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Association of red blood cell transfusion volume with postoperative complications and mortality in neonatal surgery

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ABSTRACT

Introduction: Red blood cell transfusion (RBCT) is commonly administered in neonatal surgical care in the absence of clear clinical indications such as active bleeding or anemia. We hypothesized that higher RBCT volumes are associated with worse postoperative outcomes.

Methods: Neonates within the National Surgical Quality Improvement Program–Pediatric database who underwent inpatient surgery (2012–2016) were stratified by weight-based RBCT volume: <20cc/kg, 20–40cc/kg, and >40cc/kg. Postoperative complications were categorized as wound, systemic infection, central nervous system (CNS), renal, pulmonary, and cardiovascular. Multivariable logistic regression and cubic spline analysis were used to evaluate the association between RBCT volume, postoperative complications, and 30-day mortality. Sensitivity analysis was conducted by performing propensity score matching.

Results: Among 9,877 neonates, 1,024 (10%) received RBCTs. Of those who received RBCT, 53% received <20cc/kg, 27% received 20–40cc/kg, and 20% received >40cc/kg. Relative to neonates who were not transfused, RBCT volume was associated with a dose-dependent increase in renal complications, CNS complications, cardiovascular complications, and 30-day mortality. With cubic spline analysis, a lone inflection point for 30-day mortality was identified at a RBCT volume of 30 – 35 cc/kg. After propensity score matching, the dose-dependent relationship was still present for 30-day mortality.

Conclusion: Total RBCT volume is associated with worse postoperative outcomes in neonates with a significant increase in 30-day mortality at a RBCT volume of 30 – 35 cc/kg. Future prospective studies are needed to better understand the association between large RBCT volumes and poor outcomes after neonatal surgery.

Level of evidence: Level IV, Retrospective cohort study

Abbreviations

NICU	neonatal intensive care unit
RBCT	red blood cell transfusion
NSQIP – P	national surgical quality improvement program – pediatrics
SSI	surgical site infection
CNS	central nervous system
ASA	American Society of Anesthesiology
POD	postoperative day

1. Introduction

Transfusion of blood products is one of the most common interventions in the perioperative care of neonates. This is primarily a function of inherent laboratory abnormalities in this age group including anemia, thrombocytopenia, and coagulopathy. [1–3] More specifically, a transient decrease in erythropoietin production after birth and daily phlebotomy contribute to anemia in the neonatal population. [4,5] Historically, these abnormalities resulted in liberal transfusion guidelines with >50% of extremely low and low birth weight neonates receiving red blood cell transfusion (RBCT) during initial hospitalization. [6,7] While anemia can lead to poor oxygen delivery to developing organs, liberal transfusion of blood products has an inherent associated risk, including intraventricular hemorrhage, necrotizing enterocolitis, bronchopulmonary dysplasia, and

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mortality. [6–13] Additionally, in the perioperative setting, preoperative RBCT administered to neonates has been associated with increased mortality and complications. [14–16]

Several clinical trials have evaluated the effect of liberal versus restrictive RBCT in premature neonates and have identified no significant difference in morbidity or mortality. [17–19] However, surgical patients were excluded from these studies, so the findings may not be generalizable. [17,19] Furthermore, adult and pediatric studies evaluating the association between RBCT volume and postoperative outcomes suggest that larger RBCT volume is associated with worse postoperative outcomes. [20–25] Similar studies have not been performed in the neonatal population.

Given the frequency of neonatal RBCT, an important question to address is whether there might be an RBCT volume where mortality significantly increases, or an "inflection point." Therefore, the objectives of this study were to: (1) describe the characteristics of neonatal surgical patients who receive intraoperative and/or postoperative (intra/postop) RBCT, (2) evaluate the association between preoperative hematocrit and RBCT volume, (3) identify whether there is a mortality "inflection point" based on RBCT volume, and (4) evaluate the association between RBCT volume, postoperative complications, and postoperative mortality. We hypothesized increased RBCT volume will be associated with lower preoperative hematocrit and worse postoperative outcomes.

2. Methods

2.1. Data source & study population

Data from the American College of Surgeons National Surgical Quality Improvement Program – Pediatric (NSQIP – P) was used to conduct a national cohort study of neonates who received RBCT after inpatient procedures from 2012 to 2016. The database collects over 350 variables, including preoperative comorbidities, preoperative diagnosis, procedural classification, intraoperative variables, postoperative complications, and mortality. As of 2016, more than 110 hospitals contribute data to NSQIP – P, including freestanding general acute care children's hospitals, children's hospitals within larger hospitals, specialty children's hospitals, and general acute care hospitals with a pediatric wing. [26] Data reliability is achieved through continuous training of nurse reviewers. The study was deemed not human subjects research and exempt from review by Baylor College of Medicine Institutional Review Board due to the de-identified nature of NSQIP – P. Neonates were identified through the database using the NSQIP – P variables "Neonate type" (defines neonate as term or preterm at birth) and "Neonate" (defines as neonate at time of surgery). Neonates were included for analysis if a preoperative hematocrit was recorded at least 7 days prior to surgery.

2.2. Variables

All neonates who received intra/postop RBCT within 72 h of surgery were stratified using weight-based RBCT volumes defined as <20 cc/kg, 20 – 40 cc/kg, and >40 cc/kg. [22] The presence of a preoperative RBCT is reported in the database, but the associated volume given is not recorded. So, the RBCT volume reported throughout this analysis only represents the collective RBCT volume given intraoperatively and postoperatively. Postoperative complications were grouped into six categories: wound complication (superficial surgical site infection [SSI], deep incisional SSI, superficial wound disruption or dehiscence, deep wound disruption or dehiscence, organ space SSI), systemic infection (sepsis, septic shock, central line associated blood stream infection, clostridium difficile colitis), renal (progressive renal insufficiency, acute renal failure, urinary tract infection), central nervous system (CNS) (all grades of intraventricular hemorrhage (I-IV), seizure disorder, cerebrovascular accident, coma), pulmonary (pneumonia, unplanned intubation), and cardiovascular (cardiac arrest with cardiopulmonary resuscitation, venous thrombosis requiring therapy, pulmonary embolism). Mortality was defined as death within 30-days of surgery.

2.3. Statistical analysis

The exposure of interest was volume of RBCT. The primary outcome was 30-day mortality and the secondary outcome measure was the occurrence postoperative complications. Descriptive statistics were used to describe the association between clinical characteristics, operative characteristics, and intra/postop RBCT. Univariate analysis was used to compare the intra/postop RBCT and no RBCT neonatal cohorts with Chi-squared test for categorical variables and two-sample *t*-test for continuous variables. Analysis of variance (ANOVA) with Bonferroni correction ($0.05/6 = 0.0083$) was used to compare preoperative lab values (i.e. hematocrit and platelets) between different RBCT volumes (0 cc/kg, <20 cc/kg, 20 – 40 cc/kg, >40 cc/kg). A non-parametric test of trend was applied to evaluate preoperative RBCT rates across intra/postop RBCT volumes.

To account for severity of illness in the study population, the association between RBCT volume, postoperative complications, and 30-day mortality was evaluated using multivariable logistic regression. Covariates were selected using backwards selection based on the 30-day mortality model. Covariates were initially included based on a univariate cutoff value of $p<0.10$ and excluded in the multivariable model if $p>0.05$. The final covariates were history of prematurity, race, age, cardiac risk factors, oxygen support, chronic lung disease, preoperative ventilator dependence, presence of hematologic disorder, use of preoperative steroids, presence of nutritional support, preoperative blood transfusion within 48 h, preoperative hematocrit (stratified as >40, 35 – 40, 30 – 35, 25 – 30, and <25), preoperative systemic inflammatory response syndrome or sepsis, American Society of Anesthesiology (ASA) classification, surgery classification (elective, urgent, emergent), and wound classification (clean, clean-contaminated, contaminated, dirty). In the models, neonates who had not received RBCTs served as the reference population.

To further evaluate possible changes in 30-day mortality based on RBCT volume, a cubic spline analysis was conducted. RBCT volumes were stratified into 5 cc/kg increments. Thus, our population was stratified into no transfusion (0 cc/kg), 0–5 cc/kg, 5–10 cc/kg, 10–15 cc/kg, 15–20 cc/kg, 20–25 cc/kg, 25–30 cc/kg, 30–35 cc/kg, 35–40 cc/kg, 40–45 cc/kg, 50–55 cc/kg, 55–60 cc/kg and >60 cc/kg of blood transfusion. A 30-day mortality rate was then calculated for each of these RBCT volumes. A third-degree Taylor series polynomial regression with an alpha level of 0.05 was fit to the data, comparing RBCT volume on the x-axis and the corresponding 30-day mortality percentage on the y-axis. The previously published and publicly available R software package "*RootsExtremaInflections*" [27] was used to identify the location of any inflection points which existed in the Taylor series regression. A visualization of the stratification, cubic spline regression fit, and inflection points were created using the R software package "*ggplot2*" [28].

Two sensitivity analyses were performed to further evaluate the multivariate model. The first was conducted to address possible intraoperative complications resulting in large volume intraoperative RBCTs by excluding transfusions on postoperative day (POD) 0 ($n = 722$). POD 0 was used as the cutoff for this sensitivity analysis because the NSQIP – P does not specifically delineate if a transfusion was given intraoperatively or postoperatively, therefore a conservative definition of POD 0 was used to ensure inclusion of all intraoperative transfusions. A second sensitivity analysis was conducted using propensity score analysis. RBCT volume was the treat-

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ment variable and the covariates for propensity score calculation were the same as those identified through initial backwards selection. A logit model predicting RBCT volume using the 16 covariates, and a nearest-neighbor-1:1-greedy matching algorithm was applied to match with a caliper width equal to 0.2 times the standard deviation of the logit of the propensity score. [29–32] After propensity score matching, 16 patients (2, <20 cc/kg; 2, 20 – 40 cc/kg; 12, >40 cc/kg) from the RBCT group were excluded from analysis. There were no statistically significant differences in the covariates used for matching between the RBCT volume cohorts and the matched controls. The logistic regression model was then utilized to reassess the association between RBCT volume, postoperative complications, and 30-day mortality.

Statistical significance was defined as $p<0.05$, except when using Bonferroni correction ($p<0.0083$) for evaluation of preoperative lab values between RBCT volume cohorts. All statistical analyses were performed using Stata version 16.0 (StataCorp, College Station, TX) and R computational software [33].

3. Results

3.1. Baseline clinical and operative characteristics

Over the study period, 9880 neonates were identified who underwent inpatient surgery. Three patients were excluded due to RBCT volume >1000 cc/kg. These were believed to be a clerical error in the database. The final study population was 9877 neonates. Among 9877 neonates, 1024 (10%) received intra/postop RBCT. Table 1 highlights the baseline clinical and operative characteristics based on whether intra/postop RBCT was administered. Overall, neonates who received intra/postop RBCTs had increased rates of prematurity, cardiac risk factors (minor, major, and severe), oxygen support, hematologic disorder, steroid therapy, nutritional support, ASA class III – V, preoperative sepsis and septic shock, dirty/infected wound classifications, and were smaller by weight. With regards to preoperative laboratory assessments and RBCT, patients administered intra/postop RBCT had both lower preoperative hematocrit and higher rates of preoperative transfusion.

Among those who received intra/postop RBCT, 53% ($n = 543$) received <20cc/kg, 27% ($n = 274$) received 20–40cc/kg, and 20% ($n = 207$) received >40cc/kg. Preoperative hematocrit was significantly less for the stratified RBCT volumes (<20 cc/kg, 20–40cc/kg, >40cc/kg) when compared to the no transfusion cohort (0cc/kg) (Table 2). However, there was no significant difference in preoperative hematocrit between the stratified RBCT volumes. Preoperative platelets significantly decreased with increasing RBCT volume. Preoperative RBCT administration significantly (trend test, $p<0.01$) increased with increasing intra/postop RBCT volume.

3.2. Postoperative outcomes stratified by RBCT volume

Fig. 1 shows the rate of postoperative complications and 30-day mortality based on RBCT volume. As RBCT volume increased, the rate of systemic infectious complications, renal complications, CNS complications, cardiovascular complications, and 30-day mortality increased. Intra/postop RBCT was also associated with an increased rate of pulmonary complications, but RBCT volume <20 cc/kg was associated with the highest rate of pulmonary complications. The rate of wound complications was comparable between the 0 cc/kg and 20 – 40 cc/kg cohort.

Table 3 shows the association between RBCT volume, postoperative complications, and 30-day mortality based on multivariate analysis. Relative to neonates who were not transfused, RBCT volume was associated with a dose-dependent relationship with renal complications, CNS complications, cardiovascular complications, and 30-day mortality. Intra/postop RBCT was also associated with increased odds of systemic infectious complications and pulmonary complications; however, it did not appear to have a dose-dependent relationship. Intra/postop RBCT was not associated with increased odds of wound infections, except for RBCT volume <20 cc/kg.

A third-degree Taylor series regression identified a single inflection point for 30-day mortality occurred at the 30 – 35 cc/kg RBCT volume cohort (Fig. 2). At this level, the cubic spline switched from a concave up path to a concave down path.

3.3. Sensitivity analyses

When excluding RBCT given on POD 0 from the multivariate model, neonates who received a RBCT volume <20 cc/kg had significantly increased odds of wound infection, systemic infection, CNS, and pulmonary complications (Supplemental Table 1). Additionally, with this sensitivity analysis, neonates who received >40 cc/kg had significantly increased odds of renal complications, CNS complications, and 30-day mortality.

With propensity score matching, all RBCT volume cohorts were associated with significantly increased odds of systemic infectious complications and 30-day mortality (Table 4). Neonates who received >40 cc/kg also had significantly increased odds of renal complications, CNS complications, and cardiovascular complications. The dose-dependent relationship between RBCT volume, cardiovascular complications, and 30-day mortality was also still present; however, it was no longer present for renal or CNS complications.

4. Discussion

Perioperative RBCT in neonates is common due to underlying anemia from a physiologic decrease in erythropoietin after birth and daily phlebotomy. [1,4,5] Previous studies have identified an association between RBCT volume and worse postoperative outcomes in older pediatric populations. [22–24] Our study offers several important conclusions relevant to the intra/postop administration of RBCT in critically ill neonates: (1) the reason for larger volume RBCT was not related to preoperative anemia; (2) RBCT volumes had a dose-dependent relationship with postoperative morbidity and mortality, and even, RBCT <20 cc/kg were associated with worse outcomes; and (3) practitioners should be cautious when transfusing volumes >35 cc/kg in the absence of overt surgical bleeding.

Common indications for RBCT in the neonatal population include (1) “top ups” for the correction of anemia of prematurity in the absence of clinical bleeding [34] and (2) perinatal or surgical hemorrhagic shock with the primary intent in both scenarios to improve oxygen carrying capacity. Supportive of a “top ups” approach, Goobie and colleagues identified a preoperative hematocrit <40% was independently associated with mortality in the neonatal population. [35] Additionally, other authors have suggested anemia might have a stronger negative impact on outcomes than RBCT. [36,37] These findings have supported neonatal interventions to prevent and treat preoperative anemia, such as delayed cord clamping at birth, limiting blood draws, iron therapy, and recombinant human erythropoietin. [38–40] Our results showed higher RBCT volumes were not associated with lower preoperative hematocrit. Moreover, our data suggest the association of poor postoperative outcomes in the larger RBCT volumes were due to additional factors besides preoperative anemia.

Our study identified a dose-dependent association between RBCT volume and CNS, cardiovascular, and renal complications in the neonatal population when using the original multivariate model. The dose-dependent relationship was also identified with

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Table 1
Baseline clinical and operative characteristics based on postoperative RBCT.

		No Transfusion (n = 8853)	Transfusion (n = 1024)	p-value
Clinical Characteristics				
History of prematurity (%)		41.1	68.9	<0.01
Race/Ethnicity (%)				<0.01
	White	65.2	55.6	
	African American	15.9	23.4	
	Asian	2.27	2.64	
Male Sex (%)		61.8	57.3	<0.01
Age (days)		14	20	<0.01
Weight (kg)		3.20	2.70	<0.01
Cardiac risk factors (%)				<0.01
	None	62.2	45.7	
	Minor	17.9	19.8	
	Major	18.4	30.5	
	Severe	1.46	4.00	
Oxygen support (%)		17.5	48.9	<0.01
Chronic lung disease (%)		11.5	19.3	<0.01
Structural lung abnormality (%)		10.6	20.1	<0.01
Ventilator Dependence (%)		12.2	52.0	<0.01
Tracheostomy (%)		0.49	0.59	0.7
Hematologic disorder (%)		9.50	29.5	<0.01
Steroid therapy (%)		3.15	15.2	<0.01
Nutritional support (%)		36.7	62.7	<0.01
DNR (%)		0.25	0.49	0.16
Preoperative SIRS (%)				<0.01
	None	97.3	80.5	
	SIRS	1.20	3.03	
	Sepsis	0.98	6.64	
	Septic Shock	0.54	9.86	
Operative Characteristics				
Preoperative RBCT (%)		3.64	25.0	<0.01
Preoperative hematocrit		41.1	33.5	<0.01
Preoperative hematocrit (%)				
	>40	55.8	22.8	
	35 – 40	18.2	22.3	<0.01
	30 – 35	16.7	25.5	
	25 – 30	8.0	21.5	
	<25	1.24	8.30	
ASA class (%)				<0.01
	ASA I – II	31.9	7.23	
	ASA III-V	67.7	90.3	
	None Assigned	0.32	2.44	
Case Type (%)				<0.01
	Elective	53.2	43.9	
	Urgent	23.3	14.3	
	Emergent	23.5	41.9	
Wound Class (%)				<0.01
	Clean	37.5	27.0	
	Clean/ Contaminated	53.5	41.3	
	Contaminated	5.7	9.9	
	Dirty/Infected	3.4	21.9	

Table 2
Preoperative lab values and RBCT by postoperative RBCT volume.

	0 cc/kg (n = 8853)	<20 cc/kg (n = 543)	20 – 40 cc/kg (n = 274)	>40 cc/kg (n = 207)
Preoperative hematocrit	41.1 [34.5 – 48.3]	33.6 [29.0 – 40.0]	33.0 [28.8 – 38.3]	34.2 [29.0 – 38.9]
Preoperative platelet	296.0 [222.0 – 399.0]	263.5 [182.0 – 371.0]	256.0 [175.0 – 357.0]	164.0 [100.0 – 277.0]
Preoperative RBCT (%)	3.6	16.2	24.5	48.8

RBCT = Red Blood Cell Transfusion.

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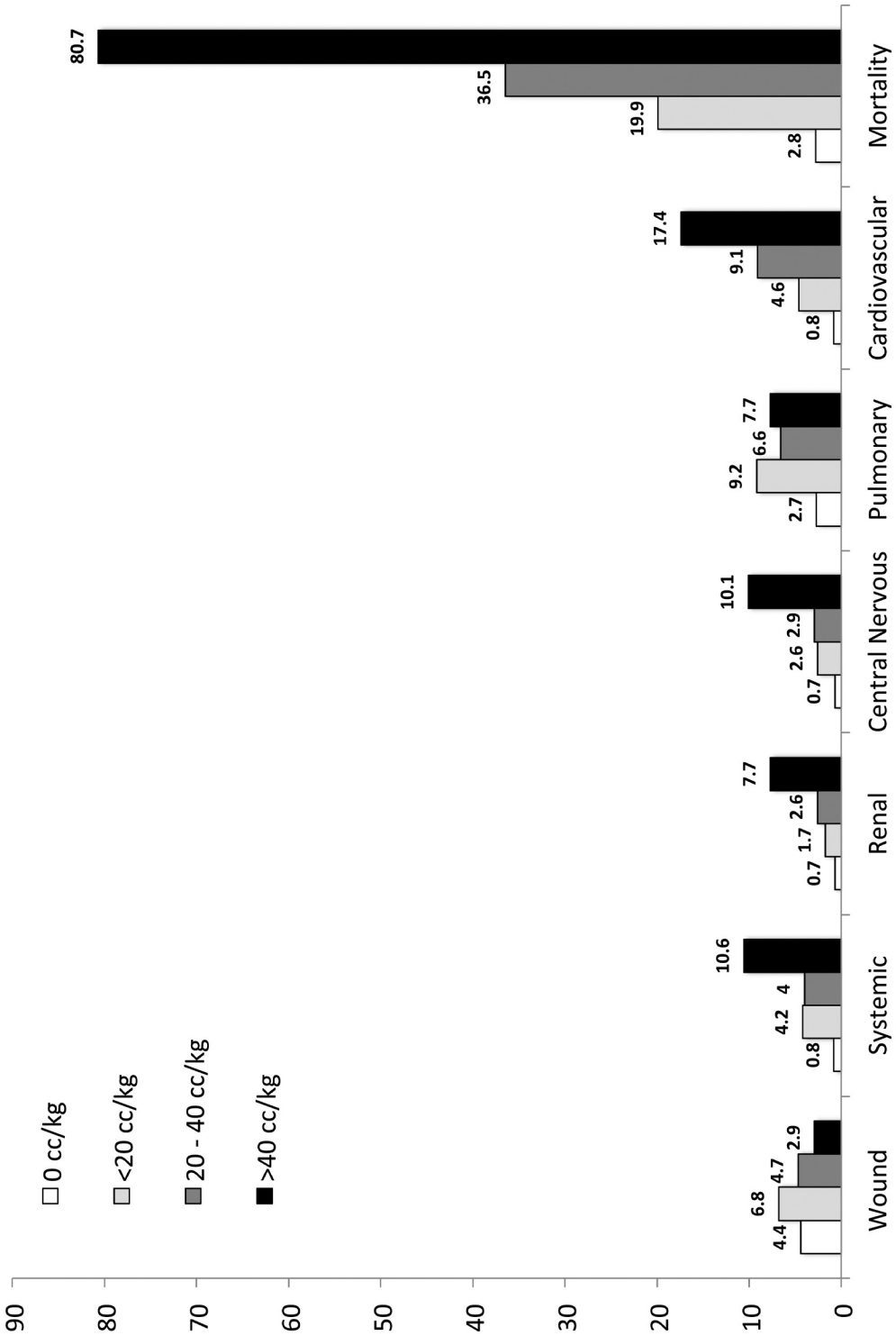

Fig. 1. Rate of postoperative complications and mortality by transfusion volume.

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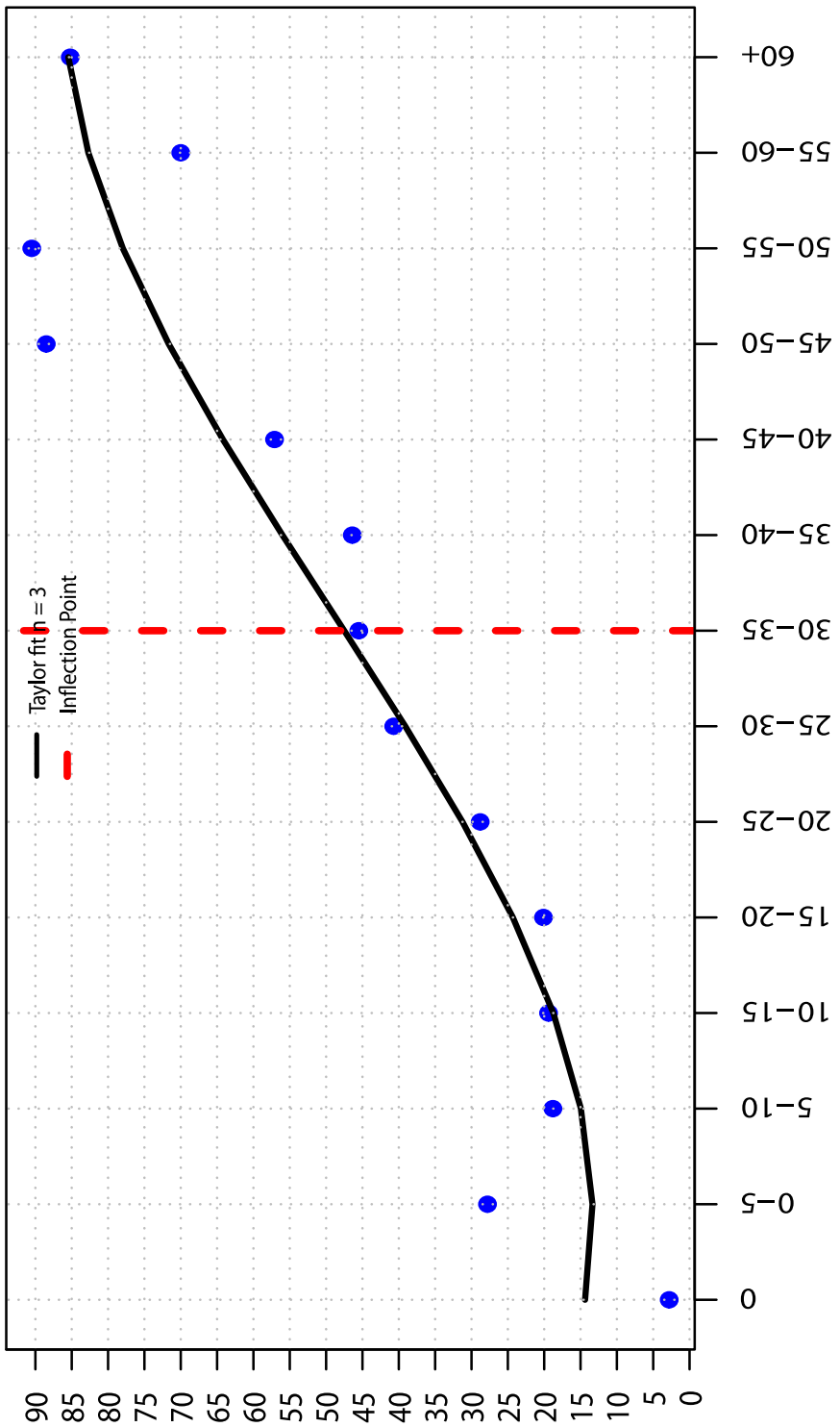

Fig. 2. Cubic spline analysis of red blood cell transfusion volume to 30-day mortality rate.

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Table 3
Association between RBCT volume, postoperative complications, and 30-day mortality.

Outcomes	*0 cc/kg*	*<20 cc/kg*	*20 – 40 cc/kg*	*>40 cc/kg*
	Odds Ratio (95% Confidence Interval)			
Wound Infection	Reference	1.60 (1.10 – 2.32)*	1.17 (0.64 – 2.14)	0.72 (0.30 – 1.73)
Systemic Infection	Reference	3.17 (1.88 – 5.37)*	2.32 (1.13 – 4.76)*	6.54 (3.45 – 12.4)*
Renal	Reference	2.17 (1.01 – 4.64)*	3.37 (1.36 – 8.36)*	9.97 (4.67 – 21.3)*
Central Nervous System	Reference	3.16 (1.62 – 6.17)*	3.68 (1.71 – 7.95)*	12.8 (6.82 – 24.0)*
Pulmonary	Reference	2.60 (1.83 – 3.71)*	1.86 (1.05 – 3.27)*	2.01 (1.04 – 3.89)*
Cardiovascular	Reference	2.43 (1.39 – 4.23)*	3.74 (2.02 – 6.93)*	5.14 (2.72 – 9.72)*
Mortality	Reference	1.69 (1.18 – 2.43)*	2.93 (1.92 – 4.46)*	20.6 (12.0 – 35.5)*

RBCT = Red blood cell transfusions.
*$p<0.05$.

Table 4
Association between RBCT volume, postoperative complications, and 30-day mortality after propensity score matching.

Outcomes	*<20 cc/kg (n = 541/541)*	*20 – 40 cc/kg (n = 272/272)*	*>40 cc/kg (n = 195/195)*
Wound Infection,%			
Controls	3.5	4.8	5.6
Transfusion	6.8	4.8	3.1
OR [95% CI]	2.03 [1.15 – 3.58]	1.04 [0.46 – 2.35]	0.54 [0.21 – 1.43]
p-value	**0.01**	0.92	0.22
Systemic Infection,%			
Controls	1.1	1.1	3.6
Transfusion	4.3	4.0	10.8
OR [95% CI]	3.52 [1.43 – 8.65]	4.66 [1.09 – 19.89]	3.16 [1.29 – 7.76]
p-value	**0.006**	**0.04**	**0.01**
Renal,%			
Controls	0.6	0.0	0.5
Transfusion	1.7	2.6	7.2
OR [95% CI]	3.06 [0.90 – 10.41]	5.90 [0.65 – 53.79]	5.44 [1.17 – 25.40]
p-value	0.07	0.12	**0.03**
Central Nervous System,%			
Controls	0.9	1.1	1.0
Transfusion	2.6	2.9	10.3
OR [95% CI]	2.49 [0.94 – 6.60]	2.28 [0.61 – 8.49]	7.24 [1.91 – 27.46]
p-value	0.07	0.22	**0.004**
Pulmonary,%			
Controls	3.7	2.6	4.6
Transfusion	9.2	6.6	7.7
OR [95% CI]	2.86 [1.68 – 4.86]	2.95 [1.19 – 7.29]	1.69 [0.69 – 4.17]
p-value	**<0.0001**	**0.02**	0.25
Cardiovascular,%			
Controls	2.6	4.0	7.2
Transfusion	4.6	8.8	18.0
OR [95% CI]	1.79 [0.90 – 3.58]	2.57 [1.21 – 5.47]	2.92 [1.49 – 5.70]
p-value	0.10	**0.01**	**0.002**
Mortality,%			
Controls	14.1	26.8	45.6
Transfusion	19.6	36.0	80.0
OR [95% CI]	1.73 [1.10 – 2.71]	2.20 [1.17 – 4.13]	18.46 [8.44 – 40.35]
p-value	**0.02**	**0.01**	**<0.0001**

RBCT = Red RBCT = Red blood cell transfusions, OR = Odds ratio, CI = Confidence interval.

propensity score matching for cardiovascular complications. Additionally, all RBCT volumes were significantly associated with systemic infectious complications in the original model and after propensity score matching. Several previous studies have evaluated the effect of RBCT on CNS complications, specifically intraventricular hemorrhage in preterm neonates. [8,9] Christensen et al. found that after implementing a restrictive RBCT strategy the incidence of intraventricular hemorrhage decreased in their NICUs. [9] Numerous mechanisms have been proposed that could increase the risk of intraventricular hemorrhage after RBCT, including increased reactive oxygen species and endothelial activation [41], and increased capillary slugging in the vulnerable neonatal germinal matrix causing upstream capillary pressure and eventual rupture [42]. Additionally, some studies have identified liberal RBCT strategies are associated with poor long-term neurologic development in children with a history of prematurity. [43,44] Possible mechanisms to support poor long-term neurologic development following RBCT administration include decreased endogenous erythropoietin production, which stimulates red blood cell production and acts as a growth factor to promote neonatal brain growth and recovery following injury. [45] In contrast, current literature evaluating the association between neonatal RBCT with both throm-

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botic (i.e. cardiovascular) [46,47] and renal [48,49] complications is primarily limited to the neonatal cardiac population. Therefore, to our knowledge, this is the first study evaluating the association between RBCT volume with thrombotic and renal complications in neonates after non-cardiac surgery. After a RBCT, a pro-inflammatory state occurs with an increase in several inflammatory cells [15] and an increase in adhesion of neutrophils to the endothelium [16]. These alterations in the physiology of a vulnerable neonate might contribute to both renal and vascular injury resulting in thrombosis. These physiologic changes could also contribute to increased susceptibility to systemic infectious complications.

The estimated total blood volume for preterm and term neonates ranges from approximately 80 – 100 cc/kg. [50] Therefore, RBCT volume >40 cc/kg correlates to half of the estimated neonatal total blood volume and has been defined as massive transfusion. [51–53] RBCT volumes of this magnitude carry several risks including electrolyte abnormalities, transfusion reactions, hemodilution, volume overload, and resuscitation-induced coagulopathy if unbalanced ratios of blood products are administered. [52] A particular risk in the neonatal population is the risk of hypocalcemia from calcium chelation by citrate anticoagulants in blood components. [52] Neonates specifically have a decreased ability to metabolize citrate, and hypocalcemia reduces cardiac contractility, which is the primary compensatory mechanism for this population to increase cardiac output in shock states. [54–56] Our results identified a dose-dependent association between RBCT volume and mortality with a significant increase even for RBCT <20 cc/kg. The dose-dependent relationship with mortality was also present after propensity score matching. Furthermore, our cubic spline analysis identified an inflection point for mortality at RBCT volume of 30 – 35 cc/kg. Our collective results could be interpreted as evidence supporting the physiologic derangements and risks previously described with important clinical implications for neonatal surgeons and intensivists. First, physicians should be cautious ordering an “innocent” RBCT (i.e. <20 cc/kg) without clear clinical indications for the transfusion. For example, administering a 10 – 20 cc/kg RBCT to a mechanically ventilated neonate due to undetermined tachypnea and/or tachycardia might put the child at risk for worse postoperative outcomes based on our results. Second, physicians should critically question the clinical need for RBCT volumes >35 cc/kg, and consider withholding RBCT if not clinically indicated. Third, these RBCT volume cutoffs could guide future prospective studies evaluating mortality based on different transfusion volumes.

There are several limitations to our study. First, and most important, is the impact of selection bias on our study cohort. As previous studies have mentioned, databases used to evaluate the association of RBCT on postoperative outcomes do not include the indication or reason for the RBCT. [21,22] In our cohort, patients who received intra/postop RBCT were overall a sicker patient population that might have been more likely to experience intraoperative complications resulting in large volume RBCT—a situation that might have inherently been associated with greater risk of poor outcomes. To account for these types of intraoperative complications, our sensitivity analysis excluding all RBCTs that occurred on POD 0 still demonstrated a significant association between the largest RBCT volume (>40 cc/kg) with renal complications, CNS complications, and mortality. A second sensitivity analysis was also conducted with propensity score matching. Our results still showed all RBCT volume cohorts were significantly associated with systemic infectious complications and 30-day mortality relative to matched controls. Still, further work is needed to better delineate whether RBCT volume plays a role in this causal pathway. A second limitation is the only blood product recorded in the NSQIP – P database is RBCT. This limits our ability to evaluate if neonates with high RBCTs received balanced resuscitation and if unbalanced resuscitation contributed to mortality. Third, while we can identify the presence of a preoperative RBCT, we are unable to evaluate the volume of RBCT in the preoperative period. Finally, data entry errors may exist in NSQIP – P, but the reliability is reported to approach 98%. [57]

5. Conclusion

RBCT is a commonly performed practice in the neonatal population. There are risks and benefits to any RBCT and the decision to transfuse should be personalized to a given neonates clinical state. However, the findings of our study in combination with the existing literature on the topic suggest a need to revisit and question liberal transfusion practices in neonatal perioperative care. Future prospective studies are needed to further delineate the causative role large RBCT volume has on poor outcomes after neonatal surgery.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jpedsurg.2021.12.025.

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