Transfusion Practices for Pediatric Oncology and Hematopoietic Stem Cell Transplantation Patients: Data from the National Heart Lung and Blood Institute Recipient Epidemiology and Donor Evaluation Study-III (REDS-III)

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Abstract

Purpose: To evaluate transfusion practices in pediatric oncology and hematopoietic stem cell transplant (HSCT) patients. Methods: This is a multicenter retrospective study of children with oncologic diagnoses treated from 2013-2016 at hospitals that participated in the National Heart Lung and Blood Institute Recipient Epidemiology and Donor Evaluation Study-III (REDS-III). Transfusion practices were evaluated by diagnosis code and pre-transfusion laboratory values. Results: A total of 4766 inpatient encounters of oncology and HSCT patients were evaluated, with 39.3% (95% CI 37.9-40.7%) involving a transfusion. Red blood cells (RBCs) were the most commonly transfused component (32.4%; 95% CI 31.1-33.8%), followed by platelets (22.7%; 95% CI 21.5-23.9%). Patients in the 1 to <6-year old age range were most likely to be transfused and HSCT, acute myelogenous leukemia, and aplastic anemia were the diagnoses most often associated with transfusion. The median hemoglobin (Hb) prior to RBC transfusion was 7.5 g/dL (10-90th percentile: 6.4-8.8 g/dL), with 45.7% of transfusions being given at 7-<8 g/dL. The median platelet count prior to platelet transfusion was 20x109/L (10-90th percentile: 8-51x109/L), and 37.9% of transfusions were given at platelet count of >20-50x109/L. The median international normalized ratio (INR) prior to plasma transfusion was 1.7 (10-90th percentile: 1.3-2.7), and 36.3% of plasma transfusions were given at an INR between >1.4-1.7. Conclusion: Transfusion of blood components is common in hospitalized children with cancer. Relatively high pre-transfusion Hb and platelet values and relatively low INR values prior to transfusion across the studied diagnoses highlight the need for evidence- based practice in this population.

Transfusion Practices for Pediatric Oncology and Hematopoietic Stem Cell Transplantation Patients: Data from the National Heart Lung and Blood Institute Recipient Epidemiology and Donor Evaluation Study-III (REDS-III)

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Abbreviations table :

ALL	acute lymphoblastic leukemia
AML	acute myelogenous leukemia
Hb	hemoglobin
RBCs	red blood cells
INR	International normalized ratio
REDS-III	Recipient Epidemiology and Donor Evaluation Study-III
NHLBI	National Heart Lung and Blood Institute

ALL	acute lymphoblastic leukemia
HSCT	Hematopoietic stem cell transplantation
IQR	interquartile range
US	United States
ICU	Intensive care unit
OR	operating room
MDS	myelodysplastic syndrome
CI	confidence interval
PLADO	Optimal Platelet Dose Strategy for Management of Thrombocytopenia
ICTMG	International Collaboration for Transfusion Medicine Guidelines

Abstract: (250 words)

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Results: A total of 4766 inpatient encounters of oncology and HSCT patients were evaluated, with 39.3% (95% CI 37.9-40.7%) involving a transfusion. Red blood cells (RBCs) were the most commonly transfused component (32.4%; 95% CI 31.1-33.8%), followed by platelets (22.7%; 95% CI 21.5-23.9%). Patients in the 1 to <6-year old age range were most likely to be transfused and HSCT, acute myelogenous leukemia, and aplastic anemia were the diagnoses most often associated with transfusion. The median hemoglobin (Hb) prior to RBC transfusion was 7.5 g/dL (10-90th percentile: 6.4-8.8 g/dL), with 45.7% of transfusions being given at 7-<8 g/dL. The median platelet count prior to platelet transfusion was $20x10^9$/L (10-90th percentile: 8-$51x10^9$/L), and 37.9% of transfusions were given at platelet count of >20-$50x10^9$/L. The median international normalized ratio (INR) prior to plasma transfusion was 1.7 (10-90th percentile: 1.3-2.7), and 36.3% of plasma transfusions were given at an INR between >1.4-1.7.

Conclusion: Transfusion of blood components is common in hospitalized children with cancer. Relatively high pre-transfusion Hb and platelet values and relatively low INR values prior to transfusion across the studied diagnoses highlight the need for evidence- based practice in this population.

INTRODUCTION

Blood transfusions can be a critical life-saving intervention for pediatric oncology and transplantation patients[1-3]. Recent nationally representative data from the United States (US) assessing inpatient transfusion utilization in children and neonates reported between 4-5% of all hospitalizations in free-standing children's hospitals utilized blood transfusions[4]. A national audit of blood transfusion practices from the United Kingdom reported that a majority of the pediatric transfusions in non-neonatal patients were given to hematology/oncology patients[5]. In another analysis of blood product utilization from > 3000 pediatric patients across 12 pediatric subspecialty services at a large tertiary care academic center in the US, pediatric oncology patients accounted for approximately 25% of all inpatient pediatric transfusions[6]. This study also reported significant variation in pre-transfusion laboratory values as well as post-transfusion targets across pediatric oncology patients.

Despite being among the most heavily transfused pediatric patient populations, there are limited data assessing and/or guiding transfusion practices in pediatric oncology and HSCT patients. Recent guidelines from the British Society for Hematology noted that there was insufficient evidence to make recommendations for pre-transfusion hemoglobin (Hb) thresholds in pediatric hematology/oncology patients and those undergoing HSCT[7].

Our study is a retrospective analysis of children with oncologic diagnoses and those who underwent HSCT between 2013 and 2016 at academic and community hospitals from four geographically diverse regions in the United States that participated in the National Heart Lung and Blood Institute (NHLBI) Recipient Epidemiology and Donor Evaluation Study-III (REDS-III). This study aims to describe the incidence of RBC, platelet, plasma and cryoprecipitate transfusions and to characterize the pre-transfusion laboratory values by age, cancer type and location of transfusion.

METHODS

General Study Design

The NHLBI REDS-III data are available as a public use dataset through BioLINCC[8]. REDS-III involved 12 academic and community hospitals from four regions of the US (Connecticut, Pennsylvania, Wisconsin and California), of which 11 included pediatric populations. The database included patient and blood component data for a 4-year period spanning January 1, 2013 to December 31, 2016. Approval for data collection had been obtained from the Institutional Review Board at each participating institution.

Study Population and Definitions

For this study, children 0 to 18 years of age with a hematologic/oncologic diagnosis based on ICD 9/10 codes (**Supplemental Table S1**) with an inpatient/outpatient encounter were evaluated. An inpatient encounter was defined as a unique patient hospitalization event with recorded dates and times of admission and discharge. Outpatient encounters only included those where a transfusion took place. An individual patient could have more than one encounter within this dataset and thus could be counted more than once.

Patient hematologic or oncologic diagnoses specifically captured for this analysis included acute lymphocytic leukemia (ALL), acute myeloid leukemia (AML), bone marrow failure/aplastic anemia, myelodysplastic syndrome (MDS), Hodgkin lymphoma, non-Hodgkin lymphoma, brain tumors (all types), sarcoma, germ cell tumor, Wilms tumor, hepatoblastoma/hepatocellular carcinoma, retinoblastoma, and neuroblastoma. Encounters where an autologous or allogeneic HSCT was designated as a diagnosis, regardless of the underlying primary diagnosis or primary reason for admission, were separately recorded and evaluated. Within these, encounters with the actual autologous/allogeneic transplant event being coded as a procedure were analyzed separately as autologous/allogeneic HSCT procedures, respectively.

Transfusion Exposures

A transfusion event occurred in this analysis when any blood product was issued from the transfusion service. Data captured for each event included product issue time, issue location (general ward, intensive care unit [ICU], operating room [OR]), and a barcode (Codabar or ISBT 128) from which product type was extracted, product ABO type and irradiation/leukoreduction status. Components used for therapeutic apheresis procedures were excluded from the analysis. As the exact volume of transfusion was not captured in the database, each individual aliquot was considered a unique transfusion event. Laboratory values closest in time prior to each transfusion and $<$ 24-hours preceding the recorded issue time for inpatient transfusions and$<$ 72-hours preceding the recorded issue time for outpatient transfusions were identified. Pre-transfusion laboratory values were recorded as Hb (g/dL), platelet count (x10^9cells/L) and international normalized ratio (INR). Pre-transfusion laboratory values for patients transfused in the OR are shown only in Figure 2 describing issue location.

Data Analysis

Demographic and clinical characteristics were described as counts and percentages or medians (with IQR or 10^{th} and 90^{th} percentiles). Transfusion incidence for inpatient encounters was calculated as the binomial proportion of encounters during which at least one blood product was issued and presented by patient demographics and selected diagnoses. Transfusion incidence was stratified by specific blood components and compared by patient age, gender, race, ethnicity, diagnosis, and issued blood component. Pre-transfusion laboratory values were also analyzed by issue location (inpatient vs outpatient), diagnosis, and patient age.

A Venn diagram was plotted to show the relative usage of various components individually and in various combinations with other components. All analyses were conducted with SAS version 9.4 (SAS Institute Inc., Cary, NC, USA) and density estimation plots and Venn diagrams were generated with R version 4.1.0 (R-project, Vienna, Austria).

RESULTS

Inpatient cohort

A total of 4,766 inpatient encounters met our study criteria and were evaluated. The inpatient cohort was 42% female, with 69% of patients being between 1 and 13 years of age; most patients were white (62%) and non-Hispanic (75%) (**Table 1**).

Number of transfusion events per encounter

A total of 1,873 inpatient encounters involved at least one blood transfusion, with many involving more than one component transfused (**Supplemental Table S2**). The median length of an encounter was 5 days (IQR 1-13). Children from birth to 1 year of age had the longest inpatient encounters, with a median of 18 days (IQR 3-139). A total of 1,546 encounters involved an RBC transfusion with 3,477 total RBC transfusion events and the diagnoses with the most RBC transfusion events per encounter included allogeneic HSCT (median 4; IQR 3-7), AML (median 3; IQR 2-5) and MDS (median 2.5; IQR 1-13). A total of 1,081 encounters involved a platelet transfusion with 4,686 total platelet transfusion events. The diagnoses with the most platelet transfusion events per encounter included allogeneic HSCT procedure (median 7; IQR 4-17), autologous HSCT procedure (median 4; IQR 2-8), and AML (median 3.5; IQR 2-8). A relatively small overall number of encounters were associated with transfusion of plasma (n=115) or cryoprecipitate (n=24), with a few patients receiving large numbers of such products.

Transfusion incidence by blood component

Among all inpatient encounters, the incidence of any blood product being transfused was 39.3% (95% CI 37.9-40.7%) (**Table 1**). RBCs were the most commonly transfused component (32.4%; 95% CI 31.1-33.8%), followed by platelets (22.7%; 95% CI 21.5-23.9%). Plasma was much less commonly transfused (2.4%; 95% CI 2.0-2.8%), and cryoprecipitate was rarely transfused (0.5%; 95% CI 0.3-0.7%). Patients in the 1 to <6-year old age range were most likely (46.4%; 95% CI 44.0-48.7%) to be transfused. **Figure 1** shows the relative distribution and combination of transfused components among inpatients who received any transfusion: 40% received only RBCs, 17% received only platelets, and 0.2% received only plasma. Assessing by combination of blood component utilization: 37% received RBCs and platelets, 0.6% received RBCs and plasma, and 0.1% received platelets and plasma. All three components RBCs, platelets, and plasma were transfused in only 1.6% patients.

Transfusion incidence by diagnosis

The most common oncologic diagnosis by inpatient encounter was ALL, followed by sarcomas, brain tumors, and neuroblastoma **(Table 2)** . The most likely diagnoses to be transfused were AML (77.6%; 95% CI 71.2-84.1%), bone marrow failure syndromes/aplastic anemia (70%; 95% CI 64.7-75.3%), and MDS (57.1%; 95% CI 31.2-83.1%). Patients least likely to be transfused included those admitted with a diagnosis of Hodgkin lymphoma (11.2%; 95% CI 5.9-16.5%), non-Hodgkin lymphoma (12.7%; 95% CI 4.9-20.4%), and germ cell tumors (16.7%; 95% CI 6.7-26.6%). RBCs were the most commonly transfused component for all evaluated diagnoses except for AML, MDS, and retinoblastoma, for which platelets were the most commonly transfused. Plasma was transfused most often for patients with admissions for the allogeneic HSCT procedure (17.5%; 95% CI 7.7-27.4%), MDS (14.3%; 95% CI 0-32.6%), or hepatoblastoma or hepatocellular carcinoma (9.5%; 95% CI 2.8-16.1%). Cryoprecipitate was transfused most often for patients with MDS (7.1%; 95% CI 0-20.6%), hepatoblastoma or hepatocellular carcinoma (1.4%; 95% CI 0-4.0%), or an allogeneic HSCT procedure (3.5%; 95% CI 0-8.3%).

Transfusion incidence by diagnosis for HSCT encounters

There were 527 transplant related encounters (**Table 2**). Of these, 57 were allogeneic and 63 autologous HSCTs with the encounter specifically for the transplantation procedure. The age, sex, race, and ethnicity data for these patients is shown in **Supplemental Tables S3A and S3B** . The most common indication for allogeneic transplant was ALL, followed by bone marrow failure and AML. The most common indication for autologous transplant was brain tumor, followed by neuroblastoma.

Patients admitted specifically for a HSCT procedure were most often transfused: (92.1%; 95% CI 85.4-98.7% for autologous transplant and 96.5%; 95% CI 91.7-100% for allogeneic transplant), with RBC's being the most common component in >80% subjects and platelets in >66% subjects overall. Fewer patients with allogeneic transplant received plasma (17.5%) and/or cryoprecipitate (3.5%). All patients with ALL and AML received RBCs during their transplant encounter and most with ALL, AML, and bone marrow failure also received platelets during the transplant encounter. The majority (75.9%, 95% CI 60.3-91.4%) of patients with brain tumors received RBCs during their transplant encounter, and 37.9% (95% CI 20.3-55.6%) received platelets. Most (92.9%; 95% CI 83.3-100%) patients with neuroblastoma received RBCs during their transplant encounter, and all received platelets. Few patients received plasma during the transplant encounter, and none received cryoprecipitate.

Pre-transfusion laboratory values

Of the inpatients studied outside of the operating room setting, a pre-transfusion Hb within 24 hours was available for 79% (2,764) of the total 3,477 RBC transfusion events (**Table 3**). The median overall pre-transfusion Hb was 7.5 g/dL (10-90th percentile: 6.4-8.8 g/dL), and 45.7% of RBC transfusions were given at Hb of 7- <8 g/dL. A pre-transfusion platelet count was available for 90% (4,206) of the 4,686 inpatient platelet transfusion events. The median platelet count was $20x10^9$/L (10-90th percentile: 8-$51x10^9$/L) and 37.9% of all platelet transfusions were given at a platelet count of >20-$50x10^9$/L. A pre-transfusion INR within 24 hours was available for 87% (340) of the 393 inpatient plasma transfusion events. The median INR was 1.7 (10-90th percentile: 1.3-2.7) and 36.3% of plasma transfusions were given at an INR of >1.4-1.7.

Utilization patterns for all transfused products were also evaluated by inpatient location (general ward, ICU, OR) of blood component issue, and stratified by patient age. Median pre-transfusion Hb values were qualitatively higher for children <1-year old and for those in the OR; pre-transfusion platelet values were highest for children of all ages in the OR, followed by those in the ICU; pre-transfusion INR values were lowest for those transfused in the operating room (**Figure 2).**

Next, pre-transfusion laboratory values were evaluated by diagnosis (**Supplemental Tables S4A-S4C and Figure 3**). The highest median pre-RBC transfusion Hb values (7.8-7.9 g/dL) were present in patients undergoing HSCT and in those with MDS, brain tumors, and neuroblastoma. The highest median pre-transfusion platelet values were present in patients with MDS ($40x10^9$/L) and brain tumors ($31x10^9$/L), as well as those undergoing allogeneic HSCT ($21x10^9$/L). The lowest median pre-plasma transfusion INR values were present in patients with brain tumors (1.2), and in patients with ALL, bone marrow failure, or neuroblastoma (1.6).

Outpatient Cohort

A total of 594 RBC and 583 platelet outpatient transfusion encounters involving patients with oncologic or HSCT diagnostic codes were evaluated **(Table 3)** . Median (10-90thpercentile) pre-RBC transfusion Hb values in outpatients was 7.1g/dL (6-8.4 g/dL) and median pre-transfusion platelet counts was $19x10^9$/L (10-$38x10^9$/L). Of note, 38.1% of all platelet transfusions were given with pre-transfusion counts between >10-$20x10^9$ and 37.1% were given between >20-$50x10^9$ (**Table 3 and Figure 3).**

Component blood types and modifications

The ABO and Rh types of blood components and transfusion recipients were evaluated (**Supplemental Table S5**), as were blood product modifications. All group O patients received RBCs from group O donors, though 29% of the group O RBCs were transfused to non-group O patients. Essentially all (99%) Rh negative recipients received RBCs from Rh negative donors, though the majority (58%) of Rh-negative

RBCs were transfused to Rh positive patients. Seventy-four percent of AB platelets and 98% of AB plasma were transfused to non-AB patients. Essentially all (99.6%) transfused RBCs administered to inpatients were leukoreduced and 96% were irradiated; 0.4% were volume reduced and 5.8% were washed. Likewise, 98% of platelets were irradiated and 18% were volume reduced.

DISCUSSION

Pediatric oncology patients can require multiple transfusions of blood components, including RBCs, platelets and plasma, during their illness. This study reports on transfusion practices among a cohort of children with cancer and those undergoing HSCT who received care in 11 of the 12 participating academic and community hospitals across four geographically diverse areas in the US. As the data evaluates patient encounters from 2013 to 2016, the findings from this study likely reflect contemporary transfusion practices. We observed that ˜40% of all pediatric oncology/transplant patients received transfusions during hospitalizations. These numbers are consistent with prior reports suggesting that pediatric hematology oncology patients are among the largest inpatient users of blood components[6].

Whereas there have been several national and international guidelines issued for red blood cell transfusion in adult hematology, oncology, and transplant patients[9, 10], there are a scarcity of transfusion guidelines specific to pediatric oncology/transplantation patients. There are recent comprehensive guidelines developed for transfusion in critically ill children and those have highlighted the need for pediatric-specific patient blood management programs[11, 12]. The Pediatric Critical Care Transfusion and Anemia Expertise Initiative (TAXI) recently issued evidence-based guidelines for the use of RBCs in critically ill children with hematologic and oncologic disease[13]. For patients in the ICU with oncologic disease or undergoing HSCT, Hb concentration of 7-8 g/dL was recommended[14]. Our current study shows that while most transfusions were administered at laboratory values supported by the best available evidence, about 25% of RBC transfusions were administered at pre-transfusion Hb levels higher than this cut-off. While some of these transfusions may be due to inadequate adoption of pediatric patient blood management programs, the exact clinical context warranting some of these transfusions (e.g., bleeding, hemodynamic compromise, patient being severely symptomatic, etc.) are unclear[15-17]. Specifically, for oncology patients receiving chemotherapy, practices such as transfusing at higher Hb thresholds for inpatients just prior to discharge or at times when there may not readily be outpatient access to blood components may also contribute to this variation.

Thrombocytopenia is present in most children with oncologic diagnoses at some point during their disease course, and platelet transfusions are often prescribed prophylactically to prevent bleeding or therapeutically to treat bleeding complications. We report that platelets were rarely transfused as an isolated blood product, but most commonly along with RBCs. The AABB has issued clinical practice guidelines for platelet transfusion, but none are specific to children[13]. Regarding procedures relevant to oncology patients, AABB suggests prophylactic platelet transfusions for patients having elective diagnostic lumbar punctures with a platelet count $< 50\times10^9$ /L, and for patients having bone marrow biopsies and elective central venous catheter placement with a platelet count $< 20\text{x}10^9$/L. The Children's Oncology Group Supportive Care Guidelines have endorsed American Society of Clinical Oncology's clinical practice guideline update for platelet transfusion for oncology patients, as well as the platelet transfusion guidelines in hypoproliferative thrombocytopenias developed by the International Collaboration for Transfusion Medicine Guidelines (ICTMG)[18, 19]; those guidelines recommend a platelet transfusion threshold of $<10 \text{ x } 10^9$ for patients with hematologic malignancies and in the setting of HSCT. However, the guidelines specify that transfusion at higher platelet count thresholds may be advisable in patients with signs of hemorrhage, high fever, hyperleukocytosis, a rapid fall in platelet count, coagulation abnormalities, and in those undergoing invasive procedures or circumstances when platelet transfusions may not be readily available in case of emergencies.

The pediatric analyses of the Optimal Prophylactic Platelet Dose Strategy to Prevent Bleeding in Thrombocytopenic Patients (PLADO) trial showed that the morning platelet count did not predict bleeding for any studied age group. Children were also noted to have a significantly higher risk of bleeding than adults over a wide range of platelet counts, indicating that factors besides platelet counts are likely involved.[20] Although transfusion indications were not available for our present study, the fact that 34% of inpatient platelet trans-

fusions were administered to children with platelet counts between 20-50x10^9/L is notable. Pre-transfusion values were higher for patients in the OR or ICU, likely reflecting active bleeding or conditions associated with a higher risk of bleeding. An international study assessing the epidemiology of platelet transfusions in critically ill children with an underlying oncologic diagnosis also showed that in ˜60% of cases, platelet transfusions were administered at a threshold of >20x10^9/L[21]. Of note, these numbers are also similar to adults in the REDS-III cohort, where 28% of inpatient platelet transfusions were administered at pre-transfusion platelet counts between 20 and 50x10^9/L [22]. Looking towards the future, the Transfusion and Anemia Expertise Initiative – Control and Assessment of Bleeding (TAXI-CAB) is performing a systematic review and developing guidelines to direct the use of platelet and plasma transfusions in critically ill children.

Generally, plasma is transfused to prevent bleeding prior to invasive procedures (prophylactic), or to correct multiple coagulation factor deficiencies in patients with active bleeding (therapeutic). Some clinicians use prophylactic plasma transfusions in patients with ALL during induction to mitigate asparaginase's prothrombotic effects. However, evidence to support this practice remains controversial[23, 24]. Further, there are very limited data in the pediatric population to identify INR values above which bleeding risk increases and a plasma transfusion is indicated, and none specifically for pediatric oncology/transplant patients. In our study, plasma was only occasionally used (˜2.5% of all encounters overall), with the highest utilization being among AML, bone marrow failure syndromes/aplastic anemia, MDS and hepatoblastoma or hepatocellular carcinoma patients. We also saw large variations in pre-transfusion INR among oncology/transplant patients, with the 10th to 90th percentile ranging from 1.3 to 2.7. However, the lowest median INR was for brain tumors at 1.2, with a notable proportion of the plasma transfusions being at an INR of 1.0.

Utilizing the REDS-III donor/component/recipient linkage, our study was able to evaluate component utilization by donor and recipient ABO/Rh type, as well as by component modification. Unexpected findings included the large number of Rh negative RBCs (58%) transfused to Rh positive patients, and the large percentage of "universal donor" AB platelet (74%) and plasma (98%) products transfused to non-AB recipients; these findings are consistent with trends reported in the 2017 National Blood Collection and Utilization Survey[25]. Reserving Rh negative RBCs[26] and AB platelets and plasma[27] for patients that require this type is recommended. The fact that essentially all RBCs and platelets transfused were irradiated was not surprising, given the risk of transfusion associated graft versus host disease in many, but not all patients studied[28]. However, the relatively high percentage (18%) of platelets transfused that were volume reduced was unexpected, and reason(s) for this modification were not clear from the accessible data.

Our study has several important limitations. This was a retrospective study of transfusion practices and was not designed to relate to specific clinical outcomes. Therefore, we were unable to establish correlations of any pre-transfusion laboratory values at any given location, age, sex, or malignancy type with clinical outcome. The exact indication for transfusion, whether for prophylactic or therapeutic purposes, could not be determined from the database, and any understanding of utilization or variability based on these remain speculative. We relied on ICD-9/ ICD-10 codes to classify oncology diagnoses as well as transplantation type, and miscoding was possible. Also, we did not have information on transfusion volumes and had to approximate by counting any aliquot as a single transfusion event. Lastly, though the studied hospitals represent academic as well as community centers and are geographically diverse, they may not be fully nationally representative.

In conclusion, our study suggests heterogeneity in transfusion practices in the pediatric oncology/HSCT population and suggests that a percentage of transfusions are administered at laboratory values higher than supported by the best available evidence. Transfusions are not risk free, with evidence emerging that transfused children may be more likely to develop some types of transfusion reactions compared with adults[29, 30]. Given that children with cancer are among the most heavily transfusion dependent patient subpopulations, there is a critical need for high quality prospective data on prevalence and incidence of transfusion related adverse events as well as guidance for indication, dosing, transfusion triggers and methods to reduce transfusion related risks.

Conflict of interest: The authors have no conflicts of interest to disclose.

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The NHLBI Recipient Epidemiology Donor Evaluation Study–IV–Pediatric (REDS-IV-P) domestic program is the responsibility of the following persons:

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FIGURE LEGENDS

Figure 1. Transfused components administered to inpatients, by component type . Venn diagram of transfusions of red blood cells (RBCs), platelets, and plasma administered to inpatients, with overlap shown by component.

Figure 2: Pre-transfusion laboratory values by location of component issued and by patient age. Distribution of pre-transfusion laboratory values for hemoglobin (g/dL) prior to RBCs, platelet count ($x10^9$/L) prior to platelets, and INR prior to plasma, separated by patient age and location of issued blood component.

Figure 3: Pre-transfusion laboratory values, stratified by diagnoses. Density plots show the distribution of pre-transfusion laboratory values for hemoglobin (g/dL), platelet count ($x10^9$/L), and INR for inpatients compared to outpatients, with select diagnoses.

TABLE 1. Incidence of transfusion in all pediatric oncology/stem cell transplantation inpatient encounters, including specific components, by demographic information % (95% CI)

	Encounters
	N (%)
Total	4766 (100)
Sex	

	Encounters
Female	2014 (42.3)
Male	2752 (57.7)
Age (years)	
0 to <1	85 (1.8)
1 to <6	1755 (36.8)
6 to <13	1546 (32.4)
13 to <18	1380 (29.0)
Race	
White	2938 (61.6)
Black	541 (11.4)
Asian	331 (6.9)
Other/Not specified	956 (20.1)
Ethnicity [a]	
Hispanic	1164 (24.4)
Non-Hispanic	3598 (75.5)
[a]4 patients with unknown ethnicity are not shown *RBC-red blood cell*	[a]4 patients with unknown ethnicity are not shown

TABLE 2 Incidence of transfusion in all oncology/stem cell transplantation inpatient encounters, including specific components, by diagnosis % (95% CI)

	Encounters	**Any Transfusion**	**Any R**
	N	**% (95% CI)**	**% (95**
Specific cancer types			
ALL	1090	46.3 (43.4-49.3)	39.8 (3
AML	161	77.6 (71.2-84.1)	67.1 (5
Bone marrow failure syndromes/aplastic anemia	290	70.0 (64.7-75.3)	55.9 (5
Myelodysplastic syndrome (MDS)	14	57.1 (31.2-83.1)	42.9 (1
Hodgkin lymphoma	134	11.2 (5.9-16.5)	11.2 (5
Non-Hodgkin lymphoma	71	12.7 (4.9-20.4)	12.7 (4
Brain Tumors (all combined)	779	34.8 (31.4-38.1)	24.5 (2
Sarcomas (Ewing, Osteosarcoma, Rhabdomyosarcoma, Soft tissue Sarcomas)	1066	27.5 (24.8-30.2)	23.3 (2
Germ Cell Tumor	54	16.7 (6.7-26.6)	14.8 (5
Wilms tumor (other renal tumors)	108	35.2 (26.2-44.2)	33.3 (2
Hepatoblastoma or Hepatocellular Carcinoma	74	37.8 (26.8-48.9)	33.8 (2
Retinoblastoma	181	24.9 (18.6-31.2)	17.1 (1
Neuroblastoma	611	46.0 (42.0-49.9)	38.8 (3
Total HSCT (diagnosis) (total)	527	54.1 (49.8-58.3)	45.0 (4
Autologous HSCT Procedure	63	92.1 (85.4-98.7)	84.1 (7
Allogeneic HSCT Procedure	57	96.5 (91.7-100)	94.7 (8

ALL-acute lymphoblastic leukemia; AML-acute myelogenous leukemia; RBC-red blood cells, HSCT-hematopoietic stem cell transplantation

TABLE 3: Pre-transfusion laboratory values for inpatient versus outpatient encounters

	Pre-Tx Hb, g/dL	**Total Episodes (percent)**
Inpatient Transfusions	No results*	713

	Pre-Tx Hb, g/dL	**Total Episodes (percent)**
	<7	755 (27.3)
	7 to <8	1,263 (45.7)
	8 to <9	514 (18.6)
	[?]9	232 (8.4)
Outpatient Transfusions	No results*	278
	<7	124 (39.2)
	7 to <8	138 (43.7)
	8 to <9	42 (13.3)
	[?]9	12 (3.8)
	Pre-Tx Plt Ct x 10^9/L	**Total Episodes (percent)**
Inpatient Transfusions	No results*	480
	[?]10	756 (18)
	>10 to 20	1,434 (34.1)
	>20 to 50	1,595 (37.9)
	>50 to 100	396 (9.4)
	>100	25 (0.6)
Outpatient Transfusions	No results*	265
	[?]10	68 (21.4)
	>10 to 20	121 (38.1)
	>20 to 50	118 (37.1)
	>50 to 100	11 (3.5)
	>100	0 (0.0)
	Pre-Tx INR	**Total Episodes (percent)**
Inpatient Transfusions	No results*	53
	[?]1.4	68 (20)
	>1.4 to 1.7	125 (36.8)
	>1.7 to 2.0	69 (20.3)
	[?]2.0	78 (22.9)

There were no outpatient plasma transfusion events.

These numbers are not included in total percentage.

Pre-tx- pre transfusion; Hb-hemoglobin; Plt Ct- platelet count; INR- international normalization ratio

Supplemental Table S1. ICD-9 and ICD-10 codes.

Diagnosis	**ICD-9**
Acute lymphoid leukemia (ALL) without remission or in relapse	204.00, 204.02
Acute myeloid leukemia (AML) without remission	205.00, 205.02
Hodgkin Lymphoma	201.4, 201.5, 201.6, 201.7, 201.9, 201.91, 201.92, 201.93, 2
Non-Hodgkin lymphoma	202.8 (all sub-codes)
Brain tumors	191 (all sub-codes)
Ewing sarcoma, soft tissue sarcoma, or osteosarcoma	170 (all sub-codes)
Germ cell tumor	181, 186.9, 183.0, 186.0
Hepatoblastoma	155.0, 155.1
Kidney/Wilms tumor	189.0, 189.1
Melanoma	172 (all sub-codes) 154.3
Neuroblastoma	194 (all sub-codes)
Retinoblastoma	190.5

Diagnosis	ICD-9
Rhabdomyosarcoma	171 (all sub-codes)
Thyroid cancer	193
Aplastic anemia/bone marrow failure	284.9, 284.89, 284.09
Myelodysplastic syndrome	238.74, 238.75, 238.73, 238.72

Supplemental Table S2. Transfused aliquots by encounter

Encounter Length

(at least 1 product transfused)

Encounter Length

(at least 1 product transfused)

Encounter Length

(at least 1 product transfused)

RBCs

RBCs

RBCs

Platelets

Platelets

Platelets

Plasma

Plasma

Plasma

Cryoprecipitate

Cryoprecipitate

Cryoprecipitate

N

Median

IQR

N

Median

IQR

N

Median

IQR

N

Median

IQR

N

Median

IQR

INPATIENT

1873

5

1-13

1546

1

1-2

1081

1

1-4

115

2

1-4

24

2

1-5

Sex

Female

811

5

2-15

686

1

1-2

446

1

1-4

46

2

1-4

8

1.5

1-2

Male

1062

5

1-12

860

2

1-2

635

1

1-4

69

2

1-4

16

2.5

2-6

Age (years)

0 to <1

35

18

3-139

29

2

1-4

22

1

1-2

5

2

1-2

1

1

1-1

1 to <6

814

5

1-13

689

1

1-2

468

1

1-4

47

2

1-5

13

3

2-7

6 to <13

561

5

1-11

463

1

1-2

321

1

1-3

25

2

1-5

3

2

1-2

13 to <18

463

5

1-14

365

2

2-3

270

2

1-5

38

2

1-3

7

2

1-4

Race

White

1156

5

1-12

948

1

1-2

678

1

1-4

71

2

1-4

14

2

1-4

Black

186

5

1-15

163

2

1-2

99

1

1-4

8

2

1-4

1

1

1-1

Asian

170

2

1-7

122

1

1-2

110

1

1-2

10

2.5

1-9

2

25

6-44

Other/Not specified

361

7

3-17

313

2

1-3

194

2

1-5

26

1.5

1-3

7

2

1-2

Ethnicity

Hispanic

471

6

2-16

405

2

1-2

264

2

1-4

26

1.5

1-4

4

2

2-18

Non-Hispanic

1400

5

1-12

1140

1

1-2

817

1

1-4

89

2

1-4

19

2

1-6

Other/Not specified

2

58

6-109

1

3

3-3

0

—

—

0

—

—

1

1

1-1

Specific cancer types

ALL

505

6

2-15

434

2

1-3

319

2

1-4

27

2

1-4

7

2

1-4

AML

125

23

8-33

108

3

2-5

112

3.5

2-8

13

2

1-7

2

6.5

6-7

Bone marrow failure

203

3

1-18

162

1

1-3

132

1.5

1-4

16

2

1-10

3

2

2-34

Myelodysplastic syndrome

8

17

16-36

6

2.5

1-13

7

1

1-19

2

13.5

13-14

1

8

8-8

Hodgkin lymphoma

15

5

2-7

15

2

2-2

4

2.5

2-10

0

—

—

0

—

—

Non-Hodgkin lymphoma

9

5

4-31

9

1

1-2

2

2.5

2-3

0

—

—

0

—

—

Brain Tumors (all combined)

271

3

1-7

191

1

1-2

178

1

1-2

11

1

1-3

2

22.5

1-44

Sarcomas (Ewing, Osteosarcoma, Rhabdomyosarcoma, Soft tissue Sarcomas)

293

5

2-7

248

2

1-2

104

1

1-2

11

2

1-3

2

1

1-1

Germ Cell Tumor

9

6

4-8

8

2

2-2

2

1

1-1

0

—

—

0

—

—

Wilms tumor (other renal tumors)

38

6

3-10

36

1

1-2

8

2

1-4

1

1

1-1

0

—

—

Hepatoblastoma or Hepatocellular Carcinoma

28

5

3-8

25

1

1-2

9

1

1-1

7

1

1-3

1

1

1-1

Retinoblastoma

45

2

1-5

31

1

1-2

36

1

1-1

1

7

7-7

0

—

—

Neuroblastoma

281

5

3-10

237

1

1-2

144

1

1-4

22

2

1-5

3

2

1-4

Autologous HSCT

58

26

5-32

53

2

1-3

44

4

2-8

3

10

1-12

0

—

—

Allogeneic HSCT

55

50

39-135

54

4

3-7

48

7

4-17

10

5

3-14

2

4

1-7

ALL-acute lymphoblastic leukemia; AML-acute myelogenous leukemia; RBC-red blood cells, HSCT-hematopoietic stem cell transplantation

Supplemental Table S3A: Incidence of transfusion in allogeneic HSCT patients, including specific components, % (95% CI)

	Encounters	**Any Transfusion**	**Any RBCs**
	N	**% (95% CI)**	**% (95% CI)**
Allogeneic HSCT Procedure	Allogeneic HSCT Procedure	Allogeneic HSCT Procedure	Allogeneic HSCT Procedure
Total	57	96.5 (91.7-100)	94.7 (88.9-100)
Sex			
Female	33	97.0 (91.1-100)	97.0 (91.1-100)
Male	24	95.8 (87.8-100)	91.7 (80.6-100)
Age (years)			
0 to <1	12	91.7 (76.0-100)	91.7 (76.0-100)
1 to <6	19	94.7 (84.7-100)	94.7 (84.7-100)
6 to <13	17	100 (100-100)	100 (100-100)
13 to <18	9	100 (100-100)	88.9 (68.4-100)
Race			
White	31	96.8 (90.6-100)	96.8 (90.6-100)
Black	8	100 (100-100)	100 (100-100)
Asian	6	100 (100-100)	83.3 (53.5-100)
Other/Not specified	12	91.7 (76.0-100)	91.7 (76.0-100)
Ethnicity			
Hispanic	14	100 (100-100)	100 (100-100)
Non-Hispanic	43	95.3 (89.1-100)	93.0 (85.4-100)
Indication			
ALL	16	100 (100-100)	100 (100-100)
AML	4	100 (100-100)	100 (100-100)
Bone marrow failure	12	100 (100-100)	91.7 (76.0-100)
Other	25	92.0 (81.4-100)	92.0 (81.4-100)

Supplemental Table S3B: Incidence of transfusion in autologous HSCT patients, including specific components, % (95% CI)

	Encounters	**Any Transfusion**
	N	**% (95% CI)**
Autologous HSCT Procedure	Autologous HSCT Procedure	Autologous HSCT Procedure
Total	63	92.1 (85.4-98.7)
Sex		
Female	21	95.2 (86.1-100)
Male	42	90.5 (81.6-99.4)
Age (years) [a]		
1 to <6	49	89.8 (81.3-98.3)
6 to <13	12	100 (100-100)
Race		
White	33	97.0 (91.1-100)
Black	6	83.3 (53.5-100)
Asian	7	85.7 (59.8-100)
Not specified/Unknown	17	88.2 (72.9-100)
Ethnicity		
Hispanic	19	89.5 (75.7-100)
Non-Hispanic	44	93.2 (85.7-100)

	Encounters	**Any Transfusion**
Indication		
Brain tumor	29	82.8 (69.0-96.5)
Neuroblastoma	28	100 (100-100)
Other	6	100 (100-100)
[a]2 patients aged 13 to <18 are not shown	[a]2 patients aged 13 to <18 are not shown	[a]2 patients aged 13 to <18 are not

Supplemental Table S4A: Pre-transfusion hemoglobin values by diagnosis

	n	mean	min	P_1	P_10	P_20	P
Total	2764	7.5	2.3	4.6	6.4	6.8	6
ALL	852	7.2	2.4	3.7	6.2	6.7	6
AML	341	7.4	3.9	4.9	6.5	6.8	6
Bone marrow failure	398	7.7	2.3	4.4	6.3	6.7	6
Myelodysplastic syndrome	39	7.9	4.7	4.7	6.8	7.1	7
Hodgkin lymphoma	17	7.4	6.2	6.2	6.2	6.5	6
Non-Hodgkin lymphoma	9	7.5	6.5	6.5	6.5	6.7	7
Brain Tumors (all combined)	201	7.9	5	5.9	6.5	7	7
Sarcomas (Ewing, Osteosarcoma, Rhabdomyosarcoma, Soft tissue Sarcomas)	262	7.6	4.4	4.8	6.5	6.8	7
Germ Cell Tumor	8	7.7	6.3	6.3	6.3	7.2	7
Wilms tumor (other renal tumors)	47	7.5	5.2	5.2	6.4	6.8	6
Hepatoblastoma or Hepatocellular Carcinoma	25	7.9	5.7	5.7	6.6	6.95	7
Retinoblastoma	28	7.3	5.9	5.9	6.7	7	7
Neuroblastoma	397	7.9	5.4	5.9	6.7	7	7
Autologous HSCT	131	8.0	6.6	6.9	7.3	7.6	7
Allogeneic HSCT	324	7.8	4.4	6.1	6.9	7.2	7

ALL-acute lymphoblastic leukemia; AML-acute myelogenous leukemia; RBC-red blood cells, HSCT-hematopoietic stem cell transplantation

Supplemental Table S4B: Pre-transfusion platelet values by diagnosis

	n	mean	min	P_1	P_10	P_20	P
Total	4206	26.2	1	3	8	11	1
ALL	1329	26.0	1	4	8	11	1
AML	696	23.0	2	4	8	10	1
Bone marrow failure syndromes/aplastic anemia	670	27.6	1	2	7	9	1
Myelodysplastic syndrome	108	38.8	5	7	13	19	2
Hodgkin lymphoma	20	15.0	3	3	5	8	9
Non-Hodgkin lymphoma	1	48.0	48	48	48	48	4
Brain Tumors (all combined)	271	38.3	3	4	13	19	2
Sarcomas (Ewing, Osteosarcoma, Rhabdomyosarcoma, Soft tissue Sarcomas)	189	23.7	1	2	9	11	1
Germ Cell Tumor	2	34.0	29	29	29	29	2
Wilms tumor (other renal tumors)	17	15.6	8	8	8	10	1
Hepatoblastoma or Hepatocellular Carcinoma	7	20.0	7	7	7	12	1
Retinoblastoma	33	21.6	5	5	9	11	1
Neuroblastoma	593	26.8	3	5	9	12	1
Autologous HSCT	264	22.2	4	5	8	11	1

	n	mean	min	P_1	P_10	P_20	P
Allogeneic HSCT	780	27.2	2	5	9	12	1

Supplemental Table S4C: Pre-transfusion INR values by diagnosis

	n	mean	min	P_1	P_10	P_20	P_
Total	340	1.9	0.9	1.0	1.3	1.4	1.5
ALL	74	1.7	0.9	0.9	1.3	1.4	1.5
AML	44	2.0	1.3	1.3	1.5	1.5	1.6
Bone marrow failure syndromes/aplastic anemia	60	1.8	1.0	1.0	1.2	1.4	1.4
Myelodysplastic syndrome	26	2.7	1.4	1.4	1.4	1.7	1.7
Brain Tumors (all combined)	13	1.4	0.9	0.9	1.0	1.0	1.0
Sarcomas (Ewing, Osteosarcoma, Rhabdomyosarcoma, Soft tissue Sarcomas)	17	2.1	1.1	1.1	1.2	1.5	1.5
Wilms tumor (other renal tumors)	1	1.5	1.5	1.5	1.5	1.5	1.5
Hepatoblastoma or Hepatocellular Carcinoma	7	2.2	1.2	1.2	1.2	1.4	1.4
Retinoblastoma	2	3.8	2.3	2.3	2.3	2.3	2.3
Neuroblastoma	59	1.7	1.0	1.0	1.4	1.5	1.5
Autologous HSCT	22	1.7	1.5	1.5	1.6	1.6	1.6
Allogeneic HSCT	92	1.9	1.1	1.1	1.5	1.6	1.6

ALL-acute lymphoblastic leukemia; AML-acute myelogenous leukemia; RBC-red blood cells, HSCT-hematopoietic stem cell transplantation

Supplemental Table S5A: ABO/Rh types of RBCs and transfusion recipients

Product ABO

Product ABO

Product ABO

Product ABO

Total

%ABO

Identical

Patient ABO

A

AB

B

O

Missing

6

0

0

9
15
A
697
0
0
508
1205
58%
AB
34
98
12
47
191
51%
B
0
0
354
257
610
58%
O
0
0
0
1,975
1,975
100%
Total
737
98
366

2,796

3,996

Product Rh

Product Rh

Product Rh

Product Rh

Total

%Rh Identical

Patient Rh

Negative

Negative

Positive

Positive

missing

2

2

7

7

9

Rh Negative

475

475

4

4

479

99%

Rh Positive

657

657

2,851

2,851

3,508

81%

Total

1,134

1,134

2,862

2,862

3,996

752 products have missing ABO and Rh data

*752 products have missing ABO and Rh data

*752 products have missing ABO and Rh data

*752 products have missing ABO and Rh data

*752 products have missing ABO and Rh data

*752 products have missing ABO and Rh data

*752 products have missing ABO and Rh data

Supplemental Table S5B: ABO/Rh types of platelets and transfusion recipients

Product ABO

Product ABO

Product ABO

Product ABO

Total

%ABO

Identical

Patient ABO

A

AB

B

O

missing

18

14

1

9

32

A

1,256

78

173

211

1718

73%

AB

108

78

34

7

227

34%

B

161

48

482

148

839

57%

O

814

79

245

1,197

2,335

51%

Total

2,357

297

935

1,572

5,151

Product Rh

Product Rh

Product Rh

Product Rh				
Total				
%Rh Identical				
Patient Rh				
Negative	Negative	Positive	Positive	missing
3	3	29	29	32
Rh Negative				
337	337	226	226	563
60%				
Rh Positive				
512	512	4,042	4,042	4,556
89%				
Total				
852	852	4,297	4,297	5,151

508 products have missing ABO and Rh data

*508 products have missing ABO and Rh data

*508 products have missing ABO and Rh data

*508 products have missing ABO and Rh data

* 2 products were pooled product and not included in the Rh table

** 2 products were pooled product and not included in the Rh table

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Supplemental Table S5C: ABO/Rh types of plasma and transfusion recipients

Product ABO

Product ABO

Product ABO

Product ABO

Total

%ABO

Identical

Patient ABO

A

AB

B

O

missing

0

4

2

0

6

A

90

2025

0

0

2115

4%

AB

0

49

0

0

49

100%

B

0

15

29

0

44

66%

O

58

57

8

164

287

57%

Total

148

2,150

39

164

2,501

Product Rh

Product Rh

Product Rh

Product Rh

Total

%Rh Identical

Patient Rh

Negative

Negative

Positive

Positive

missing

0

0

6

6

6

Rh Negative

4

4

18

18

22

18%

Rh Positive

299

299

2,174

2,174

2,473

88%

Total

303

303

2,198

2,198

2,501

95 products have missing ABO and Rh data

*95 products have missing ABO and Rh data

*95 products have missing ABO and Rh data

*95 products have missing ABO and Rh data

*95 products have missing ABO and Rh data

*95 products have missing ABO and Rh data

*95 products have missing ABO and Rh data

Supplemental Table S5D: ABO/Rh types of cryoprecipitate and transfusion recipients

Product ABO

Product ABO

Product ABO

Product ABO

Total

%ABO

Identical

Patient ABO

A

AB

B

O

missing

0

0

0

0

0

A

7

4

0

0

11

64%

AB

0

0

0

0

0

—

B

2

4

1

0

7

14%

O

1

0

1

24

26

92%

Total

10

8

2

24

44

Product Rh

Product Rh

Product Rh

Product Rh

Total

%Rh Identical

Patient Rh

Negative

Negative

Positive

Positive

missing

0

0

0

0

0

Rh Negative

0

0

0

0

0

—

Rh Positive

3

3

39

39

42

93%

Total

3

3

39

39

42

92 products have missing ABO and Rh data

*92 products have missing ABO and Rh data

*92 products have missing ABO and Rh data

*92 products have missing ABO and Rh data

*92 products have missing ABO and Rh data

*92 products have missing ABO and Rh data

*92 products have missing ABO and Rh data

* 2 products were pooled product and not included in the Rh table

** 2 products were pooled product and not included in the Rh table

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Figure 1: Transfused components (N=1872) administered to inpatients, by component type

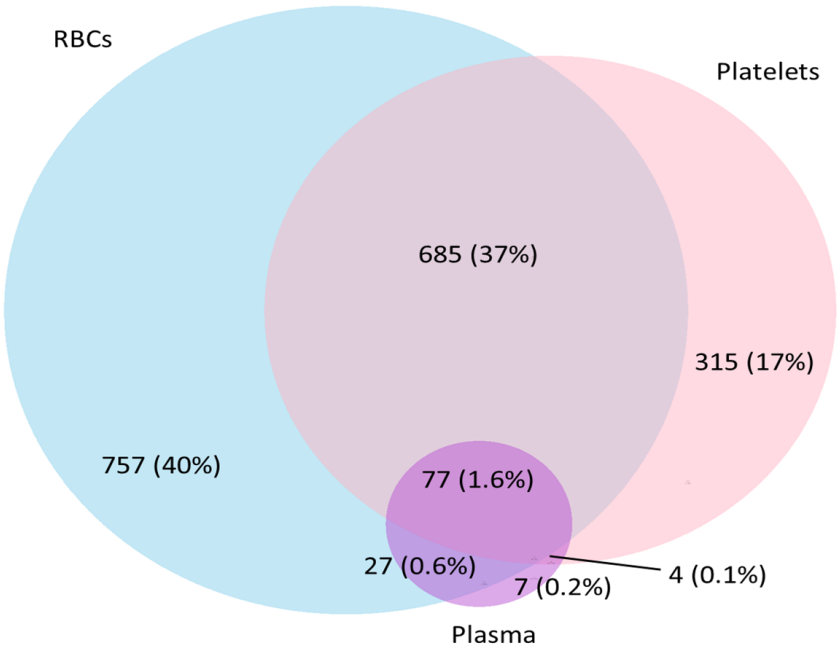
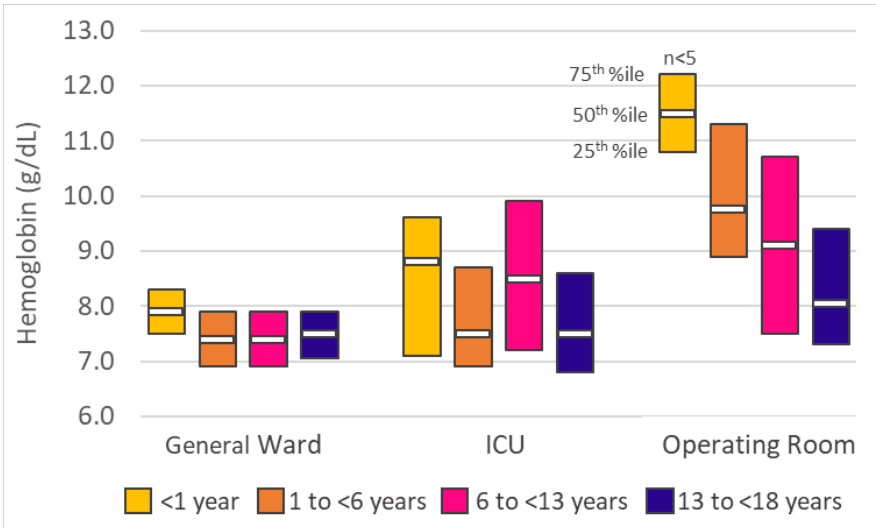
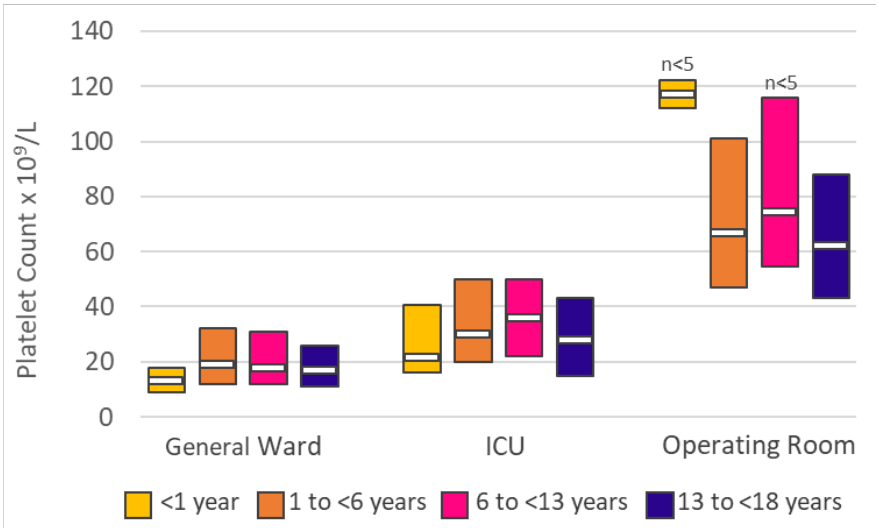


Figure 2: Pre-transfusion laboratory values by location of component issued and by patient age





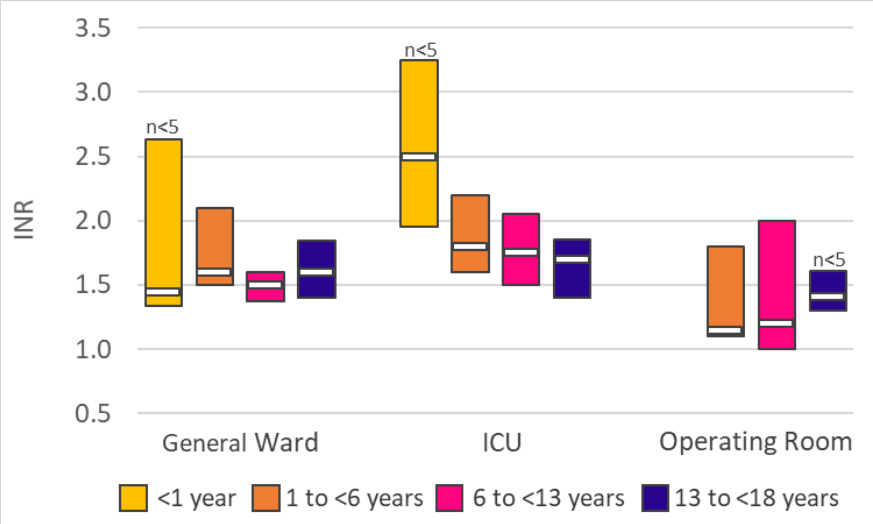


Figure 3: Pre-transfusion laboratory values for select diagnoses, of inpatients and outpatients encounters (as applicable)