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## Effect of Platelet Storage Duration on Clinical Outcomes and Incremental Platelet Change in Critically Ill Children

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### Abstract

**Background:** The safety of platelet concentrates with longer storage duration has been questioned due to biochemical and functional changes that occur during blood collection and storage. Some studies have suggested that transfusion efficacy is decreased and immune system dysfunction is worsened with increased storage age. We sought to describe the effect of platelet storage age on laboratory and clinical outcomes in critically ill children receiving platelet transfusions.

**Study Design and Methods:** We performed a secondary analysis of a prospective, observational point-prevalence study. Children (3 days to 16 years of age) from 82 pediatric

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intensive care units in 16 countries were enrolled if they received a platelet transfusion during one of the predefined screening weeks. Outcomes (including platelet count increments, organ dysfunction and transfusion reactions) were evaluated by platelet storage age.

**Results:** Data from 497 patients were analyzed. The age of the platelet transfusions ranged from 1–7 days but the majority were 4 (24%) or 5 (36%) days of age. Nearly two-thirds of platelet concentrates were transfused to prevent bleeding. The indication for transfusion did not differ between storage age groups ( $p=0.610$ ). After adjusting for patient and product variables, there was no association between storage age and incremental change in total platelet count or organ dysfunction scoring. A significant association between fresher storage age and febrile transfusion reactions ( $p=0.002$ ) was observed.

**Conclusion:** The results in a large, diverse cohort of critically ill children raise questions about the impact of storage age on transfusion and clinical outcomes which require further prospective evaluation.

### Keywords

platelet transfusion; storage age; critical illness; children

## INTRODUCTION

Traditionally, platelet concentrates are stored at 20–24°C for up to five to seven days. [1–3] Over time, as the stored platelets age, there are changes in their functional integrity, in their ability to aggregate, activate, and in their effect on immune and endothelial function and microvesiculation. [4, 5] In addition, in vitro studies have shown that older platelet concentrates contain higher levels of inflammatory cytokines, such as IL-8. [6] Platelets of older storage age have been independently associated with adverse outcomes in certain adult cohorts including poorer response to platelet transfusions, [7] increased transfusion reactions, [8] and adverse inflammatory events. [9]

Critically ill children are at particular risk of requiring platelet transfusions because of underlying organ dysfunction, including suppression of bone marrow and/or hepatic insufficiency, administration of medications that may suppress functional ability to clot, platelet consumption due to bleeding or microangiopathy, as well as frequent invasive procedures. Platelet transfusions have been independently associated with increased mortality in this patient population. [10] However, there has been limited work to explore the clinical consequences of transfusing platelet concentrates of older storage age in children.

In this study, we sought to describe the effect of platelet storage age on platelet count increments, organ dysfunction and transfusion reactions in critically ill children requiring platelet transfusions.

## MATERIALS AND METHODS

This study is an *a priori* secondary analysis of a prospective, point-prevalence observational study examining the epidemiology of platelet transfusions in critically ill children (“Point Prevalence Study of Platelet Transfusions in Critically Ill Children,” otherwise known as

P<sup>3</sup>T). The full methodology has been previously published. [10] The study was approved by the Institutional Review Board at Weill Cornell Medicine, as well as by all participating sites. Eighty-two sites from sixteen countries contributed data. Each site was assigned six random weeks (between September 2016 to April 2017) during which they screened subjects for eligibility and enrollment. A child was enrolled if he/she was between 3 days and 16 years of age and received a platelet transfusion prescribed by the pediatric intensive care team during one of the screening days. Patients were excluded if life expectancy was considered to be less than 24 hours, gestational age of the patient was less than 37 weeks at the time of admission, or the patient had already been enrolled in a previous screening week. In total, 16,934 patients were screened and 559 eligible patients receiving platelet transfusions were enrolled. Data for the P<sup>3</sup>T study were recorded in the Research Electronic Data Capture (REDCap<sup>TM</sup>) web data application and extracted for this secondary analysis.

Data regarding the age of the platelet concentrate were collected from the blood bank for the platelet transfusion administered at time of enrollment but did not include data from every platelet transfusion received during the subject's PICU stay. If a patient received more than one platelet transfusion on the day of enrollment, the data regarding the platelet concentrate only pertained to the first transfusion. For patients who received multiple platelet transfusions in the same day or pooled platelets, their results were only included in the analysis if the age of units was the same. The storage age was analyzed both as a categorical variable in three groups: 1–2 days, 3–4 days and 5–7 days of age, as well as a continuous variable. ABO incompatibility was defined as follows. A transfusion was considered to have major incompatibility if platelets from A, B or AB donors were given to O recipients, or from AB donors given to A or B recipients. Transfusions with bidirectional incompatibility (A donor to B recipient or B donor to A recipient) were included in the major incompatibility group. Minor incompatibility was defined as platelets from O donors to A, B or AB recipients, or from A or B donors to AB recipients.[11]

Data collected included patient demographics, reason for admission, any prior platelet transfusions during the current ICU admission, validated measures of organ dysfunction (PELOD-2 scoring),[12] information regarding the platelet product (including the storage age of the platelet concentrate), and any adverse reactions that occurred during the transfusion. Organ dysfunction was assessed by the change in PELOD-2 scoring 24 hours before and 24 hours following the platelet transfusion of interest. The adverse reactions were documented via passive reporting and included fever of  $\geq 38.5^{\circ}\text{C}$ , hypotension, bronchospasm, urticaria, and hemolytic reactions. The total platelet count before and after transfusion was recorded if obtained as standard of care. The timing of the assays was determined by the medical team. The pre-transfusion platelet count was measured within 36 hours of start of the transfusion and recorded according to the following time intervals: < 1 hour, 1–2 hours, 2–6 hours, 6–12 hours, 12–24 hours and 24–36 hours. The timing of the post-transfusion platelet count was recorded in relation to the completion of the transfusion of interest with the same time intervals as listed above. The corrected count increment (CCI) was calculated for those patients in whom a post-transfusion platelet count was obtained less than one hour after the completion of the transfusion.

Demographic and clinical characteristics were described as counts and percentages or median and interquartile range (IQR) as appropriate. Categorical variables were compared using either Chi-squared or Fisher's exact test, depending on the size of the sample. Continuous variables were compared using Kruskal Wallis test. Two-sided p values below 0.05 were considered significant and there was no adjustment made for multiple comparisons.

Multivariable linear and logistic models were developed to assess the association between storage duration (as a continuous variable) and clinical outcomes (incremental platelet count change, change in PELOD-2 score and transfusion reactions). Variables were considered potential predictors if they were associated with the outcome in univariate analysis ( $p < 0.10$ ). The final model was selected using a bidirectional step-wise selection on the potential predictors with a significance criterion of  $p < 0.05$  to enter in the model and  $p > 0.1$  to be removed. All analyses were conducted using SPSS version 25 (IBM Corp, Armonk, NY).

## RESULTS

### Patient Characteristics

Four hundred and ninety-seven enrolled patients had complete storage age data and were included in the analysis. The patients were treated in the following locations: 349/497 (70%) in North America, 76/497 (15%) in Europe, 33/497 (7%) in Oceania, 26/497 (5%) in Asia, and 13/497 (3%) in the Middle East. Fifty-six percent (277/497) were male with a median (IQR) age of 3.9 (0.5–10.6) years. The most common admitting diagnoses were respiratory insufficiency/failure (199/497, 40%), septic shock (109/497, 22%), and cardiac bypass surgery (65/497, 13%). Nearly two-thirds of platelet concentrates were transfused to prevent bleeding (prophylaxis, 321/497, 65%) as opposed to treat bleeding (therapeutic, 176/497, 35%).

### Storage Age and Patient Characteristics

Figure 1 describes the storage ages of the platelet concentrates transfused. The majority were either 4 (117/497, 24%) or 5 (179/497, 36%) days of age. Table 1 describes the demographics and clinical characteristics of the patients by storage age of platelets received at time of enrollment. Patients who received the oldest category of platelet transfusions had been admitted for a longer period of time prior to enrollment as compared to patients who received fresher platelet transfusions ( $p = 0.04$ ). In addition, patients who received the oldest category of platelet transfusions were more likely to have received a platelet transfusion prior to enrollment as compared to the other groups ( $p = 0.002$ ) but for those who had received a prior platelet transfusion, there was no difference in the doses received between the three groups ( $p = 0.41$ ). Those patients with septic shock as an admitting diagnosis were more likely to receive fresher platelets ( $p < 0.01$ ). The indication for transfusion did not differ between storage age groups ( $p = 0.61$ ).

### Transfusion Product Characteristics

Table 2 describes the characteristics of the platelet concentrates grouped by storage age. There were differences in the source of platelets (apheresis versus whole-blood derived)

( $p<0.001$ ), leukoreduction ( $p=0.048$ ), volume reduction ( $p<0.001$ ), pathogen-inactivation ( $p=0.001$ ) and ABO compatibility ( $p=0.016$ ) between the three storage age groups. The median (IQR) dose of platelet concentrates transfused was 9 (5–13) mL/kg and did not differ across storage age groups ( $p=0.73$ ).

### Unadjusted Clinical Outcomes

The median (IQR) incremental change in total platelet count (corrected for every 10mL/kg of platelet concentrate transfused) was 27 (8–67)  $\times 10^9$  cells/L. This value did not differ between platelet storage age groups broken down for indication (see Figure 2). The patients had post-transfusion platelet counts assayed in the following time intervals: 41/497 (8%) in less than one hour following transfusion completion, 77/497 (16%) in 1–2 hours, 166/497 (33%) in 2–6 hours, 121/497 (24%) in 6–12 hours, 66/497 (13%) in 12–24 hours, and 11/497 (2%) in 24–36 hours. Three percent of patients (15/497) did not have a post-transfusion platelet count checked within 36 hours of the transfusion. All patients with post-transfusion platelet counts were included in the analysis. In the subset of patients who had post-transfusion platelet counts assayed less than one hour following completion of the transfusion, the median (IQR) CCI was 24 (9–88)  $\times 10^9$  cells/L. The CCI did not differ between storage age groups ( $p=0.60$ ).

The patients had significant organ dysfunction prior to platelet transfusion as represented by a median (IQR) PELOD-2 score of 7 (4–9). However, they did not have significant worsening of their organ dysfunction 24 hours following the transfusion, as represented by a median (IQR) change in PELOD-2 score of 0 (–2 – 1). The change in organ dysfunction scoring was not significantly different between the storage age groups ( $p=0.19$ ). These results did not change when analysis was repeated for each indication ( $p=0.63$  for therapeutic transfusions and  $p=0.37$  for prophylactic transfusions).

Table 3 demonstrates the rates of transfusion reactions for each storage group. On direct comparison, although rates were relatively low overall, there were increased febrile reactions observed in patients receiving fresher platelet concentrates ( $p=0.01$ ). There were no hemolytic reactions observed.

### Adjusted Clinical Outcomes

Given the differences in patient characteristics and transfusion characteristics between the storage age groups, multivariable linear and logistic regression models were developed to assess the association between storage duration (as a continuous variable) and clinical outcomes (incremental platelet count change, change in PELOD-2 score and transfusion reactions). After adjusting for days since PICU admission, platelet transfusions prior to enrollment, compatibility, source of platelets (apheresis versus whole-blood derived), leukoreduction, volume-reduction, and pathogen-inactivation, there was no statistically significant association between storage age and incremental change in total platelet count ( $p=0.23$ ) or organ dysfunction scoring ( $p=0.33$ ). However, there was a significant association between fresher storage age and febrile transfusion reactions ( $p=0.002$ ), as shown in Table 4.

# DISCUSSION

This study reports on an exploratory analysis of the impact of platelet concentrate storage age and clinical outcomes in critically ill children. Patients included represent a diverse cohort based on both location and diagnoses. Though the majority of platelet concentrates were 4 or 5 days old, the storage age of the platelets was widely distributed. There were no differences in the response to platelet transfusions (represented by incremental change in total platelet count) or organ dysfunction based on the storage age of the platelet concentrate. However, the fresher platelet concentrates appeared to be independently associated with more febrile transfusion reactions. These results should be interpreted as hypothesis generating.

Many biochemical and functional changes occur in platelet concentrates over time. Because of the interactions between platelets and their storage containers and conditions, platelet lysis and activation occur with subsequent elevation in lactate dehydrogenase, von Willebrand factor and serotonin. [13–15] Glucose is depleted, lactate accumulates and acidification occurs within the platelet concentrate media over time. [16] In addition, the surface proteins expressed on stored platelets change over time affecting their thrombin sensitivity and they become more sensitized to nitric oxide which impairs their ability to aggregate. [17–19] Counter to the reduced aggregation with increased storage time, the accumulation of platelet microparticles amplifies thrombin formation. [20] All of these changes may impact the clinical outcomes of patients receiving platelet transfusions of differing storage age.

There is a much broader literature assessing the impact of storage age of red cells on clinical outcomes. In view of these concerns highlighted over many years, a number of large pragmatic randomized trials have been completed and published which include ABLE, [21] RECESS, [22] INFORM, [23] TRANSFUSE, [24] and more recently ABC-PICU. [25] No such comparable randomized trials exist for platelet storage age. However, it has been argued that a range of clinical, methodological and statistical problems do affect the analysis and interpretation of trial results for red cell storage age, and indeed the levels of reassurance for clinicians may not be that strong. [26]

A number of studies have identified variable associations between the storage age of platelet concentrates with laboratory parameters and inflammatory adverse events [7–9]. In adults, a cohort study of 381 critically ill trauma patients, reported that exposure to older apheresis platelet concentrates did not impact mortality or rates of acute respiratory distress syndrome, renal or liver failure, but was independently associated with higher rates of sepsis. [27] In contrast, in a larger cohort of more than 2000 adults following aortocoronary bypass surgery, platelet storage age was not associated with 30-day mortality, prolonged hospital stay, or post-operative infections. [28] The differences in these findings may be related to heterogeneity among the recipients or the platelet donors. [29]

Fewer studies have been published that explore a similar association in children. Given the differences in physiology and etiologies of critical illness that exist between children and adults, pediatric patients may have different clinical outcomes associated with the storage

age of the platelet concentrates. A sub-analysis of the Platelet Dose (PLADO) Trial, which included non-critically ill children and adults, examined the association between platelet concentrate attributes, including storage age, and the risk of transfusion related adverse events. [30] Though there was no significant association, there appeared to be a trend toward increased transfusion reactions in the freshest platelet concentrates (0–2 days), similar to our findings. While this finding may seem counterintuitive given the increased presence of leukocyte-derived cytokines present in 5-day stored platelets, [6] [31] recent metabolomic studies have shown that platelet concentrates stored for a short period (0–3 days) have decreased mitochondrial function, down regulation of the TCA cycle and the accumulation of ATP degradation products. [32] ATP has been shown to have immunomodulatory effects on cytokines in human whole blood, in particular decreasing the rise in concentrations of TNF-alpha, interferon-gamma and IL-1beta [33]. It is therefore plausible that these metabolic changes may contribute to increased transfusion reactions.

There are important limitations of this study. These are inherent to the design of the main study and the analysis undertaken in this secondary work. The point prevalence study did not collect data for all platelet transfusions received by each enrolled subject during his/her admission; the age of all of the platelet transfusions that a patient received throughout his/her PICU course is unknown. Therefore, the only clinical outcomes that could be assessed in relation to the storage age of the platelet concentrate were the incremental change in platelet count, transfusion reactions and organ dysfunction. Additionally, because of the study design, we could not compare subsequent aliquots transfused from a single donor unit. As an observational study, post-transfusion platelet counts were assessed at the medical team's discretion and thus not limited to a one hour post-transfusion assessment. We did not assess for clinical signs of platelet refractoriness such as splenomegaly. We did not collect information on pre-transfusion medications administered which may affect the rates of fever. There was a low incidence of any transfusion reactions in our cohort and the original study was not designed to be powered for this specific analysis. There are also multiple other potential confounding factors which may affect the modelling analysis. The analysis takes no consideration of other important variables for the platelet product such as manufacturing methods (collection, processing, and storage solutions). [34–36] It is of interest that one study in Canada highlighted the potential importance of processing and use of additive solutions on clinical outcomes. [37] Each platelet product contains a varying number of platelets which may affect the potential mechanisms through which harmful effect of platelets might be mediated, as demonstrated in other recent randomized trials (PATCH, PlaNeT2).[38, 39] We did not include the assessment of other clinical outcomes associated with transfusion such as thrombosis. Finally, leukoreduction techniques vary between North America and Europe [40] and the effects on the leukocytes present in the platelet concentrates were not assessed. Given the differences in blood bank practices as well as a relative shortage of platelet concentrates, a randomized controlled trial that controlled for other variables and only assessed different storage ages may be difficult to perform. However, a comparative effectiveness study within a larger database would be necessary to confirm our findings.

Our study highlights the potential importance of storage age as a further variable to be explored when considering the effectiveness and safety of platelet transfusions. Whereas we



did find increased transfusion reactions with fresher platelet concentrates, we did not find any differences in organ dysfunction or platelet count increments in patients receiving older platelet units. Future work should consider the lessons learned from the literature assessing storage age of red cells, and should assess mechanistic pathways through which storage age may have a clinical impact.

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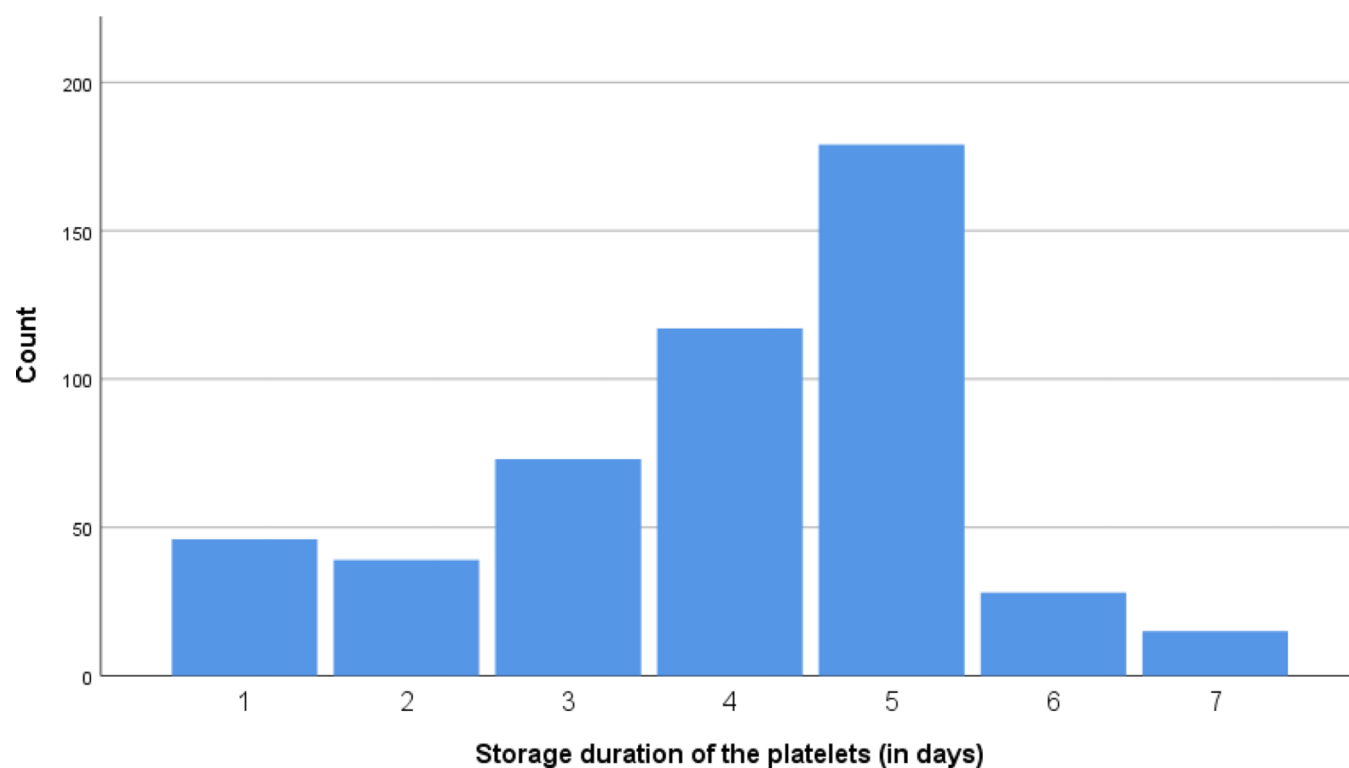
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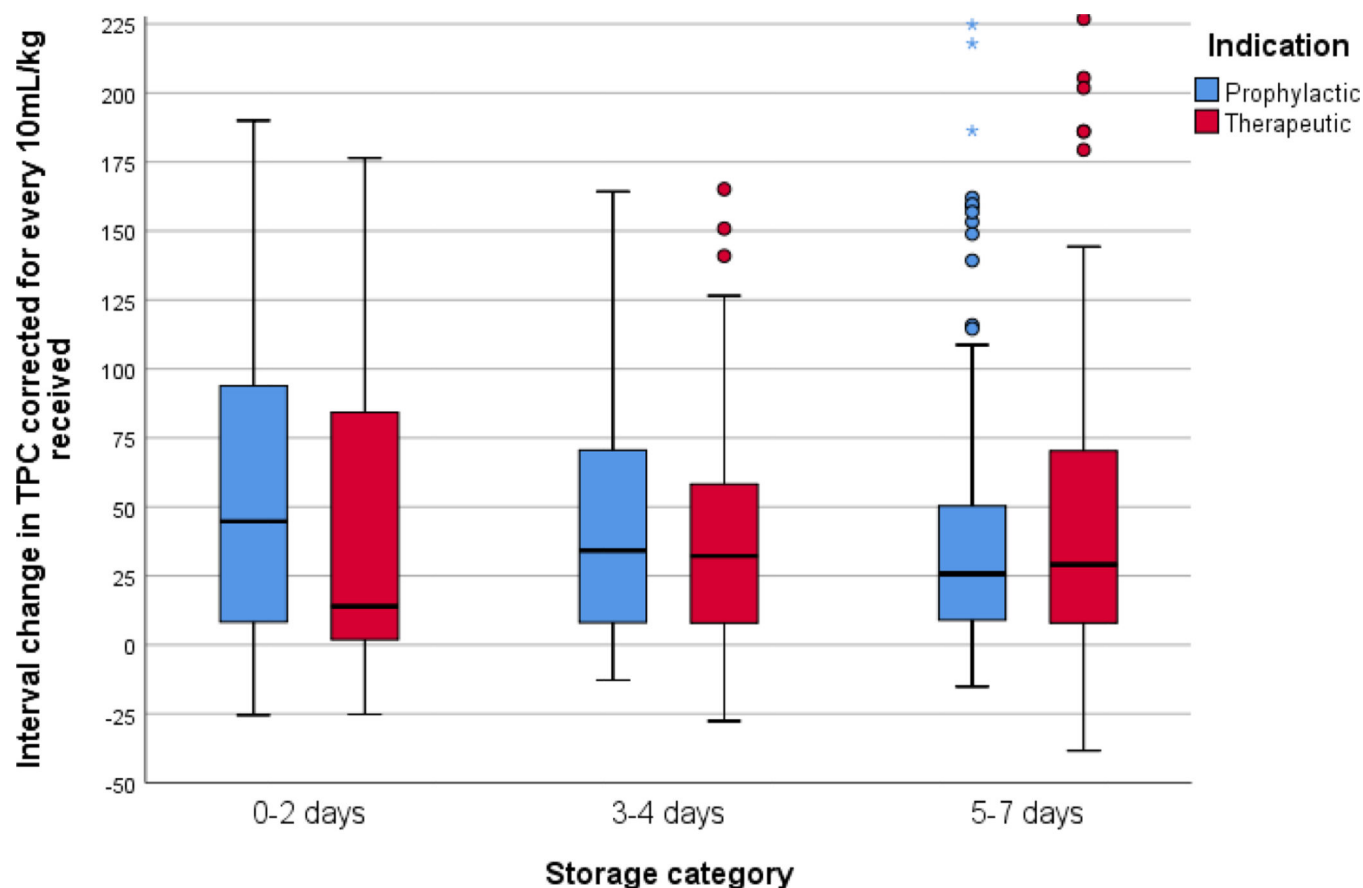
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**Figure 1.**  
Distribution of Storage Age of Platelet Concentrates Transfused



**Figure 2.**  
Incremental change in total platelet count observed for each platelet storage age category broken down by indication

**Table 1.**

Patient demographics and clinical characteristics by storage age of platelets received at time of enrollment

| Patient Variable                                 | 1–2 days of age (n = 85) | 3–4 days of age (n = 191) | 5–7 days of age (n = 221) | p-Values |
|--------------------------------------------------|--------------------------|---------------------------|---------------------------|----------|
| Age (yr), median (IQR)                           | 4.6 (0.5–9.8)            | 3.5 (0.8–9.0)             | 4.1 (0.5–11.1)            | 0.69     |
| Sex (male), n (%)                                | 44 (52)                  | 104 (55)                  | 129 (58)                  | 0.52     |
| Days since admission, median (IQR)               | 1 (0–4)                  | 2 (0–6)                   | 3 (0–9)                   | 0.04     |
| Mechanical ventilation, n (%)                    | 56 (66)                  | 119 (62)                  | 147 (67)                  | 0.22     |
| Underlying oncologic diagnosis, n (%)            | 30 (35)                  | 82 (43)                   | 98 (44)                   | 0.35     |
| PELOD-2 Score prior to transfusion, median (IQR) | 7 (4–10)                 | 7 (4–9)                   | 7 (5–9)                   | 0.32     |
| Reason for PICU Admission, n (%):                |                          |                           |                           |          |
| Organ Failure                                    |                          |                           |                           |          |
| Respiratory insufficiency/failure                | 39 (46)                  | 74 (39)                   | 86 (39)                   | 0.48     |
| Renal failure                                    | 12 (14)                  | 19 (10)                   | 18 (8)                    | 0.29     |
| Hepatic failure                                  | 4 (5)                    | 11 (6)                    | 9 (4)                     | 0.73     |
| Shock                                            |                          |                           |                           |          |
| Septic shock                                     | 31 (37)                  | 42 (22)                   | 36 (16)                   | <0.01    |
| Hemorrhagic shock                                | 1 (1)                    | 13 (7)                    | 17 (8)                    | 0.1      |
| Other shock                                      | 2 (2)                    | 12 (6)                    | 9 (4)                     | 0.31     |
| Trauma                                           | 1 (1)                    | 7 (4)                     | 6 (3)                     | 0.51     |
| Cardiac                                          |                          |                           |                           |          |
| Cardiac surgery-bypass                           | 9 (11)                   | 27 (14)                   | 29 (13)                   | 0.72     |
| Cardiac surgery-no bypass                        | 0 (0)                    | 4 (2)                     | 4 (2)                     | 0.42     |
| Cardiac – non-surgical                           | 8 (9)                    | 16 (8)                    | 24 (11)                   | 0.69     |
| Post-operative                                   |                          |                           |                           |          |
| Emergency surgery                                | 3 (4)                    | 11 (6)                    | 4 (2)                     | 0.1      |
| Elective surgery                                 | 0 (0)                    | 13 (7)                    | 11 (5)                    | 0.05     |
| Post-op liver transplant                         | 1 (1)                    | 3 (2)                     | 8 (4)                     | 0.29     |
| Neurosurgical                                    |                          |                           |                           |          |
| Traumatic brain injury                           | 1 (1)                    | 5 (3)                     | 3 (1)                     | 0.56     |
| Intracranial bleed/intracranial hypertension     | 1 (1)                    | 5 (3)                     | 6 (3)                     | 0.72     |
| Neurologic                                       |                          |                           |                           |          |
| Seizure                                          | 3 (4)                    | 7 (4)                     | 3 (1)                     | 0.29     |
| Encephalopathy                                   | 10 (12)                  | 9 (5)                     | 19 (9)                    | 0.1      |
| Meningitis                                       | 0 (0)                    | 4 (2)                     | 1 (1)                     | 0.15     |
| Veno-occlusive disease                           | 0 (0)                    | 2 (1)                     | 5 (2)                     | 0.28     |
| New leukemia/hyperleukocytosis                   | 4 (5)                    | 5 (3)                     | 9 (4)                     | 0.62     |
| Hemophagocytic lymphohistiocytosis               | 1 (1)                    | 2 (1)                     | 3 (1)                     | 0.96     |
| Therapies Received, n (%)                        |                          |                           |                           |          |
| Medications                                      |                          |                           |                           |          |
| Milrinone                                        | 14 (17)                  | 29 (15)                   | 41 (19)                   | 0.66     |
| Non-steroidal anti-inflammatory agent            | 0 (0)                    | 5 (3)                     | 5 (2)                     | 0.34     |
| Aspirin                                          | 0 (0)                    | 5 (3)                     | 8 (4)                     | 0.21     |



| Patient Variable                                                                  | 1–2 days of age (n = 85) | 3–4 days of age (n = 191) | 5–7 days of age (n = 221) | p-Values |
|-----------------------------------------------------------------------------------|--------------------------|---------------------------|---------------------------|----------|
| Devices                                                                           |                          |                           |                           |          |
| Extracorporeal Membrane Oxygenation                                               | 9 (11)                   | 33 (17)                   | 36 (16)                   | 0.35     |
| Continuous renal replacement therapy                                              | 8 (9)                    | 23 (12)                   | 21 (10)                   | 0.66     |
| Intermittent hemodialysis                                                         | 2 (2)                    | 2 (1)                     | 4 (2)                     | 0.69     |
| Molecular adsorbent circulating system                                            | 0 (0)                    | 2 (1)                     | 3 (1)                     | 0.57     |
| Received platelet transfusion prior to enrollment, n (%)                          | 17 (20)                  | 64 (34)                   | 92 (42)                   | 0.002    |
| Median (IQR) dose (mL/kg) of platelet transfusions received prior to enrollment * | 15 (8–38)                | 25 (12–67)                | 43 (14–105)               | 0.41     |

\* Calculated only for those patients who had received at least one platelet transfusion prior to enrollment. Admitting diagnoses were not mutually exclusive and patients may have had more than one diagnosis on admission.

P-values comparing medians were calculated using Kruskal Wallis test and categorical variables using Chi-square test.

**Table 2.**

Characteristics of the platelet concentrates grouped by storage age

| Transfusion Variable    | 1–2 days of age (n = 85) | 3–4 days of age (n = 191) | 5–7 days of age (n = 221) | p-Values |
|-------------------------|--------------------------|---------------------------|---------------------------|----------|
| Source                  |                          |                           |                           |          |
| Apheresis               | 58 (68)                  | 179 (94)                  | 194 (88)                  | <0.001   |
| Whole blood derived     | 27 (32)                  | 12 (6)                    | 27 (12)                   |          |
| Leukoreduction          | 78 (92)                  | 180 (94)                  | 215 (97)                  | 0.048    |
| Irradiation             | 67 (79)                  | 153 (80)                  | 176 (80)                  | 0.890    |
| HLA-matched             | 1 (1)                    | 0 (0)                     | 2 (1)                     | 0.328    |
| Volume reduced (washed) | 23 (27)                  | 7 (4)                     | 11 (5)                    | <0.001   |
| Pathogen inactivation   | 2 (2)                    | 6 (3)                     | 18 (8)                    | 0.001    |
| ABO compatibility       |                          |                           |                           |          |
| Compatible              | 60 (71)                  | 124 (65)                  | 135 (61)                  | 0.016    |
| Major incompatibility   | 13 (15)                  | 50 (26)                   | 65 (29)                   |          |
| Minor incompatibility   | 2 (2)                    | 9 (5)                     | 13 (6)                    |          |
| Unknown                 | 10 (12)                  | 8 (4)                     | 8 (4)                     |          |

All values represent n (%). P-values comparing categorical variable were calculated using Chi-square test.

**Table 3.**

Transfusion reactions observed by storage age of platelet concentrates

| Transfusion Reaction | 1–2 days of age (n = 85) | 3–4 days of age (n = 191) | 5–7 days of age (n = 221) | p-Values |
|----------------------|--------------------------|---------------------------|---------------------------|----------|
| Fever                | 5 (6)                    | 7 (4)                     | 1 (0.5%)                  | 0.01     |
| Urticaria            | 0 (0)                    | 2 (1)                     | 1 (0.5%)                  | 0.55     |
| Bronchospasm         | 0 (0)                    | 0 (0)                     | 1 (0.5%)                  | 0.54     |
| Hypotension          | 2 (2)                    | 4 (2)                     | 6 (3)                     | 0.92     |
| Hemolytic reaction   | 0 (0)                    | 0 (0)                     | 0 (0)                     | NC       |

All values represent n (%). P-values comparing categorical variable were calculated using Chi-square test. NC = not calculated.

**Table 4.**

Multivariable model to evaluate associations between storage age of platelet concentrates and clinical outcomes

| Clinical Outcome                           | Adjusted OR or $\beta$ Coefficient (95% CI) | p-Values |
|--------------------------------------------|---------------------------------------------|----------|
| Incremental Change in Total Platelet Count | $\beta = -3.429$ (-9.037–2.178)             | 0.230    |
| Change in Organ Dysfunction Scoring        | $\beta = 0.096$ (-0.099–0.291)              | 0.333    |
| Febrile Transfusion Reactions              | OR = 0.562 (0.342–0.807)                    | 0.002    |

Storage age analyzed as continuous variable. Reported as Adjusted Odds Ratio (OR) for categorical outcomes or Beta regression coefficient for continuous outcomes. Model adjusted for days since PICU admission, the receipt of platelet transfusions prior to enrollment, compatibility, source of platelets (apheresed versus whole-blood derived), leukoreduction, volume-reduction and pathogen-inactivation.