Platelet Transfusions Practices in Critically Ill Children

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At a Glance Commentary:

Scientific Knowledge on the Subject: Though platelet transfusions are prescribed both to prevent and treat bleeding in critically ill children, little is known about the epidemiology, indications or outcomes in this population.

What This Study Adds to the Field: This study demonstrates that the majority of platelet transfusions prescribed in the pediatric intensive care unit are given prophylactically to non-bleeding children. The targeted thresholds in platelet count were heterogeneous.

ABSTRACT

Rationale: The epidemiology, indications, and outcomes for critically ill children transfused red blood cells or plasma have been described recently in large multicenter studies. This information is not known regarding platelet transfusions in this population.

Objectives: To describe the epidemiology, indications, and outcomes of platelet transfusions among critically ill children.

Methods: This point-prevalence study was conducted in 82 pediatric intensive care units in 16 countries during six assigned weeks. All children included received a platelet transfusion prescribed during one of the screening days.

Measurements and Main Results: During six weeks of screening, 16,934 patients were eligible, of whom 559 received at least one platelet transfusion (prevalence 3.3%). The indications for transfusion included prophylaxis in 67%, minor bleeding in 21% and major bleeding in 12%. Thirty-four percent of prophylactic platelet transfusions were prescribed when the platelet count was $\geq 50 \times 10^9$ cells/L. The median (IQR) change in platelet count was 48×10^9 cells/L (17-82) for major bleeding, 42×10^9 cells/L (16-80) for prophylactic transfusions, 38×10^9 cells/L (17-72) for minor bleeding, and 25×10^9 cells/L (10-47) for prophylaxis in patients at risk of bleeding from a device. Overall mortality for all patients was 25%.

Conclusions: The majority of platelet transfusions prescribed are given as prophylaxis to non-bleeding children and significant variation in platelet thresholds exists. Studies are needed to clarify appropriate indications, with a particular focus on prophylactic transfusions.

Abstract: 234 words

INTRODUCTION

Platelet transfusions are commonly prescribed in critical illness but uncertainty remains regarding their efficacy and safety for all indications. Platelet units are transfused to either prevent or reduce the risk of bleeding (considered "prophylactic transfusion"), or to treat clinically significant bleeding secondary to platelet dysfunction, thrombocytopenia or empirically with life-threatening bleeding (considered "therapeutic transfusion"). In 2015, an AABB survey reported that 48,000 children in the United States received 165,000 apheresis platelet units.[1] Unfortunately, there is no information in these surveys or in large multicenter studies regarding the epidemiology, indications, and outcomes for critically ill children receiving platelet transfusions.

Evidence-based guidelines for platelet transfusions administered to children are generally lacking. The current guidelines from the AABB are based primarily on expert opinion. Recommendations combine neonates (<1 month of age) with children (1 month to 18 years of age) and state that platelet transfusions are indicated for children: 1) with a total platelet count of $< 10 \times 10^9$ cells/L due to hypoproliferative thrombocytopenia, 2) with active bleeding in association with a qualitative platelet defect, 3) with unexplained excessive bleeding in patients undergoing cardiopulmonary bypass or 4) undergoing extracorporeal membrane oxygenation (ECMO) with a total platelet count of $< 100 \times 10^9$ cells/L.[2]

Little is known about the practice of platelet transfusion in pediatric critical illness. In order to develop interventional studies to evaluate platelet transfusion strategies in critically ill children and to eventually guide platelet transfusion practices, it is important to know the epidemiology, indications, and outcomes in this population. The primary objective of the study

was to describe the patterns of platelet transfusions among critically ill children, including transfusion thresholds, indications, post transfusion platelet count increment, and outcomes.

METHODS

Study Population

This point prevalence study was an international, prospective, cross-sectional design. Sites were recruited through the Pediatric Critical Care Blood Research Network (Blood Net), the Pediatric Acute Lung Injury and Sepsis Investigators (PALISI) network, the Canadian Critical Care Trials Group (CCCTG), the Australia and New Zealand Intensive Care Society (ANZICS), the Paediatric Intensive Care Society (UK), the Israeli Society of Pediatric Intensive Care, and sites who previously participated in a published point prevalence study on plasma transfusions (PlasmaTV).[3] 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 considered *eligible* if he/she was admitted to the pediatric intensive care unit during one of the seven screening days of the assigned week and was between 3 days and 16 years old. He/she was *enrolled* if he/she received a platelet transfusion prescribed by the intensive care medical 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 was enrolled in a previous screening week. The study was approved by the Institutional/Ethical Review Board at each individual participating site, except for the UK in which the study was approved by the Health Research Authority of the National Health Service. Waiver of consent was granted at all sites except one site in Italy that required written consent

for participation. Sites in Switzerland required a description of the study to be posted in the waiting room with an opt-out possibility for families.

Data Collection

For each enrolled subject, the site chose from the following list of indications for transfusion (more than one indication could be selected): (1) total platelet count < 10 x 10^9 cells/L with failure of platelet production; (2) total platelet count < 30 x 10^9 cells/L in neonate with failure of platelet production; (3) major bleeding: as defined by (a) bleeding that requires massive transfusion; (b) bleeding in specific sites: intracranial, intraocular, retroperitoneal, intra-spinal, or non-traumatic intra-articular; or (c) bleeding requiring a surgical intervention of drainage (i.e. hemothorax requiring drainage); (4) minor bleeding (surgical or non-surgical): as defined by any bleeding that does not meet the above criteria for major bleeding; (5) preparation for surgery; (6) preparation for invasive procedure; (7) known qualitative platelet defect with risk of bleeding; (8) at risk of bleeding from device (ECMO, Ventricular Assist Device (VAD), other) or (9) other. Indications 1, 2, 5, 6, and 7 were all categorized as "prophylactic" transfusions.

Data collected included patient demographics, reason for admission, any prior platelet transfusions during the current ICU admission, information regarding the platelet product, the transfusion event itself and any adverse reactions, as well as assays of total platelet count and function assessed before and after the platelet transfusion. All lab data was collected up to 36 hours following the platelet transfusion of interest. Outcome data, including length of stay, length of mechanical ventilation and mortality, as well as severity of disease, as measured by

PELOD-2 score, were also collected. Study data were collected and managed using REDCap electronic data capture tools hosted at Weill Cornell Medical College.

Statistical Approach

Demographic and clinical characteristics were described as N (%) or mean +/- standard deviation (SD) or median and interquartile range (IQR) as appropriate. Categorical data were compared by Fisher's Exact/Chi-square tests. Continuous variables were compared by ANOVA/Kruskal-Wallis tests or t-test/Wilcoxon Rank Sum for parametric /non-parametric data, respectively. 95% confidence intervals were constructed for estimates of interest to analyze precision. All p-values were two-sided with statistical significance evaluated at the 0.05 alpha level. All analyses were performed in R version 3.4.0 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Prevalence

Eighty two sites from sixteen countries contributed data. The majority of sites were urban (97%), academic (98%), trauma centers (85%) and ECMO centers (80%). Of the participating sites, 48 (58%) were located in North America, 23 (28%) in Europe, 4 (5%) in Oceania, 4 (5%) in the Middle East and 3 (4%) in Asia.

During the six weeks of screening, 16,934 patients were eligible, constituting an average of 13.6 eligible patients in each participating site at the start of the screening week. Of those, 559 received platelet transfusions and were enrolled for a transfusion prevalence of 3.3%. On average, each individual institution enrolled 4% of eligible patients (95% CI 0-8.3).There were 9

sites (11%) who did not transfuse platelets during the entire study period and hence, did not enroll any subjects.

Subjects

Subject demographics are summarized in Table 1 and categorized according to indication for platelet transfusion including major bleeding, minor bleeding, at risk of bleeding due to device, or prophylactic transfusion. The median (IQR) age of the subjects was 4.1 years (0.5 - 10.8) and 55% were male. The three most common reasons for admission were respiratory insufficiency/failure (39.2%), septic shock (22.4%) and cardiac surgery involving bypass (12.1%). Nearly half of the subjects (43.5%) had an underlying oncologic diagnosis. The majority of subjects were mechanically ventilated (64.4%) and admitted to the PICU for a median length of 2 days (IQR 2-7) before enrollment. The median PELOD-2 score at enrollment was 7 (IQR 5-10). The frequency of subjects receiving medications that affect platelet function was: milrinone (17.2%), aspirin (2.6%) and non-steroidal anti-inflammatories (2.2%). The frequency of subjects requiring the following interventions at the time of platelet transfusion was: extracorporeal life support (16.8%), continuous renal replacement therapy (10.6%), intermittent hemodialysis (1.3%), and molecular adsorbent recirculation system (0.9%). Approximately one-third (36%) of the children had received at least one other platelet transfusion in the PICU during the admission prior to enrollment in the study.

Indications

The indications for each platelet transfusion are summarized in Figure 1. Of note, the majority of transfusions were prophylactic; major or minor bleeding was the indication in only one-third of transfusions (33%).

Transfusion

The majority of the platelets transfused were collected by apheresis (87.1%) versus whole blood derived (12.9%). The transfusions were commonly leukoreduced (93.4%), and irradiated (79.9%). They were infrequently volume reduced (8.3%), pathogen inactivated (4.5%) by INTERCEPT™ blood system, or HLA-matched (0.8%). The median platelet dose per transfusion event was 9.4 mL/kg (IQR 5.5-13.1). Subjects received a median 4 (IQR 2-11) platelet transfusion events during their PICU course for a total median dose of 32.4 mL/kg (IQR 14.0-91.4).

Reported adverse reactions to the platelet transfusion were uncommon. A new fever or increase in temperature by 1°C, if already febrile, occurred most frequently (3.0%), followed by hypotension (2.6%), urticaria (0.6%), and bronchospasm (0.2%). There were no hemolytic reactions and no confirmed septic reactions.

Laboratory Assays

The total platelet count was known within 24 hours prior to transfusion in the vast majority of cases (99.1%). The median (IQR) platelet count prior to transfusion was 40×10^9 cells/L (20-66). Thirty-four percent of transfusions were prescribed when the platelet count was $\geq 50 \times 10^9$ cells/L. For those children with an underlying oncologic diagnosis, the median (IQR) platelet count prior to transfusion was 25×10^9 cells/L (15-41) and for those supported by

ECMO, it was 70 x 10^9 cells/L (52-90). Viscoelastic testing, such as thromboelastography (TEG) and rotational thromboelastometry (ROTEM) were rarely analyzed prior to the transfusion (4.5% and 2.2% respectively). Other measures of platelet function, including response to P2Y12 inhibitors (VerifyNow, Accriva Diagnostics, San Diego, CA, USA), PFA-100, and impedence aggregometry were each only assessed once (0.2%) prior to transfusion.

Figure 2 depicts the change in total platelet count following transfusion at various times and for various platelet indications corrected for transfusion dose. The median change in platelet count varied across groups based on indication (p=0.03). For every 10 mL/kg of platelets transfused, the median (IQR) change in platelet count was 48 x 10^9 cells/L (17-82) for patients with major bleeding, 42 x 10^9 cells/L (16-80) for prophylactic transfusions, 38 x 10^9 cells/L (17-72) for patients with minor bleeding, and 25 x 10^9 cells/L (10-47) for patients at risk of bleeding from a device. The incremental change in platelet count did not vary between those who had an underlying oncologic diagnosis and those who did not (p=0.57).

Outcomes

The median length of stay in the PICU was 13 days (6-29) with patients being mechanically ventilated a median length of 7 days (0-19). The mortality rate for all children analyzed was 25%. The outcomes based on indication are summarized in Table 2.

DISCUSSION

This international point prevalence study is the first published analysis of the epidemiology, indications, and outcomes in critically ill children transfused with platelets.

Approximately two–thirds of platelet transfusions were prescribed in a prophylactic manner to non-bleeding children. Thirty-four percent of prophylactic transfusions were prescribed when the platelet count was $\geq 50 \times 10^9$ cells/L. While the observed rise in the platelet count following transfusion varied based on indication, those at risk of bleeding from a device had the smallest increase. Mortality in patients who receive platelet transfusions was high, ranging from 17-35% according to indication.

Platelet transfusion practices observed in this study resemble those published in adults. In one large observational study in critically ill adults in the UK, wide variation in platelet use was reported.[4] The prevalence of platelet transfusion was reported to be 9%. More than half of platelet units were given as "prophylactic transfusions" in patients with no documented clinically significant bleeding. One-third of these transfusions were given to critically ill adults with a total platelet count $> 50 \times 10^9$ cells/L. Similar findings were reported in a retrospective study from 3 adult ICUs in Canada; platelet transfusions were commonly prescribed when the platelet count was $\geq 50 \times 10^9$ cells/L.[5] The median platelet count reported prior to platelet transfusion was 87×10^9 cells/L. In these same two studies, the increment in total platelet count following transfusion was modest, $18.5 \pm 30.4 \times 10^9$ cells/L and 23×10^9 cells/L.[4,5]

Pediatric data from one single center prospective study reported the prevalence of critically ill children receiving at least one platelet transfusion to be 7.2%. The average platelet count was $49 \pm 34 \times 10^9$ cells/L prior to transfusion, similar to thresholds reported in this study.[4] They report a wide range of incremental changes in platelet count following transfusion (from 30 to nearly 100×10^9 cells/L), based on the indication for the transfusion. The incremental change in platelet count in critically ill children following platelet transfusion may be higher than that observed in critically ill adults because of better ABO compatibility, which has been implicated

in improved post-transfusion platelet increment in adults with hematologic malignancies.[6] The incremental change in platelet count as corrected for platelet dose that we report also varied by indication for transfusion. The smallest incremental change was seen in those at risk of bleeding from a device which can be explained by alloimmunization and consumption related to the device itself. Surprisingly, children with major bleeding had a greater median rise in platelet count than those with minor bleeding or no bleeding. One would expect that the incremental change in the more severely bleeding patient would be more modest based on consumption and loss in surgical drains. No cold platelets were administered to patients included in this study. It is possible that platelets stored at room temperature are relatively inert and are not being consumed at a high enough rate to show reduced increments compared to non-bleeding patients. "Cold" platelets (stored at 4C) have been shown to have increased hemostatic efficacy and increased safety relative to bacterial contamination.[7,8,9] Two randomized controlled trials of whole blood derived platelets and platelets within whole blood indicate cold storage reduces bleeding and is associated with improved platelet function.[10,11] Additional trials are being performed that will examine the effect of storage temperature of platelets collected by apheresis.[12]

Our study confirms that clinicians rely on very few assays, other than total platelet count alone, to prescribe platelet transfusions. Whiting et al[13] suggest that viscoelastic testing, such as TEG or ROTEM, are more effective than standard lab testing to guide transfusion therapy in adults undergoing cardiac surgery or following trauma. A recent Cochrane review analyzing the benefit of viscoelastic testing to monitor hemostatic treatment versus usual care in 17 trials in adults or children with bleeding reported that application of TEG- or ROTEM-guided transfusion strategies may reduce the need for blood products, and improve morbidity in patients with bleeding.[14] The PLADO trial comparing different platelet doses recruited adults and children

with hematological malignancies, and reported a poor relationship between degree of severity of thrombocytopenia and bleeding risk.[15] More work needs to be done to understand how to define bleeding risk other than by use of isolated platelet counts in critically ill children who are at risk of bleeding.

Given there are few evidence-based guidelines for platelet transfusion in critically ill children, it is not surprising that significant variation in prescribing practices exists. Randomized trials represent the goal for evidence based practitioners but we must recognize considerable challenges undertaking such trials of platelet transfusions in critically ill children, and in a setting where validated outcome measures of bleeding are not described. Alternative designs of studies such as comparative effectiveness methods need to be considered. Since nearly half of the children in this cohort had an underlying oncologic diagnosis, this specific patient population should be investigated. Furthermore, children being supported by devices that place them at risk for bleeding receive the highest exposure to platelet transfusions with a high mortality. Future studies should focus on this population as well.

This study represents the largest prospective data on platelet transfusions in critically ill children reported to date. Since the data was predominantly collected with a waiver of consent, the study is without selection bias. Given the number of sites involved globally, the results should be externally valid for pediatric intensive care units with platelet transfusions readily available in their blood banks. The results of the study, though primarily descriptive in nature, provide important preliminary data that identifies at risk patient populations and will facilitate the design of randomized controlled trials.

Some limitations exist. Ideally, in a study examining the use of platelet transfusions as a hemostatic agent, some measure of bleeding should be collected. However, since there is no

validated bleeding assessment tool in critically ill children, it was not included as an outcome. Additionally, data was not collected on transfusion of other hemostatic products, such as plasma cryoprecipitate, factor concentrates or antifibrinolytics. The design of the study does not permit direct comparison between patients transfused and not transfused with platelets as we were not able to collect data on the 16,375 non-transfused patients. The population of critically ill children transfused with platelets had increased acuity compared to the general PICU population, in both PELOD-2 scores (7 versus 4) and mortality (25% versus 6%).[16]

In conclusion, this international point prevalence study demonstrates that the majority of platelet transfusions prescribed in the pediatric intensive care unit are given prophylactically to non-bleeding children and significant variation in platelet thresholds exists. Studies are needed to clarify appropriate indications for platelet transfusion and subsequent responses in critically ill children according to their illness, with a particular focus on prophylactic transfusions.

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Table 1. Demographics of Subjects

	Major Bleeding (n=64)	**Minor Bleeding (n=115)**	**Risk of Bleeding from Device (n=79)**	**Prophylactic Transfusions (n=278)**	**p-Values**
Age (yr), median (IQR)	3 (0,11)	4 (0,10)	0 (0,3)	5 (1,11)	< 0.001
Sex (male), n (%)	33 (52%)	66 (57%)	44 (56%)	152 (55%)	0.897
Weight (kg), median (IQR)	13.7 (5.9,36.5)	16.0 (8.5, 28.5)	6.4 (3.5, 18.8)	19.1 (8.6,38.1)	< 0.001
Days Since Admission, median (IQR)	1 (0,3)	2 (0, 8.8)	5 (2, 13)	2 (0,6)	< 0.001
Mechanical Ventilation, n (%)	48 (75%)	82 (71%)	74 (94%)	141 (51%)	< 0.001
Reason for PICU Admission, n (%)					
Respiratory	15 (23%)	51 (44%)	48 (61%)	96 (35%)	< 0.001
Septic Shock	4 (6%)	22 (19%)	9 (11%)	85 (31%)	< 0.001
Hemorrhagic Shock	16 (25%)	5 (4%)	2 (3%)	6 (2%)	< 0.001
Other Shock	4 (6%)	5 (4%)	4 (5%)	11 (4%)	0.810
Trauma	4 (6%)	7 (6%)	1 (1%)	2 (1%)	0.002
Traumatic Brain Injury	3 (5%)	2 (2%)	0 (0%)	3 (1%)	0.114
Burn	0 (0%)	1 (1%)	0 (0%)	1 (0%)	0.731
Cardiac surgery-bypass	14 (22%)	17 (15%)	13 (16%)	21 (8%)	0.004
Cardiac surgery-no bypass	1 (2%)	4 (3%)	1 (1%)	3 (1%)	0.366
Cardiac – non-surgical	3 (5%)	10 (9%)	12 (15%)	16 (6%)	0.047
Emergency surgery	4 (6%)	1 (1%)	3 (4%)	6 (2%)	0.131
Elective surgery	3 (5%)	7 (6%)	5 (6%)	8 (3%)	0.312
Seizure	1 (2%)	6 (5%)	0 (0%)	8 (3%)	0.181
Encephalopathy	6 (9%)	15 (13%)	4 (5%)	16 (6%)	0.078
Meningitis	0 (0%)	1 (1%)	2 (3%)	2 (1%)	0.390
Renal failure	3 (5%)	15 (13%)	8 (10%)	29 (10%)	0.371
Hepatic failure	3 (5%)	8 (7%)	2 (3%)	13 (5%)	0.576
Post-op liver transplant	2 (3%)	3 (3%)	1 (1%)	7 (3%)	0.879
Other	23 (36%)	27 (23%)	15 (19%)	92 (33%)	0.026
PELOD-2 Score prior to transfusion, median (IQR)	7 (5.5, 10.5)	7 (6, 11)	8 (7, 11)	7 (4, 9)	0.001

Figure 1. Indications for Platelet Transfusions

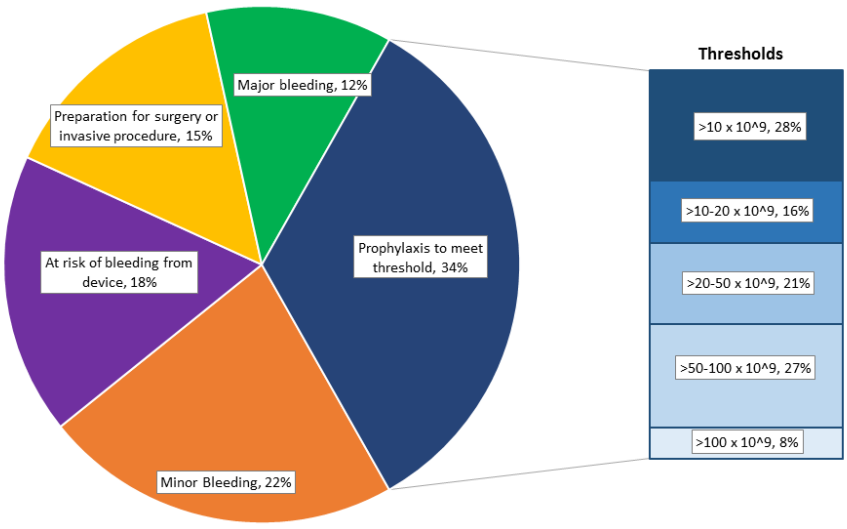

Figure 2. Change in Platelet Count Following Transfusion By Indication

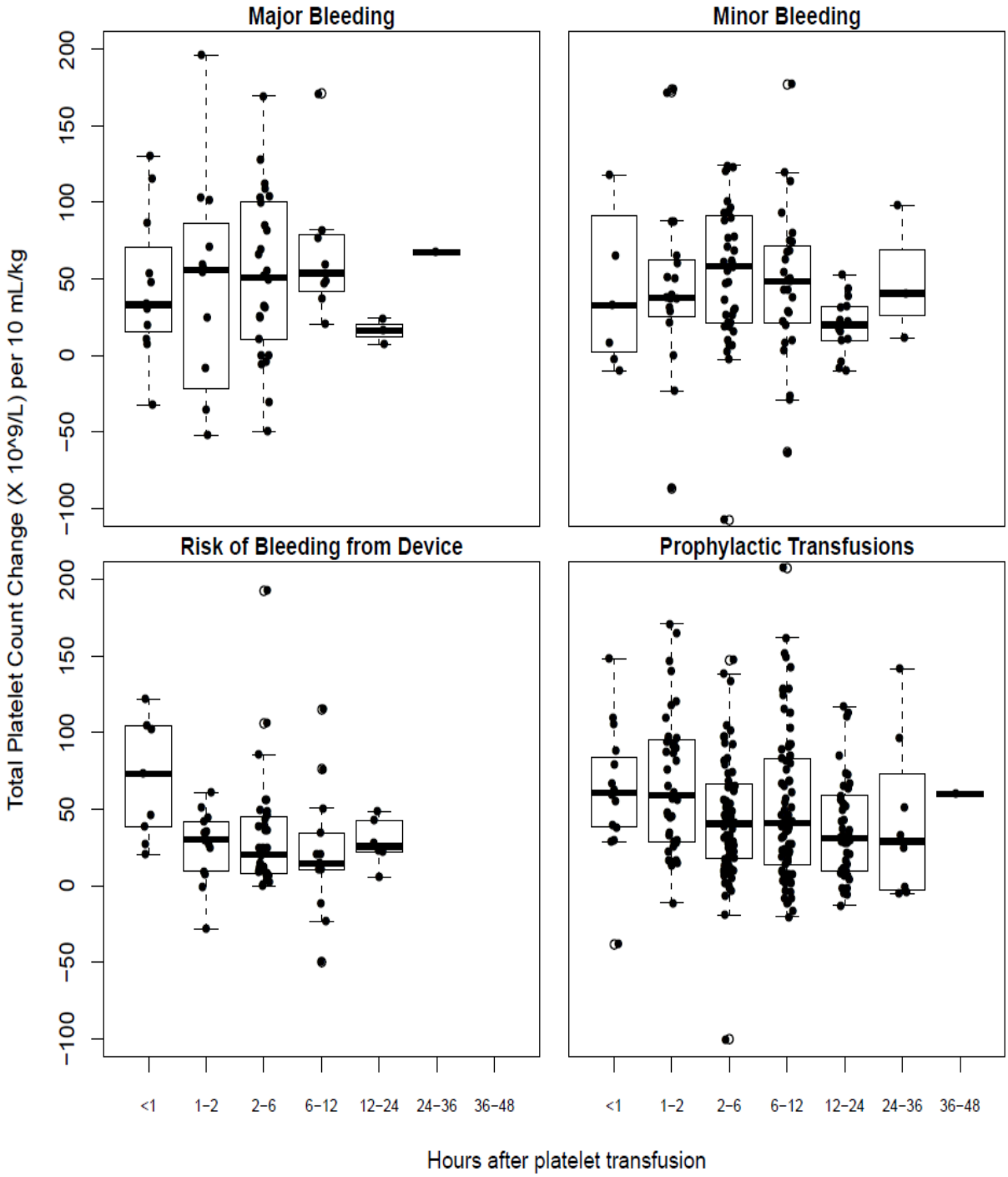

Table 2. Outcomes Based on Indication for Platelet Transfusion

	Major Bleeding (n=60)	**Minor Bleeding (n=113)**	**Risk of Bleeding from Device (n=75)**	**Prophylactic Transfusions (n=274)**	**p-Values**
PICU Length of Stay (days), median (IQR)	10 (4, 27)	14 (7-27)	25 (12-50)	11.5 (5-26)	< 0.001
Length of Mechanical Ventilation (days), median (IQR)	4 (2, 16)	9 (2, 17)	17 (10, 43)	4 (0, 15)	< 0.001
Total platelet dose (mL/kg), median (IQR)	30.9 (13.5, 67.3)	27.3 (10.4, 62.1)	97.7 (40.0-243.0)	28.6 (12.3, 79.8)	< 0.001
Mortality, n (%)	18 (28,1%)	40 (35.4%)	27 (35.1%)	48 (17,3%)	< 0.001

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