts) for odds of higher platelet count increment.

	Platelet count increment		Overall (N = 161)	Odds ratio (95% CI)	p-Value
	Lower (N = 84)	Higher (N = 77)			
Treatment assignment					.332
Lower threshold	25/84 (30%)	38/77 (49%)	63/161 (39%)	Reference	
Higher threshold	59/84 (70%)	39/77 (51%)	98/161 (61%)	1.82 (0.54;6.13)	
Age ≤ 28 days	37/84 (44%)	36/77 (47%)	73/161 (45%)	1.85 (0.55;6.24)	.318
Veno-arterial cannulation ^a	84/84 (100%)	73/77 (95%)	157/161 (98%)	N/A	N/A
Time from cannulation to randomization (h)	17.0 [11.5;20.1]	18.0 [17.0;22.4]	18.0 [16.4;20.7]	1.02 (0.93;1.13)	.638
Pre-transfusion platelet count	72.5[46.0;84.0]	55.0 [43.0;82.0]	68.0 [46.0;83.0]	1.03 (1.00;1.05)	.078
Pathogen reduced	77/84 (92%)	42/77 (55%)	119/161 (74%)	0.14 (0.03;0.64)	.011
ABO compatibility ^a					
Compatible	43/84 (51%)	57/77 (74%)	100/161 (62%)	Reference	.851
Incompatibility	41/84 (49%)	20/77 (26%)	61/161 (38%)	0.91 (0.32;2.57)	
Storage duration ^b					.081
≤ 4 days	20/84 (24%)	9/77 (12%)	29/161 (18%)	0.48 (0.14;1.73)	
> 4 days	12/84 (14%)	12/77 (16%)	24/161 (15%)	Reference	
Unknown	52/84 (62%)	56/77 (73%)	108/161 (67%)	6.34 (0.57;70.68)	
Apheresis platelet ^c	82/84 (98%)	76/77 (99%)	158/161 (98%)	N/A	N/A
Platelet storage solution ^c					N/A
PAS	73/84 (87%)	39/77 (51%)	112/161 (70%)	N/A	
Non-PAS	2/84 (2%)	2/77 (3%)	4/161 (2%)	N/A	
Unknown	9/84 (11%)	36/77 (47%)	45/161 (28%)	N/A	
Irradiated	7/84 (8%)	35/77 (45%)	42/161 (26%)	7.08 (1.57;31.96)	.011
Low yield platelet unit ^c	2/84 (2%)	3/77 (4%)	5/161 (3%)	N/A	N/A
Unknown platelet yield	10/84 (12%)	36/77 (47%)	46/161 (29%)		
Time from pre-transfusion to post-transfusion count (h)	5.8 [4.8;6.4]	6.0 [4.8;7.7]	5.9 [4.8;7.1]	1.11 (0.89;1.38)	.370
Time from pre-transfusion to transfusion initiation (h)	1.4 [1.1;1.9]	1.7 [1.2;2.2]	1.5 [1.1;2.0]	1.10 (0.77;1.57)	.597
Platelet dose (mL/kg)	10.0 [10.0;14.6]	15.0 [10.3;19.8]	10.7 [10.0;16.3]	1.13 (0.99;1.28)	.072
Unknown total platelet count in platelet unit ^a	84/84 (100%)	77/77 (100%)	161/161 (100%)		

Note: Transfusion-level summaries are presented as median and interquartile range, or number and column percentage, as appropriate.

Abbreviations: CI, confidence interval; ECMO, extracorporeal membrane oxygenation; PAS, platelet additive solution.

^aThis variable was dichotomized for the univariable modeling but was originally summarized with three levels.

^bp-value is .287 when unknown category is removed.

^cUnivariable modeling was not conducted due to excessive missingness or extreme imbalance in the variable.

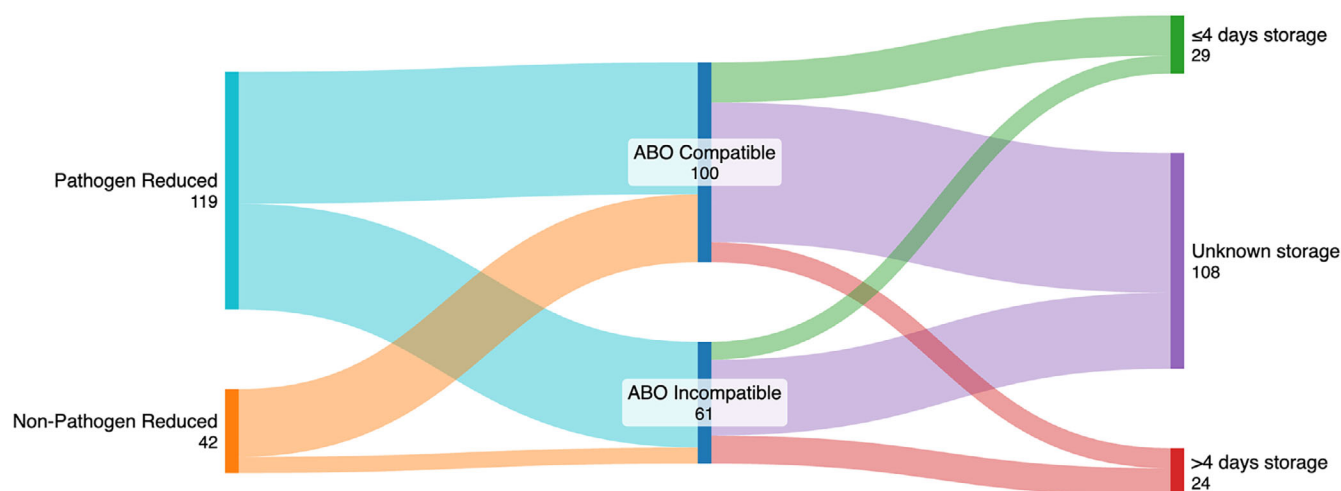


FIGURE 1 Sankey diagram showing cross-classification of platelet units across three product attributes: pathogen reduction (yes vs. no), ABO compatibility (compatible vs. incompatible), and storage duration (≤4 days, >4 days, unknown).

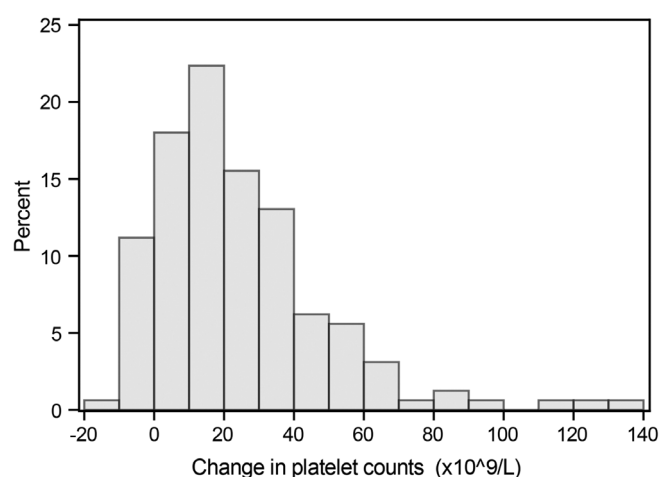


FIGURE 2 Histogram of post-transfusion platelet count increments (change in platelet count, ×10⁹/L) following 161 transfusions in ECMO patients. The median increment was 19 × 10⁹/L (IQR 8–36).

incompatibility, 98% (158/161) were apheresis-derived, 70% (112/161) contained PAS, and 26% (42/161) were irradiated. While 67% (108/161) were stored for an unknown duration, 53 included transfusions had known storage duration, of which 45% (24/53) were stored more than 4 days. Figure 1 represents the cross-classification of the transfusions including ABO compatibility, PR status, and storage duration.

3.3 | Platelet count increment

The lower platelet count increment group (increase of 19 × 10⁹/L or less) had a median increment of

8.0 × 10⁹/L (IQR 1.5; 13.0), whereas the higher platelet count increment group (increase of 20 × 10⁹/L or more) had a median increment of 36.0 × 10⁹/L (IQR 26.0; 50.0). The median platelet increment was 19 × 10⁹/L (IQR 8–36). Three transfusions were associated with a platelet count change greater than 100 × 10⁹/L (Figure 2). There were 52% (84/161) transfusions categorized as lower platelet increment (i.e., ≤19 × 10⁹ cell/L) and 48% (77/161) as higher (i.e., ≥20 × 10⁹ cell/L).

Factors associated with platelet count increment are shown in Table 2. In univariable analysis (adjusted for patient and site with random intercepts), PR was significantly associated with a lower platelet count increment (odds ratio [OR] 0.14, 95% confidence interval [CI] 0.03; 0.64, $p = .011$), while irradiation was significantly associated with a higher platelet count increment (OR 7.08, 95% CI 1.57; 31.96, $p = .011$). As all non-PR platelets were irradiated and all PR platelets were not irradiated, these ORs were reciprocal. In the univariable models, the intraclass correlation coefficient (ICC) for site was relatively large. Other than for storage duration when excluding unknown values (site ICC = 0), the ICC for site in these models ranged from 0.15 to 0.35 on the latent scale, indicating that a substantial proportion of the variability in post-transfusion platelet increments was explained at the site level. This suggests that inter-site differences in transfusion characteristics and practices may have influenced the observed associations. Furthermore, pre-transfusion platelet count was associated with platelet count increment in the adjusted analysis. Because the parent ECSTATIC trial assigned patients to higher and lower platelet transfusion strategies, we also evaluated whether treatment assignment itself was associated with higher versus lower platelet count increment. As shown

TABLE 3 Multivariable logistic regression mixed model for odds of higher platelet count increment.

	Higher platelet count increment	
	Adjusted odds ratio (95% CI)	p-Value
Last pre-transfusion platelet count	1.03 (1.00;1.07)	.049
Storage duration		.118
≤4 days	0.42 (0.11;1.63)	
>4 days	Reference	
Unknown	4.78 (0.36;62.78)	
Pathogen-reduced		.048
No	Reference	
Yes	0.16 (0.03;0.99)	
Platelet dose (mL/kg)	1.16 (0.97;1.38)	.102

Note: Results are based on a multivariable model with random effects for patient and site, adjusting for each of the predictors in this table.

in Table 2, assigned treatment arm was not significantly associated with increment group and therefore was not entered into the multivariable model. Platelet count increment was also examined according to original treatment assignment. Among transfusions with a lower platelet count increment, 25/84 (30%) occurred in the lower platelet transfusion strategy arm and 59/84 (70%) in the higher platelet transfusion strategy arm. Among transfusions with a higher platelet count increment, 38/77 (49%) occurred in the lower platelet transfusion strategy arm and 39/77 (51%) in the higher platelet transfusion strategy arm. In univariable analysis, treatment assignment was not significantly associated with the odds of a higher platelet count increment (OR 1.82, 95% CI 0.54; 6.13; $p = .332$).

Given the redundancy in the PR and irradiated variables, we omitted the irradiated variable in the multivariable model. Multivariable analysis identified higher pre-transfusion platelet count (adjusted odds ratio [aOR] 1.03, 95% CI 1.00; 1.07, $p = .049$) as an independent predictor of higher platelet count increment, while PR (aOR 0.16, 95% CI 0.03; 0.99, $p = .048$) was significantly associated with lower platelet count increment (Table 3 and Figure 3).

4 | DISCUSSION

In this secondary analysis of the multicenter ECSTATIC pilot trial in children supported by ECMO, we found that higher pre-transfusion platelet count was independently

associated with greater post-transfusion platelet count increments. In multivariable analysis, PR was independently associated with lower platelet count increment, consistent with the univariable result. Importantly, site-level clustering accounted for a substantial proportion of variability, suggesting inter-site variation in transfusion practices and product availability may have influenced our findings.

The magnitude of platelet count increment following transfusion in children supported by ECMO is consistently lower than that observed in other critically ill or hematology/oncology populations. In our study, the median platelet count increment was 19×10^9 cell/L (IQR 8; 36). In an observational study of 90 children on ECMO in 13 countries, the median platelet count increment corrected for a 10 mL/kg transfusion was higher at 34×10^9 /L (IQR 10–74 $\times 10^9$ /L).¹⁶ Similarly, in a general PICU population, Nellis et al. reported substantially higher increments, with a median platelet count increase of 48×10^9 /L for major bleeding, 42×10^9 /L for prophylactic transfusions, and 38×10^9 /L for minor bleeding, following a 10 mL/kg dose.¹⁷ Because pathogen-reduced platelets were uncommon in that cohort (5%), whereas they were much more frequent in our study (74%), direct comparison between the two studies is more challenging. However, this may also reflect active consumption of platelets within the circuit during the transfusion.

The association between PR platelets and post-transfusion platelet count increment is complex and context-dependent. PR involves treating blood products with agents such as amotosalen or riboflavin combined with ultraviolet light, or with photochemical methods like methylene blue plus light, to inactivate pathogens by damaging their nucleic acids and preventing replication. These technologies have demonstrated efficacy against a broad spectrum of viruses, bacteria, and parasites, including both enveloped and non-enveloped viruses.¹⁸ However, some biomolecular changes to platelets may occur.¹⁹ Clinically, PR platelet products are consistently associated with lower post-transfusion platelet count increments compared to standard, untreated platelets. Multiple randomized controlled trials and meta-analyses have demonstrated that both 1- and 24-h corrected count increments are significantly reduced following transfusion of PR platelets.^{20–22} In the present analysis, PR platelet transfusion was independently associated with a lower platelet count increment in pediatric ECMO patients, in both univariable and multivariable analyses. Therefore, larger prospective observational studies are required to evaluate the safety and efficacy of PR platelets.

In our study, a higher pre-transfusion platelet count was independently associated with a greater increment.

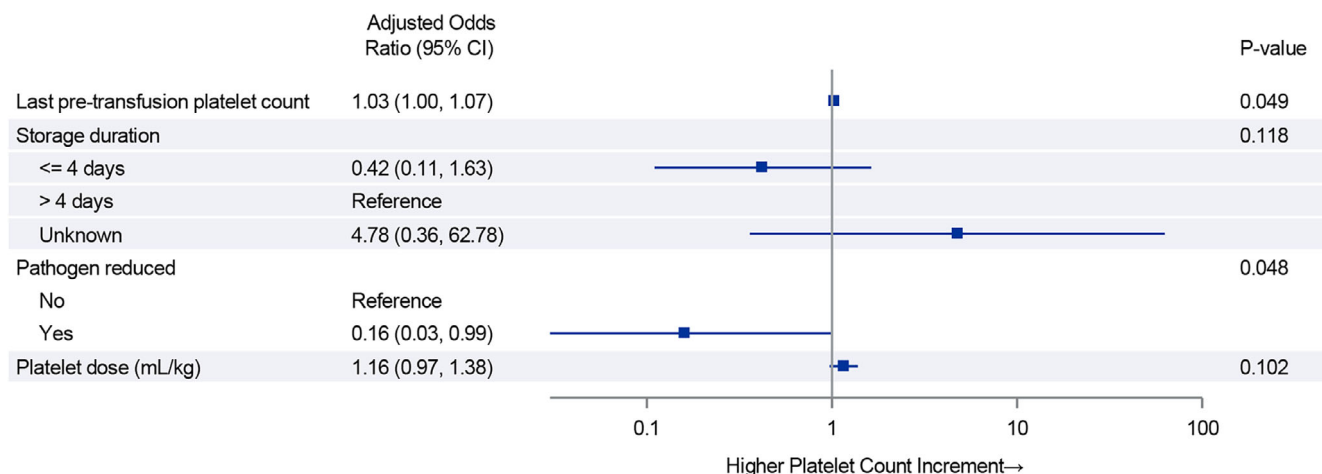


FIGURE 3 Forest plot of adjusted odds ratios with 95% confidence intervals from the multivariable mixed-effects logistic regression (random intercepts for patient and site) for the odds of a higher platelet increment ($\geq 20 \times 10^9/L$). Higher pre-transfusion platelet count was independently associated with higher odds of higher platelet increment, while pathogen reduction (PR) was significantly associated with lower platelet count increment.

One plausible explanation is that patients with higher baseline counts may have less ongoing consumptive coagulopathy, resulting in reduced immediate post-transfusion platelet consumption and a more robust increment. This relationship is consistent with observations in other settings, where patients with severe consumptive states, such as sepsis, active bleeding, or disseminated intravascular coagulation, often exhibit lower increments due to rapid platelet consumption or destruction.²³ An alternative explanation is that a lower pre-transfusion platelet count may reflect more prolonged thrombocytopenia, with greater cumulative exposure to platelet transfusions and potential alloimmunization. Similar patterns have been observed in oncology patients, where alloantibody development contributes to reduced post-transfusion platelet increments.²⁴

This study represents one of the first exploring the relationship between platelet transfusion characteristics and post-transfusion platelet count in pediatric ECMO patients. This relationship is important to understand given the volume of platelet transfusions that this population consumes. However, this analysis has several important limitations. The small sample size and the large proportion of transfusions with missing storage duration limited statistical power and precision. The patients included in this secondary analysis were predominantly neonates. However, this age distribution is consistent with the epidemiology of pediatric ECMO.²⁵ We therefore interpret our findings in the context of a young cohort that remains broadly representative of the real-world pediatric ECMO population. Because more included transfusions came from the higher platelet transfusion strategy arm, treatment assignment may have influenced the overall distribution of transfusions included in this

secondary analysis, although assigned treatment arm was not significantly associated with whether platelet count increment fell into the higher versus lower increment group. Although patients who received at least one included platelet transfusion had a higher PELOD-2 score on study day 1, we were unable to meaningfully adjust for severity of illness at the time of each transfusion. Daily PELOD-2 scores reflect the worst values observed over a 24-h period, mixing pre- and post-transfusion physiology, with some components potentially influenced by the transfusion itself. As a result, we could not assess the relationship between severity of illness and platelet count increment at the time of each individual transfusion. We acknowledge that the use of absolute platelet count increment, rather than corrected count increment, may limit direct comparability with some prior studies. However, platelet dose in this trial was protocolized within a narrow range, detailed platelet content of individual units was unavailable, and 1-h post-transfusion platelet counts were not routinely collected because the trial did not mandate laboratory measurements beyond those considered clinically warranted at each site. Although regression models adjusted for site using a random effect, residual confounding related to site-specific blood bank practices, including preferential use of irradiated or pathogen-reduced platelets in certain patient subgroups, may still have influenced the observed associations. Furthermore, platelet transfusion dose may have reflected site-specific practice and consideration of extracorporeal circuit characteristics, which were not fully captured in the dataset. Because the association between pre-transfusion platelet count and post-transfusion platelet count increment was derived from an

adjusted regression model in a small secondary analysis, residual confounding may remain despite adjustment for patient and site. This finding should therefore be interpreted cautiously and considered hypothesis-generating. Product characteristics were unevenly represented, with very few whole blood-derived, low-yield, or non-PAS units, preventing robust evaluation of these factors. Because irradiated and pathogen-reduced platelets were mutually exclusive in this cohort, we were unable to separate the independent effects of these two product characteristics. This likely reflects site-specific blood bank practice, precludes mechanistic interpretation of the observed association with irradiation, and limits causal interpretation of the observed associations. These findings should therefore be considered hypothesis-generating. We did not collect center-specific blood bank practices regarding platelet component manipulation or modification, including strategies used to reduce the volume of incompatible plasma in ABO-incompatible transfusions. As a result, we were unable to assess whether such practices may have influenced post-transfusion platelet increments. Clinical sites were unable to obtain information on the platelet content of individual units from blood banks, further constraining interpretation. At the patient level, we lacked patient-specific factors on several clinically important determinants of platelet transfusion response, including splenomegaly, concurrent renal replacement therapy, disseminated intravascular coagulation, and other markers of platelet consumption or sequestration. In addition, contemporaneous data on severity of illness, lactate, vasoactive-inotrope score, and anticoagulation intensity were not available at the time of each transfusion, as these variables were only collected daily in the parent trial. This limited our ability to account for important clinical confounders that likely influence platelet increments. Although platelet transfusion dose was incorporated into the analysis, dosing practices were not fully standardized beyond the 10–20 mL/kg protocol range. Exact doses may have varied across sites according to local recommendations and may also have been individualized based on the clinical situation, which could have influenced post-transfusion platelet increments. In addition, higher doses may have reflected greater clinical severity or concern for bleeding risk, factors that were not fully captured in the dataset. In addition, bleeding and clotting events were too infrequent to allow meaningful statistical evaluation. Finally, substantial between-site variability, evident in both univariable and multivariable models, suggests the presence of strong confounders related to local transfusion practices and patient selection.

In conclusion, in this secondary analysis of the ECSTATIC trial, we found that higher pre-transfusion platelet counts were independently associated with greater post-transfusion platelet count increments in

critically ill children supported by ECMO, while PR was independently associated with lower platelet count increments. The overall platelet increments observed were modest compared with general PICU populations, highlighting the attenuated transfusion response in ECMO. Taken together, our results suggest that both product characteristics and patient context contribute to transfusion effectiveness, and that considerable inter-site variability may also influence outcomes. Prospective, adequately powered studies that incorporate product-level variables and account for patient- and site-level factors are needed to optimize platelet transfusion strategies for children on ECMO, with the goal of improving both transfusion efficacy and patient outcomes. These future studies should also evaluate clinical endpoints such as bleeding, thrombosis, and circuit complications in relation to platelet characteristics.

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CONFLICT OF INTEREST STATEMENT

The authors have disclosed no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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