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Red Blood Cell Storage Duration is Not Associated with Clinical Outcomes for Acute Chest Syndrome in Children with Sickle Cell Disease

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Abstract

Background—Providers commonly transfuse sickle cell disease (SCD) patients with fresh red blood cells (RBCs) as treatment for acute chest syndrome (ACS). The objective of this study is to determine if there is an association between the storage duration of RBCs and length of hospitalization and oxygen requirement after transfusion in pediatric SCD patients with ACS.

Study Design and Methods—This is a retrospective cohort study of pediatric SCD patients with ACS treated with a simple RBC transfusion over 8.5 years at a single institution. Multivariate generalized estimation equation analysis was used to identify associations between storage duration of RBCs and outcome measures.

Results—Two hundred thirty-four ACS episodes in 131 subjects were included. The median storage duration of the oldest unit of transfused RBCs was 17 days (IQR 11 – 26). The majority of ACS episodes, 77.4% were treated with 1 unit of transfused RBCs, 20.9% received 2 units and 1.7% received 3 or more units of RBCs. There was no association between the storage duration of the oldest unit of transfused RBCs, and either duration of hospitalization or supplemental oxygen requirement after transfusion in multivariate analyses.

Conclusion—This retrospective study is one of the first to investigate the role of the storage lesion in children with SCD, and does not support the preferential transfusion of fresh RBCs for

ACS. Ultimately, a randomized controlled trial (RCT) is necessary to determine whether the storage age of RBCs affects outcomes for patients with SCD and ACS.

Keywords

Sickle cell disease; sickle cell anemia; acute chest syndrome; storage lesion; transfusion

Introduction

Globally, 14 million children with sickle cell disease (SCD) will be born between 2010 – 2050, with 1 out of 700 African-American infants affected in the United States^{1,2}. SCD pathophysiology includes decreased oxygen affinity of hemoglobin S, chronic hemolytic anemia, and obstruction of the microcirculation, promoting endothelial activation, inflammation, and tissue ischemia^{3,4}. Acute chest syndrome (ACS) is the most common cause of death within the SCD population, and is a common complication of the disease, with 30% of patients experiencing at least one episode during their lifetime^{5,6}.

RBC transfusion is a cornerstone of therapy for SCD patients, with 60 percent of patients requiring at least one RBC transfusion^{7,8}. RBC transfusion as therapy for ACS results in improved oxygenation as measured by the partial pressure of arterial oxygen, alveolar-arterial oxygen gradient, arterial-alveolar oxygen ratio and oxygen saturation^{9–11}. While often beneficial, transfusion therapy also has risks. There is limited understanding of the clinical implications of physical and metabolic changes that RBCs undergo during storage, known as the storage lesion. RBCs remain metabolically active during storage, consuming adenosine triphosphate, nicotinamide adenine dinucleotide, and 2,3-diphosphoglycerate. These metabolic changes have several implications, including oxidative injury to the RBC membrane leading to the release of pro-thrombotic and pro-inflammatory micro-vesicles, decreased RBC deformability and bioavailability of nitric oxide, and increased methemoglobin and free iron^{12–14}. Thus, transfused RBCs may reduce oxygen delivery and perfusion to the microvascular tissue, and increase the risk of infection and hypercoagulable events^{14–16}, triggering negative clinical outcomes in children with SCD.

Animal models of sepsis suggest an association between the storage lesion and mortality¹⁷, but the clinical impact of the storage lesion remains controversial in humans. There are two reports of independent associations between increased storage duration of transfused RBCs and multiorgan dysfunction syndrome (MODS) in pediatric critical care populations, but a recent RCT did not find an improvement in clinical outcomes with the transfusion of fresh RBCs compared to moderately aged RBCs in premature, very low-birth-weight neonates^{18–20}. Fasano et al. published the only investigation into the role of the storage lesion within SCD, and were unable to make a conclusion regarding the role of storage age and alloimmunization²¹. Regardless of the limited literature supporting this practice, national surveys indicate that 25 – 60% of institutions preferentially transfuse SCD patients with RBCs stored for 14 days^{22,23}. In this hypothesis-generating, retrospective study of children with SCD and ACS, we aimed to determine if an association between the storage duration of transfused RBCs and clinical outcomes exists. We hypothesized that transfusion

of RBCs with increased storage duration will be associated with increased length of hospitalization and supplemental oxygen requirement.

Materials and Methods

We performed a retrospective cohort study of SCD patients admitted to St. Louis Children's Hospital (SLCH) with ACS requiring treatment with a simple RBC transfusion from January 2005 through July 2013. ICD-9 codes identified SCD patients transfused at SLCH during the study period. We reviewed all RBC units dispensed to SCD patients to determine units transfused for ACS therapy.

Patients aged ≥ 2 years with any phenotype of SCD were included. Patients admitted with concomitant conditions were included if they fulfilled the definition for ACS. ACS episodes treated with an exchange transfusion, or occurring while the patient received chronic RBC transfusion therapy or after a stem cell transplant were excluded to reduce selection bias. Patients with inadequate medical records were excluded if insufficient information was available to confirm the diagnosis of ACS, and abstract the severity score of ACS episode, admission weight, storage age and outcome measures.

ACS was defined as an acute infiltrate on chest x-ray, and one of the following symptoms: cough, fever ≥ 38.5 degrees Celsius, age-defined tachypnea, wheezing or chest pain¹⁰. The number of ACS episodes prior to the event included within the study was determined by reviewing discharge diagnoses at SLCH prior to the date of the included event. We assumed a history of 2 ACS episodes prior to the included ACS event for 3 subjects because a history of ACS was reported in the medical record, but no admissions at SLCH for ACS were found. Total ACS severity score was a sum of individual clinical, radiological and oxygen requirement scales. A validated ACS severity score does not exist, so a combination of reported severity scores and clinical experience was used to create the score depicted in table 1^{24,25}. A history of asthma was determined by reviewing diagnoses and past medical history in the medical records. Concomitant complications were included if the diagnosis was documented by a provider or there was a confirmatory laboratory result. Baseline hemoglobin was defined as the value obtained at the most recent clinic visit that was ≥ 2 weeks from an inpatient admission. Pre- and post-transfusion hemoglobin values were obtained within 24 hours of the first and last RBC transfusion. If multiple values were available within this 24-hour period, we used values obtained closest to the transfusion.

The primary outcome, length of stay after transfusion, was measured in days, and calculated by subtracting the transfusion date from the discharge date. The secondary outcome, length of oxygen requirement after transfusion, was measured in days, and calculated by subtracting the transfusion date from the stop date for oxygen, or the start date from the stop date if the requirement developed after transfusion. The stop date for supplemental oxygen was defined as the date of final termination of oxygen prior to discharge. A duration of 0.5 days was used if the oxygen requirement terminated on the day of the transfusion, or the new requirement was <1 day.

Transfusion/Blood Banking

Standard RBC transfusion practice for ACS amongst hematologists at SLCH is to provide a simple transfusion of RBCs first if hemoglobin concentration is < 9.5 g/dL, and then progress to manual exchange transfusion or erythrocytapheresis if the patient's clinic status deteriorates despite simple transfusion. RBCs selected for SCD patients at SLCH are stored in AS-1 additive solution, leukoreduced, HbS-negative, and matched for C, E, and K. Irradiation and CMV-seronegative RBCs are not routinely provided unless a specific indication warrants special processing. If multiple units were transfused, we defined our storage age variable as the storage duration of the oldest transfused unit. The age of non-irradiated RBC units was calculated by subtracting the difference between expiration and transfusion dates from 42 days, which is the maximum storage duration for AS-1 units. The age of irradiated RBC units was calculated by subtracting the collection date from the transfusion date. The first unit dispensed defined date and time of transfusion. All transfused units were summed to define the volume transfused per ACS episode.

Statistical Analysis

The lack of published literature investigating the storage lesion in SCD precludes an estimation of effect size and calculation of an *a priori* power analysis. Generalized Estimating Equation (GEE) modeling with Poisson probability distribution and an exchangeable correlation structure was used to account for the correlation of multiple ACS episodes within each patient. Univariate analysis evaluated the same potential *a priori* determined confounding variables for each outcome. Bivariate Spearman rank correlations < 0.5 confirmed a lack of collinearity between potential predictors, except for a correlation of 0.72 between the variables of concomitant vaso-occlusive crisis (VOC) and concomitant complication. P-value < 0.2 in the univariate analysis dictated inclusion in the multivariate GEE model. *A priori* decision mandated inclusion of transfused volume standardized by weight and age of the oldest unit of transfused RBCs in the multivariate model regardless of significance level. Covariates included in the multivariate models for the primary outcome were age, baseline and pre-transfusion hemoglobin, number of previous ACS episodes, hydroxyurea therapy, corticosteroid therapy, total severity score, concomitant VOC and concomitant complications (splenic sequestration, infection, etc.). Covariates included in the multivariate models for the secondary outcome were age, ABO blood type, corticosteroid therapy, concomitant VOC, concomitant complication and total severity score. Gender, SCD genotype, history of asthma, transfer to intensive care unit prior to transfusion and year of treatment did not meet criteria for inclusion in any multivariate models. Multivariate modeling was performed with backward elimination without replacement until all included covariates had a p value ≤ 0.05 or less. Separate models were created evaluating storage age as a continuous or categorical variable for both outcome measures. Adequacy of the functional form for fitted models was assessed using cumulative residual plots with 10,000 simulations. An adjusted incidence rate ratio with 95% confidence interval was calculated for each variable included in the final multivariate model to quantify the association between the covariate and outcome measure. All statistical tests were two-sided at significance level 0.05. All analyses were performed in SAS 9.3 (SAS Institute, Cary NC).

Results

Between January 2005 and July 2013, we identified 234 episodes of ACS among 131 patients (72 female, 59 male; 106 HbSS, 7 HbS β^0 , 12 HbSC, 3 HbS β^+ , 2 HbSS + hereditary persistence of fetal hemoglobin, 1 phenotype unknown secondary to diagnosis at another institution). Figure 1 provides details regarding the 54 episodes of ACS that were excluded, and table 2 provides a description of the cohort.

The median storage duration of the oldest unit of transfused RBCs was 17 days (interquartile range (IQR) 11 – 26), with a range of 2 to 41 days. When evaluated as a categorical variable, 36.8% of the transfused units were stored for < 14 days; 25.6% were stored between 14–20 days; 17.1% were stored between 21–27 days; 20.5% were stored for $\geq$ 28 days. Subjects received a mean of 13.1 ml/kg (standard deviation (SD) $\pm$ 5.3 ml/kg) of transfused RBCs. The majority of ACS episodes, 77.4% (n = 181), were treated with 1 unit of transfused RBCs (mean storage age 18.1 days, SD $\pm$ 9.1), while 20.9% (n = 49) received 2 units (mean storage age of the oldest unit 19.6 days, SD $\pm$ 9.6) and only 1.7% (n = 4) of episodes required transfusion of $\geq$ 3 units of RBCs (mean storage age of the oldest unit 22.5 days, SD $\pm$ 8.5). There was not a statistically significant difference by analysis of variance testing (p = 0.39) between the mean storage age of the oldest unit when categorized by number of units transfused. The mean pre- and post-transfusion hemoglobin was 6.0 g/dL (SD $\pm$ 1.1 g/dL) and 8.5 g/dL (SD $\pm$ 1.2 g/dL) respectively.

The median hospital stay after transfusion was 3.0 days (IQR 2 – 5 days). There was not a significant difference in length of hospitalization after transfusion regardless of categorization of the RBC storage duration (Table 3). When evaluating the storage duration of transfused RBCs as a continuous or categorical variable, neither storage duration of the oldest unit of transfused RBCs nor transfused volume standardized by weight were significantly associated with length of hospitalization after transfusion in multivariate analyses. Significant predictors of a longer length of hospitalization after transfusion in the multivariate models included older patient age at time of ACS episode, hydroxyurea therapy, treatment of ACS with corticosteroids, higher hemoglobin before transfusion, concomitant VOC, and concomitant complication (Table 4).

The median duration of supplemental oxygen requirement after transfusion was 1 day (IQR 0.5 – 3 days). There was not a significant difference in length of oxygen requirement after transfusion regardless of categorization of the RBC storage duration (Table 5). When evaluating storage age as a continuous or categorical variable, neither storage duration of the oldest unit of transfused RBCs nor transfused volume standardized by weight were significantly associated with duration of supplemental oxygen requirement after transfusion in the final multivariate models. A higher total severity score for the ACS episode and a concomitant complication were significantly associated with longer duration of supplemental oxygen requirement in all final models, while treatment with corticosteroids was only significantly associated with increased duration of oxygen requirement after transfusion when the storage duration was treated as a continuous variable (Table 6).

Discussion

This hypothesis-generating, retrospective cohort study is the first investigation into the role of the RBC storage lesion with duration of hospitalization and oxygen requirement in SCD patients with ACS treated with simple RBC transfusion. We did not find a significant relationship between the storage age of transfused RBCs and the duration of hospital stay or supplemental oxygen requirement after transfusion in this specific population of children with SCD, despite accounting for significant covariates: age, hydroxyurea and corticosteroid therapy, pre-transfusion hemoglobin, severity of the ACS episode, and concomitant complications.

Our results agree with previous ACS publications, starting with Vichinsky et al.'s landmark prospective study of 671 ACS episodes, reporting an association between duration of hospitalization and the covariates of age and concomitant VOC in the extremities¹⁰. Similarly, we identified an association between corticosteroid treatment and greater length of hospitalization, as did Strouse et al. and Sobota et al. in 2 independent retrospective analyses^{25,26}. Hydroxyurea therapy was not a significant predictor in the latter two reports, but is a marker of disease severity²⁶. Our results, plus Strouse and Sobota's studies, contrast with Bernini et al.'s report of decreased length of stay when ACS is treated with dexamethasone versus placebo, and their multivariate analysis showing an association between number of previous ACS episodes, gender and length of hospitalization²⁴. This difference in results is likely secondary to variance in study design and inclusion criteria. The consistency between our findings and previous publications supports the accuracy of our data collection and analysis, further strengthening our conclusion that the storage duration of transfused RBCs is not associated with clinical outcomes in pediatric SCD patients with ACS treated with simple RBC transfusion.

The literature investigating the storage lesion within pediatrics is limited. Karam et al. and Gauvin et al. found an association between RBC storage duration and MODS in pediatric ICU patients in prospective cohort studies^{18,19}. The Age of Red Blood Cells in Premature Infants RCT showed no difference in the composite outcome of mortality and morbidities in premature infants randomized to transfusion with RBCs stored for < 7 days (mean 5.1 days) and standard-issue RBCs (mean 14.6 days)²⁰. The ongoing Age of Blood in Children in Pediatric Intensive Care Units RCT (NCT #01977547) investigating the storage duration in critically ill children will further our understanding of this issue within the ICU population. Most recently, Fasano et al. published the only investigation of the storage lesion within SCD. While a significant association between storage age of transfused RBCs and alloimmunization was seen in both univariate and multivariate analyses, the authors were unwilling to draw a conclusion regarding the role of storage age and alloimmunization secondary to sample size concerns²¹. The need to examine the clinical implications of the RBC storage lesion in SCD with prospective studies is warranted because many providers currently reserve fresh RBCs for this population secondary to the biologic plausibility that RBCs of increased storage duration may have adverse effects, yet our retrospective study did not find an association between RBC storage duration and outcomes for ACS in a pediatric SCD population treated with simple RBC transfusion.

Limitations to our study exist after attempting to control for pitfalls commonly described within retrospective storage lesion research²⁷. Retrospective designs are at risk for selection bias, measurement bias and confounding. Our strict inclusion and exclusion criteria, thorough review of medical records, clear definitions of covariates and outcome measures, and use of a standardized data abstraction form limit selection and measurement bias. Our univariate analysis of 18 covariates, evaluation for co-linearity and multivariate analysis as recommended by van de Watering et al. reduce confounding within the retrospective design, yet there is still potential unmeasured confounding²⁷. The retrospective design prevents investigation of causal relationships, and covariates and outcome measures are limited to those consistently recorded in the medical record. Our outcomes of hospital duration and oxygen requirement are standard within ACS literature, but they are not precise surrogates for efficacy and safety of RBC transfusions.

Second, we used a novel ACS severity scale because a validated score does not exist. Validation of this score will be critical for future prospective trials. Third, the skewed distribution of storage duration within our data prevents an ideal comparison of “fresh” versus “old” RBCs, but is informative as a hypothesis-generating, retrospective analysis. Our data reflects the standard practices of a blood bank that does not consider storage age in the release of RBCs for simple transfusion of SCD patients, and should be representative of practices at other blood banks.

Lastly, a standardized definition of the storage time variable does not exist. The use of age of the oldest RBC unit as our storage time variable is a limitation because we attribute outcomes to the storage duration of a single unit, disregarding the role of other transfused units²⁷. Using age of the oldest RBC unit also potentially overestimates adverse outcomes in the inherently sicker subgroup that required multiple units of transfused RBCs, because patients receiving multiple transfusions are more likely to receive a unit with a longer storage duration secondary to greater variance in the storage age of the received units²⁷. However, we did not find a significant difference in the mean storage duration of units transfused for children who received 1, 2 or 3 units. Additionally, volume transfused is a marker for disease severity that we accounted for by forcing into our multivariate models.

In conclusion, we report the first study investigating the impact of storage duration of RBCs on length of hospitalization and oxygen requirement in children with SCD and ACS. While this is a hypothesis-generating, retrospective study, our results do not support preferentially transfusing RBCs with a storage duration of <14 days to children with SCD and ACS requiring a simple RBC transfusion^{22,23}. Providing fresher RBCs to specific populations increases economic and logistical challenges for blood banks, necessitating prospective evaluation with a RCT to elucidate any causal relationship between the storage lesion and clinical outcomes in SCD patients with ACS.

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Figure 1.

Table 1

ACS Severity Score

	0 Points	1 Point	2 Points
Clinical Score	Asymptomatic	Age-Defined Tachypnea	Age-Defined Tachypnea AND Retractions
Radiological Score	Patchy OR Single Lobe Infiltrate	Multilobar Consolidation	-
Oxygen Requirement Score	No Requirement	Nasal Canula OR Facemask	Bipap OR Mechanical Ventilation

* Total Severity Score is the sum of the Clinical, Radiological and Oxygen Requirement Scores

Table 2**Cohort Description per ACS Episode**

Calendar year of ACS episode, N (%)	
2005	14 (6%)
2006	39 (16.7%)
2007	32 (13.7%)
2008	45 (19.2%)
2009	37 (15.8%)
2010	15 (6.4%)
2011	14 (6.0%)
2012	25 (10.7%)
2013	13 (5.5%)
Age at ACS episode (Years), Mean (SD)	9.3 (5.6)
Baseline hemoglobin (g/dL), Mean (SD)	7.8 (1.2)
Previous ACS episodes, Median [IQR]	2 [1,5]
History of asthma, N (%)	135 (57.7%)
Treatment with hydroxyurea, N (%)	26 (11.1%)
Treatment with corticosteroids, N (%)	116 (49.6%)
Concomitant complication at time of ACS episode, N (%)	185 (79.1%)
VOC	156 (66.7%)
Splenic sequestration	9 (3.9%)
Bacterial infection	14 (6%)
Viral infection	30 (12.8%)
Other complication not listed above *	17 (7.3%)
Total severity score, N (%)	
0	7 (3.0%)
1	23 (9.8%)
2	84 (35.9%)
3	85 (36.3%)
4	33 (14.1%)
5	2 (0.9%)

* Other complications: Hepatic sequestration, priapism, hypertension, migraine, febrile seizure, gastritis, ileus, cholecystitis, ischemic colitis, fracture, or burn, but not splenic sequestration, infection or VOC

Table 3

Length of Hospitalization After Transfusion by Storage Time Variable

Storage Duration	Number of ACS Episodes	Mean $\pm$ SD Length of Hospitalization After Transfusion (Days)	P Value
14 Days	102	4.6 $\pm$ 4.6	0.42 [*]
> 14 Days	132	4.1 $\pm$ 3.3	
21 Days	151	4.3 $\pm$ 4.1	0.75 [*]
> 21 Days	83	4.4 $\pm$ 3.5	
28 Days	192	4.3 $\pm$ 3.9	0.65 [*]
> 28 Days	42	4.6 $\pm$ 4.0	
< 14 Days	86	4.5 $\pm$ 4.8	0.91 [†]
14–20 Days	60	4.1 $\pm$ 3.2	
21 – 27 Days	40	4.2 $\pm$ 2.9	
28 Days	48	4.5 $\pm$ 3.9	

* Two-sample t-test

† One-way ANOVA

Table 4

Multivariate Models Predicting Length of Hospitalization after Transfusion

	Multivariate Models by Storage Duration Variable				
	Continuous Variable	Unordered Categorical Variable < 14d Vs. 14-20d Vs. 21-27d Vs. ≥ 28d	Dichotomized Variable Vs. > 14d	Dichotomized Variable Vs. > 21d	Dichotomized Variable Vs. > 28d
RBC Storage Age (Days)					
	P = 0.71	P = 0.64	P = 0.44	P = 0.45	P = 0.58
Transfused Volume (ml/kg)					
	P = 0.09	P = 0.08	P = 0.07	P = 0.09	P = 0.09
Age (Years)					
	P = 0.04 aIRR = 1.03 (1.00, 1.05)	P = 0.04 aIRR = 1.03 (1.00, 1.05)	P = 0.01 aIRR = 1.04 (1.02, 1.06)	P = 0.04 aIRR = 1.03 (1.00, 1.05)	P = 0.04 aIRR = 1.03 (1.00, 1.05)
Hydroxyurea					
	P = 0.04 aIRR = 1.43 (1.09, 1.87)	P = 0.03 aIRR = 1.43 (1.10, 1.85)	NS	P = 0.04 aIRR = 1.42 (1.08, 1.86)	P = 0.04 aIRR = 1.42 (1.09, 1.85)
Corticosteroid					
	P = 0.03 aIRR = 1.28 (1.04, 1.58)	P = 0.04 aIRR = 1.28 (1.02, 1.60)	P = 0.02 aIRR = 1.30 (1.05, 1.61)	P = 0.03 aIRR = 1.30 (1.04, 1.60)	P = 0.03 aIRR = 1.28 (1.03, 1.58)
Hemoglobin Prior to Transfusion					
	NS	NS	P = 0.03 aIRR = 1.10 (1.02, 1.19)	NS	NS
Concomitant Complication[†]					
	NS	NS	P < 0.001 aIRR = 1.66 (1.31, 2.10)	NS	NS
Concomitant VOC					
	P < 0.001 aIRR = 1.47 (1.25, 1.73)	P < 0.001 aIRR = 1.49 (1.26, 1.76)	NS	P < 0.001 aIRR = 1.50 (1.25, 1.74)	P < 0.001 aIRR = 1.48 (1.26, 1.75)
Other Concomitant Complication[§]					
	P = 0.03 aIRR = 2.09 (1.40, 3.13)	P = 0.03 aIRR = 2.13 (1.42, 3.21)	P = 0.049 aIRR = 1.69 (1.18, 2.40)	P = 0.02 aIRR = 2.09 (1.41, 3.09)	P = 0.02 aIRR = 2.08 (1.40, 3.09)

* Adjusted incidence rate ratio and 95% CI quantify the relationship between covariate and outcome

[†] NS = Not significant[‡] Concomitant complication: Splenic sequestration, infection, VOC and any other complication[§] Other complications: Hepatic sequestration, priapism, hypertension, migraine, febrile seizure, gastritis, ileus, cholecystitis, ischemic colitis, fracture, or burn, but not splenic sequestration, infection or VOC

Table 5

Length of Oxygen Requirement After Transfusion by Storage Time Variable

Storage Duration	Number of ACS Episodes	Mean $\pm$ SD Length of Oxygen Requirement After Transfusion (Days)	P Value
14 Days	102	1.9 $\pm$ 2.0	0.94 [*]
> 14 Days	132	1.9 $\pm$ 2.4	
21 Days	151	1.9 $\pm$ 1.9	0.92 [*]
> 21 Days	83	1.9 $\pm$ 2.7	
28 Days	192	1.8 $\pm$ 1.8	0.42 [*]
> 28 Days	42	2.3 $\pm$ 3.5	
< 14 Days	86	1.9 $\pm$ 2.0	0.50 [†]
14–20 Days	60	1.9 $\pm$ 1.8	
21 – 27 Days	40	1.5 $\pm$ 1.3	
28 Days	48	2.2 $\pm$ 3.3	

* Two-sample t-test

[†] One-way ANOVA

Table 6

Multivariate Models Predicting Length of Oxygen Requirement after Transfusion

	Multivariate Models by Storage Duration Variable				
	Continuous Variable	Unordered Categorical Variable < 14d Vs. 14–20d Vs. 21–27d Vs. 28d	Dichotomized Variable Vs. > 14d	Dichotomized Variable Vs. > 21d	Dichotomized Variable Vs. > 28d
RBC Storage Age (Days)	P = 0.88	P = 0.32	P = 0.48	P = 0.59	P = 0.50
Transfused Volume (ml/kg)	P = 0.16	P = 0.16	P = 0.11	P = 0.12	P = 0.10
Concomitant Complication[‡]	P < 0.001 aIRR = 2.22 (1.64, 3.00)	P < 0.001 aIRR = 2.25 (1.66, 3.03)	P < 0.001 aIRR = 2.24 (1.67, 3.01)	P < 0.001 aIRR = 2.22 (1.64, 3.00)	P < 0.001 aIRR = 2.17 (1.61, 2.93)
Total Severity Score	P < 0.001 aIRR = 1.51 (1.30, 1.75)	P < 0.001 aIRR = 1.51 (1.30, 1.75)	P < 0.001 aIRR = 1.53 (1.32, 1.78)	P < 0.001 aIRR = 1.54 (1.32, 1.77)	P < 0.001 aIRR = 1.52 (1.32, 1.76)
Corticosteroid	P = 0.049 aIRR = 1.33 (1.00, 1.75)	NS	NS	NS	NS

* Adjusted incidence rate ratio and 95% CI quantify the relationship between covariate and outcome

[‡] NS = Not significant[‡] Concomitant complication: Splenic sequestration, infection, VOC and any other complication