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Carter, Harmony F
Lau, Carol
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Title: Intraoperative Red Blood Cell Transfusion in Infant Heart Transplant Patients Is Not Associated with Worsened Outcomes

1. Author: Harmony F. Carter MD

- Title: Assistant Professor
- Affiliation: Department of Anesthesiology, Loma Linda University School of Medicine, Loma Linda, CA, USA
- Email: hfcarter@llu.edu
- Contribution: Harmony F. Carter participated in study design, study conduct, data collection, data analysis and manuscript preparation.
- Attestation: Harmony Carter approved the final manuscript and attests to the integrity of the original data and the analysis reported in this manuscript.
- Conflicts of Interest: None

2. Author: Carol Lau MD

- Title: Assistant Professor
- Affiliation: Department of Anesthesiology, Loma Linda University School of Medicine, Loma Linda, CA, USA
- Email: clau@llu.edu
- Contribution: Carol Lau participated in study design, study conduct, data collection, data analysis and manuscript preparation.
- Attestation: Carol Lau approved the final manuscript and attests to the integrity of the original data and the analysis reported in this manuscript.
- Conflicts of Interest: None

3. Author: David Juma MPH

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- Title: Consulting Coordinator and Senior Consultant
- Affiliation: Research Consulting Group, Loma Linda University, Loma Linda, CA, USA
- Email: djuma@llu.edu

- Contribution: David Juma participated in data analysis and manuscript preparation.
- Attestation: David Juma approved the final manuscript and attests to the integrity of the original data and the analysis reported in this manuscript.
- Conflicts of Interest: None

4. Author: Briana Wells MS

- Title: Research Analyst
- Affiliation: Research Consulting Group, Loma Linda University, Loma Linda, CA, USA
- Email: bmwells@llu.edu

- Contribution: Briana Wells participated in data analysis and manuscript preparation.
- Attestation: Briana Wells approved the final manuscript and attests to the integrity of the original data and the analysis reported in this manuscript.
- Conflicts of Interest: None

5. Author: Richard L. Applegate II MD

- Title: Professor
- Affiliation: Department of Anesthesiology, Loma Linda University School of Medicine, Loma Linda, CA, USA
- Email: rapplegate@llu.edu

- Contribution: Richard Applegate participated in study design, study conduct, data collection, data analysis and manuscript preparation.

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- Attestation: Richard Applegate approved the final manuscript and attests to the integrity of the original data and the analysis reported in this manuscript. Richard Applegate is the archival author.
- Conflicts of Interest: None

Name of Department(s) and Institution(s):

Department of Anesthesiology

Loma Linda University School of Medicine

Short Title: Transfusion during infant cardiac transplant

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Corresponding Author:

Name: Richard L. Applegate II MD

Department: Anesthesiology

Institution: Loma Linda University School of Medicine

Mailing address: LLUMC Room 2532, 11234 Anderson Street, Loma Linda, CA 92354

Phone: 1-909-558-4475

Fax: 1-909-558-4143

Email: rapplegate@llu.edu

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IRB Chair: Rhodes L. Rigsby, M.D., Department of Medicine

(909) 558-2341, rrigsby@llu.edu

IRB Administrator: Linda G. Halstead, M.A., Director Research Protection Programs

(909) 558-4531, lhalstead@llu.edu

IRB Specialist: Anu Diekmann, M.P.H., Research Protection Programs, (909) 558-4531, adiekmann@llu.edu

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Abstract

Background

Red blood cell (RBC) transfusion is common during infant cardiac surgery. A previous report of pediatric heart transplant recipients showed increased RBC transfusion volume was independently associated with increased length of ICU stay. It is unclear whether transfusion to infants as a subgroup carries similar risks. This study investigated relationships between intraoperative RBC transfusion during heart transplantation and postoperative length of stay, morbidity and mortality in infants.

Methods

Retrospective analysis of medical records from infants <1 year old undergoing primary heart transplantation at Loma Linda University Medical Center from 1985 to 2012 was conducted. Exclusion criteria included preoperative exchange transfusion or extracorporeal membrane oxygenation. Data sought included patient characteristics; intraoperative RBC transfusion volume and cardiopulmonary bypass details; and postoperative vasoactive support, ventilator support, morbidity, length of stay (LOS) and 30-day mortality. The relationship of RBC transfusion volume (ml/kg) to these postoperative variables was assessed by univariate analysis. Multiple regression analysis of postoperative LOS included variables that were independent predictors of length of stay or associated with ≥10% change in the beta estimate for RBC effect.

Results

Data from 307 infants showed most (66.8%) had single ventricle physiology. Median age at transplant was 50 days; weight 3.95 kg; intraoperative transfusion volume 109 ml/kg. Transfusion volume was inversely related to age and weight. Median postoperative LOS was 18.2 days. Univariate linear regression analysis of transfused volume showed no relationship to

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log transformed postoperative LOS ($F(1,305)=0.00$; $p=0.960$; $R^2=0.000$; Beta Coefficient = 0.004; 95% CI = -0.1542 to 0.1623). Transfused volume was not related to 30-day mortality (difference -0.162; -0.048 to 0.371 ml/kg; $p=0.112$) nor to postoperative ventilator support ($R^2=0.047$) but was greater in patients who required reoperation (difference -0.246; -0.494 to -0.025; $p=0.004$). Multiple regression analysis for all patients revealed age, preoperative ventilator support, prolonged postoperative ventilatory or vasoactive support, transplant year and 30-day mortality but not major adverse events to be significant confounding variables. Adjusting for these variables, transfused volume was not associated with prolonged postoperative LOS.

Conclusions

In contrast to a prior report, we found no correlation between intraoperative RBC transfusion and postoperative LOS when studying only infants. Infants have maturing organ systems, less physiologic reserve and increased surgical blood loss (evaluated as ml/kg) during cardiac surgery than their larger, older counterparts, distinguishing them from the general pediatric population. These differences necessitate additional studies to determine outcome impact of transfusion strategies in the infant subgroup.

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Introduction

Pre-existing anemia and surgical blood loss make red blood cell (RBC) transfusion a common and necessary perioperative intervention for the pediatric cardiac surgical patient. Despite ongoing surgical losses, oxygen carrying capacity must be maintained. For small infants requiring cardiopulmonary bypass (CPB), the pump priming volume is quite large relative to the patient's blood volume; the resultant hemodilution often necessitates RBC transfusion.[1,2] Although transfusions may be lifesaving, there is increasing concern regarding the deleterious effects of blood product administration. Some studies in the pediatric population have associated perioperative RBC transfusions with increased postoperative morbidity.[3-10] In a retrospective study of RBC transfusion to heart transplant recipients ≤18 years old, multiple regression analysis revealed that increased RBC transfusion volume was independently associated with increased length of ICU stay and higher initial inotrope scores.[5] Transfusion volume greater than 60 ml/kg was associated with an increased risk of major adverse events. While a large prospective noninferiority trial in stable critically ill pediatric intensive care unit (ICU) patients[11] showed no significant outcome differences with a restrictive transfusion strategy, subgroup analysis of post-cardiac surgery patients showed an upward trend toward more organ dysfunction.[12] A unique concern for transplant recipients is the risk of allosensitization following transfusion.[13,14]

The International Society for Heart and Lung Transplantation Registry reports that approximately 25% of pediatric heart transplant recipients are infants under 1 year of age.[15] Many physiologic changes occur during the first 12 months of life, distinguishing infants from the general pediatric population. Infant heart transplant recipients may have a relative physiologic immunodeficiency[16-18] which could affect their response to RBC transfusion. They

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are also more likely to undergo cardiac transplant for cyanotic heart disease and clinically need higher baseline hemoglobin levels. In light of these differences, this study aims to evaluate the outcome impact of intraoperative RBC transfusion to infant heart transplant surgery recipients on postoperative length of stay, morbidity and mortality in this unique pediatric subgroup.

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Methods

After Institutional Review Board approval and waiver of consent, charts of all pediatric patients less than one year of age undergoing heart transplantion at Loma Linda University Medical Center from 1985 to 2012 were reviewed, with data collection and preliminary analysis completed in 2013. At this institution, cardopulmonary bypass perfusion protocols and transfusion strategies for infant heart transplant recipients have remained fairly stable over the past three decades, with important changes as noted. The perfusion protocol included active surface cooling during line placement and surgical dissection, hemodilution on initiation of CPB, deep hypothermia during low flow states or circulatory arrest,[19] and alpha-STAT management to maintain capillary microcirulation integrity,[20] while relying on dissolved oxygen to supply the cerebral metabolic demands.[21] The CPB prime included calcium-free crystalloid prime and 100 ml of albumin 25% added to maintain osmolality for a total volume of approximately 550 ml. The circuit included a DeBakey roller pump, arterial filter, and in-line hemoconcentrator. After appropriate heparinization and cannulation, CPB was initiated with rapid cooling (over approximately 15 minutes) to 18 degrees C. Initially longer deep hypothermic circulatory arrest (DHCA) times were utilized; however, with increased experience the DHCA times decreased. More recent cases were done with selective cerebral perfusion. Upon rewarming, continuous ultrafiltration was initiated (reversing hemodilution by removing approximately 500-800 mL ultra-filtrate). Washed irradiated RBCs were transfused per institutional protocol during and after CPB, providing further hemodilution correction during rewarming and replacing ongoing blood loss with the goal hematocrit between 30% and 35%. To eliminate the confounding effect of significant blood product exposure prior to surgery, exclusion criteria included prior heart

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transplant, preoperative extracorporeal membrane oxygenation and preoperative exchange transfusions.

Total intraoperative RBC transfusion volumes (ml/kg) were extracted from medical records, blood bank records, and the Loma Linda University International Heart Institute database. Preoperative, intraoperative, and postoperative patient characteristics were recorded. Vasoactive support included use of either inotrope or vasopressor infusions. Postoperative duration of mechanical ventilation was defined from end of surgery to the first sucessful tracheal extubation lasting at least 24 hours.

Statistical Analysis: The primary outcome measure chosen for this study was the relationship between RBC transfusion and post-transplant LOS as this summates postoperative morbidity. We did not use 30 day mortality as our primary outcome because the number who died within 30 days after transplant was 25. This limits our ability to adjust for potential confounding variables and other significant predictors of 30 day mortality. LOS was defined as the time from postoperative ICU admission until discharge home. It is standard practice at this institution to discharge patients home directly from the pediatric cardiac ICU. Histograms and Kolmogorov-Smirnov test statistics were examined to determine whether the distribution of LOS was reasonably modeled by a normal distribution on the original or log scale. The log transformation of LOS better approximated normality than the untransformed LOS. Year of transplant was dichotomized based on implementation of selective cerebral perfusion in 1995. Transfused volume was converted to 100 ml/kg to facilitate data analysis and comparison to clinical transfusion practices.

Secondary outcomes examined included postoperative major adverse events defined as cardiac arrest, primary open chest (open sternum at conclusion of primary operation), reoperation

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(additional postoperative surgical intervention), new dialysis, or new onset of seizures. Other secondary outcomes were duration of postoperative vasoactive support, postoperative ventilator days, and 30 day mortality. Categorical data are given as number (%) and differences were compared using the Wald test for proportions. Continuous data were analyzed for normal distribution by the Shapiro Wilk test with $p<0.05$ indicating the data were not normally distributed. Continuous data are given as mean or median and 95% confidence interval (CI) as appropriate to the data. Differences between categorical variables for continuous data that were not normally distributed were compared by the Hodges Lehman method assuming data symmetry and given as difference and 95% CI.

Initial univariate analysis was conducted to evaluate the relationships between RBC transfusion volume, logLOS and the secondary outcomes. Identified significant confounding variables were subjected to multiple regression analysis to evaluate the effects of confounding factors on LOS. Variables were included in the model if they were independent predictors of LOS or if they were associated with a ≥10% change in the beta estimate for RBC effect. All regression assumptions were checked by visually investigating residual plots. Linearity was additionally assessed via partial regression plots between the predictors and the log transformed LOS. Results are presented as beta coefficients and their standard error. Significance was set at 0.05. The analysis was performed using SAS/STAT software, Version 9.4 of the SAS System for Windows, SAS Institute Inc, Cary, NC, USA.

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Results

A total of 313 infants who underwent primary cardiac transplant were identified. Six were excluded for missing data yielding 307 study patients. Characteristics of those who survived >30 days after transplant (n=282) are compared to those who died within 30 days of transplant (n=25) in Table 1. Median age at transplant was 50 days and weight 3.95 kg. Most infants had single ventricle physiology (66.8%); cardiomyopathy and other complex congenital cardiac defects accounted for most of the remaining patients. Preoperative prostaglandin infusion was common and about one-third required ventilator support prior to transplantation. The mean preoperative hemoglobin was 13.1 g/dl (range 7.8 to 19.5 g/dl). Median postoperative LOS was 18.2 days. Two patients were discharged home with continued mechanical ventilation (one had a 222 day LOS but required ventilator support for 423 days).

Transfusion volume was inversely related to age and weight (Figure 1). The median volume of RBCs transfused during surgery was 109 ml/kg (range 28-328 ml/kg). All patients were transfused during CPB, with the majority receiving 1-2 units; 275 patients required additional transfusion after separation from CPB, while 32 patients did not. As shown in Figure 2, the majority of RBC transfusion occured during CPB. The first postoperative hemoglobin recorded averaged 12.0 g/dl (range 7.4-18.1). Postoperative LOS was evaluated and found to be heavily right skewed (KS: 0.1960; p-value < 0.010; mean = 24.21 versus median = 18). LOS was log transformed to better approximate normality. Univariate analysis showed no relationship of logLOS to RBC transfusion volume (Figure 3). Univariate analyses of preoperative and postoperative characteristics compared to RBC transfusion are summarized in Table 2, and to logLOS in Table 3.

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Following univariate and bivariate analyses, multiple regression analysis was performed in a stepwise manner. Model development steps for all transplant recipients and for only those who survived >30 days post-transplant are shown in Supplemental Digital Material Tables 1 and 2. Multiple regression analysis (Table 4) revealed age, year of transplant group, preoperative ventilator support, and prolonged postoperative ventilatory or vasoactive support to be significant confounding variables for logLOS. Multiple regression analysis showed occurrence of one or more postoperative major adverse event was not a significant predictor of LOS in the presence of the other covariates so major adverse events was excluded from the final model (Supplemental Digital Material). Age and weight had a direct linear correlation ($r = 0.8157$; $p<0.0001$) and therefore only age was used. After adjusting for all identified confounding variables, volume of RBC transfusion was not significantly associated with log transformed LOS (-0.126; -0.274 to 0.022; $p = 0.098$). Increased age at transplant was associated with a reduction in LOS (-0.093; -0.157 to 0.0289; $p = 0.0053$) while increased duration of postoperative ventilation was associated with longer LOS (0.261; 0.184 to 0.338; $p < 0.0001$). Similarly, multiple regression analysis of only those who survived > 30 days after transplant showed that RBC transfusion volume had no effect on LOS when confounding variables are considered (Table 5). The 30-day postoperative mortality was 8.87% (25 cases), thus limiting logistic regression analyses to univariate and bivariate models. Univariate and bivariate logistic regression modelling of variables related to 30-day mortality are shown in Tables 6 and 7.

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Discussion

RBC transfusion is a medical intervention in which the risks and benefits must be carefully weighed. Non-infectious risks account for the majority of fatal transfusion complications; the majority of pediatric reports are associated with human errors such as overtransfusion and misunderstanding neonatal requirements.[22] Withholding transfusion may be equally dangerous as a significant portion of intraoperative pediatric cardiac arrests are associated with inadequate resuscitation of surgical bleeding.[23] We found no positive correlation between intraoperative RBC transfusion volume and increased LOS by univariate analysis or multiple regression analysis (-0.126; -0.274 to 0.022; $p = 0.098$). Univariate analysis showed that infants with delayed chest closure or reoperation for other surgical reasons had larger intraoperative RBC transfusion volumes at the time of transplant, but we did not find significant intraoperative RBC transfusion volume differences in infants who required prolonged postoperative ventilator or vasopressor support, nor in those who who developed postoperative new seizures, new need for dialysis, cardiac arrest or death within 30 days of transplant (Table 2). Further, multiple regression analysis showed postoperative major adverse events were not a significant predictor of LOS in the presence of the other covariates (Supplemental Digital Material). Our findings differ from a previous report.[5] Several factors may have contributed to this difference.

Infants ≤ 30 days of age are at greatest risk for blood loss during pediatric cardiac surgery, with blood loss varying inversely with age and notable differences between age groups.[24] While the CPB perfusion strategy in this study was different (hemodilution with large volume acellular prime, followed by hemoconcentration during rewarming though continuous ultrafiltration and concurrent RBC transfusion), the median transfusion volume we found (109

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ml/kg) was not significantly greater than that reported in infants <12 months of age in a prior report (95±53 ml/kg).[5] That group reported RBC transfusion volume, but not age, to be independently associated with the studied outcomes. They also found that major adverse events (new dialysis, sepsis, graft failure, ECMO and open chest) were associated with larger transfusion volumes. In contrast we found that patient age and weight were directly linked and were independent predictors of LOS while RBC transfusion volume was not. Younger, smaller infants had longer LOS and prolonged vasoactive and ventilator support, possibly reflecting organ system maturation during the first year of life. The outcome differences between studies may highlight a sampling bias: our analysis was restricted to infants up to 12 months of age (median age 50 days), while the prior report[5] included pediatric cardiac transplant recipients ≤ 18 years of age (median age 11.7 years). Not surprizingly, infants in that report received the largest blood transfusion volume in ml/kg; only those weighing >30kg averaged transfusion volumes <15ml/kg, placing the majority of transplant recipients <30kg in the high exposure group. Though age was not shown to be statistically significant in that report, it has obvious clinical significance; this discrepancy is likely due to a age differences, with only a small number of infants and small children included in that report. Further, we did not find relationships between transfused volume and several postoperative major adverse events, prolonged postoperative ventilatory or vasoactive support, or death within 30 days of transplant. We postulate that the infant's immature immune system[16-18] and transfusion of washed irradiated RBCs may not elicit the same inflammatory and immunomodulatory effects seen with transfusions to older children and adults, but this will require further investigation.

Previous investigators found that increased transfusion during CPB was associated with excessive postoperative bleeding and worsened outcomes following pediatric cardiac surgery.[25]

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Those investigators reported notable risk factors for excessive postoperative bleeding included age and weight. Those with excessive bleeding averaged 138 days age and 5.3 kg weight compared to 657 days and 10.3 kg weight in those without excessive bleeding.[25] Similarly, infants that required intraoperative and postoperative transfusions despite undergoing a blood-sparing approach to pediatric cardiac surgery had worsened outcomes (increased ventilator days and ICU LOS) compared with non-transfused infants.[26,27] However, considering the uniform intraoperative transfusion protocol and maximal blood-sparing approach (including miniaturized CPB circuit down to 95 ml priming volume), it is possible that the need for RBC transfusion is a marker for rather than the cause of patient morbidity. Another retrospective study of infants undergoing heart surgery reported that a comprehensive blood conservation strategy, including reduction of circuit priming volume from 600 to 300 ml, was associated with significant decreases in intraoperative and postoperative blood transfusion, inotropic scores, ventilator duration, and hospital LOS (despite lower hemoglobin values after implementation).[28] However, it is possible that the other improvements in CPB and patient management implemented in this study contributed favorably to those outcome differences.

Many retrospective studies have linked increased blood transfusions with worsened outcomes. Perhaps the underlying association is the severity of surgical bleeding and preoperative morbidity rather than the amount of blood transfused,[29] as one study found the volume of chest tube drainage at 24 hours to be the strongest independent predictor of mortality.[30] Underlying confounders are difficult to tease out in these retrospective studies. All-cause mortality and secondary outcomes (stroke, MI, acute renal failure, infections, arrhythmias, bleeding, ICU and hospital LOS) were evaluated in a meta-analysis of 21 prospective randomized controlled trials involving transfusion protocols during cardiac or vascular surgery

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which randomized to either a restrictive or liberal transfusion study arm (including studies using acute normovolemic hemodilution as a restrictive approach). Four of the studies involved pediatric patients.[31] Pediatric patients in the restrictive study arms had significantly less blood utilization, but there were no statistically significant differences in mortality or secondary outcomes. Of note, both ICU and hospital LOS were increased by one day in the pediatric patients randomized to a restrictive approach. This meta-analysis also reported numerically more adverse events (death, stroke, infections) in the restrictive group.[31] A review of the literature searching for prospective studies involving RBC transfusion management during surgery for repair of congenital heart disease in the pediatric population found only a small number of heterogeneous trials with insufficent evidence to assess the outcome impact of RBC transfusions in this subgroup.[32]

The lowest "safe" hematocrit during CPB has yet to be determined, and there is some evidence that intraoperative anemia may be associated with negative outcomes. A randomized trial in infants < 9 months age to assess the effect of hemodilution (goal hematocrit 20% vs 30%) prior to low flow CPB during cardiac surgery found that during the postoperative period the low hematocrit group had decreased cardiac index, higher serum lactate levels, and increased total body water, with no difference in total blood product exposure. At 1 year of age, those evaluated in the low hematocrit group demonstrated >0.5 standard deviation lower Psychomotor Development Index scores.[33] The same group of investigators combined these results with a similar study evaluating the difference between hematocrit of 25% versus 35% which demonstrated that decreased hematocrit prior to low flow CPB was associated with increased intraoperative fluid balance and slight increase in lactate levels 60 minutes after CPB. More importantly there was a significant nonlinear increase in Psychomotor Development Index scores

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at 1 year of age with increasing hematocrit (plateauing at hematocrit of 23.5%), raising concern regarding the practice of extreme hemodilution to minimize blood transfusion in infant cardiac surgery.[34,35]

Our analysis showed age and weight to significantly correlate with LOS. This demonstrates the importance of comparing the outcome impact of RBC transfusion within specific age groups to minimize sampling bias. Additional studies are needed to address the effects of blood transfusion strategies in varied pediatric subgroups, as age and size are linked to estimated blood volume, the resultant dilutional effect of CPB circuit prime, and the amount of physiologic reserve. Infants are more likely to have cyanotic heart disease, require more complex repairs, and have longer duration of CPB and cross clamp times, which results in increased nonhemostatic thrombin generation, fibrin degredation, and subsequent increased bleeding.[36]

Weaknesses of this study include its retrospective design over an extended time period during which changes have occurred in the approach to infant heart transplantation, blood product storage, and hospital discharge criteria. We have addressed this by evaluating outcomes based on year of transplant and before and after implementation of selective cerebral perfusion during CPB. However, it is possible that other confounding variables remain not accounted for in this study. There were transfusion guidelines that specified a target postoperative hemoglobin, and postoperative hemoglobin was within the target range on average. However, this target range was not met in all patients. Washed irradiated RBCs were utilized per protocol, so there was no control group to evaluate whether or not this practice impacted outcomes. Both lactate and potassium levels rise during blood storage and the standard protocol for RBC transfusion in transplant recipients involves irradiation, which further weakens the RBC membrane increasing potassium leakage. Washing irradiated RBCs can reduce potassium and lactate loads, prevent

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hyperkalemia in infants during CPB and remove pre-storage additives (which may have an unknown effect on the neonate).[37-39] This is also an area in need of further research.

There are other limitations to generalizing our findings. Tranexamic acid was not part of the perioperative protocol for infant cardiac transplant as the risk-benefit ratio in pediatric cardiac surgery had not been adequately established.[40] Our study design did not include RBC transfusion or chest tube output during the first 48 hours postoperatively, which could have provided additional pertinent information. The Index for Mortality Prediction After Cardiac Transplantation (IMPACT) score[41] was not utilized as it was not suitable to distinguish differences within our specific patient population.

Pediatric transfusion medicine is a developing field with large gaps in evidence-based practice.[42] Whether increased blood transfusion is the cause of increased morbidity or simply a marker of it remains unclear. Neonates and infants are an important subgroup within the pediatric population requiring unique consideration to account for their maturing organ systems, decreased physiologic reserve, and increased surgical blood loss and RBC transfusion requirement (in ml/kg) compared to their larger counterparts. This retrospective study of RBC transfusion to infants undergoing heart transplantation failed to show a positive correlation between intraoperative RBC transfusion volume and postoperative LOS, while decreased age (which directly correlated with weight) was an independent predictor of increased LOS. The difference in outcomes between this and a prior report[5] highlight the possibility of sampling bias in pediatric studies covering a large developmental time period including patients from the first day of life to 18 years of age. Additional prospective studies are needed to determine the outcome impact of RBC transfusion strategies to infants as a unique pediatric subgroup.

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Legends

Figure Legends

Figure 1: Intraoperative red blood cell transfusion (RBC) volume in 307 infant heart transplant recipients <1 year of age was inversely related to patient (A) age and (B) weight.

Figure 2: Comparison of intraoperative red blood cell transusion (RBC) volume (median, bar indicates 95% confidence interval) given to 307 infant heart transplant recipients <1 year of age. The majority of the intraoperative RBC volume was administered during cardiopulmonary bypass (CPB).

Figure 3: Postoperative hospital length of stay (LOS) in 307 infant heart transplant recipients <1 year of age. Univariate analysis showed Log LOS was not related to the red blood cell (RBC) volume transfused during surgery.

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Table Legends

Table 1: Comparison of characteristics in infants <1 year of age who survived >30 days (Survivors) compared to those who died within 30 days (Non-survivors) after heart transplant. Data were tested for normal distribution using the Shapiro Wilk test, with $p<0.05$ indicating data were not normally distributed. Normally distributed data are given as mean; 95% confidence interval (CI) and differences were tested using the t-test. Data that were not normally distributed are given as median; smoothed empirical quantiles and differences were compared using the Hodges Lehman method assuming data symmetry. Categorical data are given as number (%) and differences were compared using the Wald test for proportions. Year of transplant was grouped based on implementation of selective cerebral perfusion during bypass starting in 1995.

Table 2: Intraoperative red blood cell transfusion (100 ml/kg) compared to patient and perioperative characteristics. Continuous data were compared by linear regression. Differences in continuous data between categorical variables were compared by the Hodges Lehman method assuming data symmetry.

Table 3: Length of stay (LOS) compared to patient and perioperative characteristics. The log transformation of LOS better approximated normality than the untransformed LOS. Continuous data were compared to Log LOS by linear regression and differences in continuous data between categorical variables were compared by Hodges Lehman assuming data symmetry.

Table 4: Final multiple regression model of factors influencing Log length of stay (LOS) for 307 infants <1 year undergoing cardiac transplantation included in the study. The model indicates that RBC transfusion has no impact on LOS. Year of transplant group had an effect on LOS for all patients, but not when those who died within 30 days of transplant were excluded (Table 5). For every 10% increase in age one would expect an 8.9% reduction in LOS (exp(-0.093) =

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0.911). Those intubated prior to transplantation had a 15.82% increase in LOS over those who were not intubated (exp(0.1469) = 1.158). There was a 63% decrease in LOS for those who died within 30 days (exp(-1.0038) = 0.366). For each 10% increase in days on postoperative ventilator support, one would expect a 2.52% increase in the LOS (1.1^(0.2612)=1.025) and for each 10% increase in days on postoperative vasoactive support one would expect a 15.82% increase in the LOS (1.1^(0.1468)=1.1582).

Table 5: Final multiple regression model of factors influencing Log length of stay (LOS) for 282 infants <1 year of age undergoing cardiac transplantation who survived >30 days postoperatively. The model indicates that there is no impact of intraoperative red blood cell transfusion (RBC) on LOS. For every 10% increase in age one would expect a 0.91% decrease in LOS. Those intubated prior to transplantation had a 17.70% increase in LOS compared to those who were not intubated (exp(0.16268) = 1.1767). For each 10% increase in days on postoperative ventilator support, one would expect a 3.44% increase in the LOS (1.1^(0.29615)=1.344).

Table 6: Univariate Logistic Regression modeling odds of 30-day mortality in 25 heart transplant recipient infants <1 year of age who died within 30 days of transplant compared to 282 who survived >30 days after transplant. One patient has missing data for time on CPB, so the analysis of CPB time contains one fewer. **Bold** indicates significance; *italic* indicates variables that do not hold well in the logistic regression analysis because of the small sample size. Log of odds was linear with the continuous independent variables. H-L Chi Square p-value: Hosmer and Lemeshow Goodness-of-fit test. Odds ratios were calculated as the odds of the outcome for the first listed categorical variable compared to the odds of the outcome for the second listed categorical variable.

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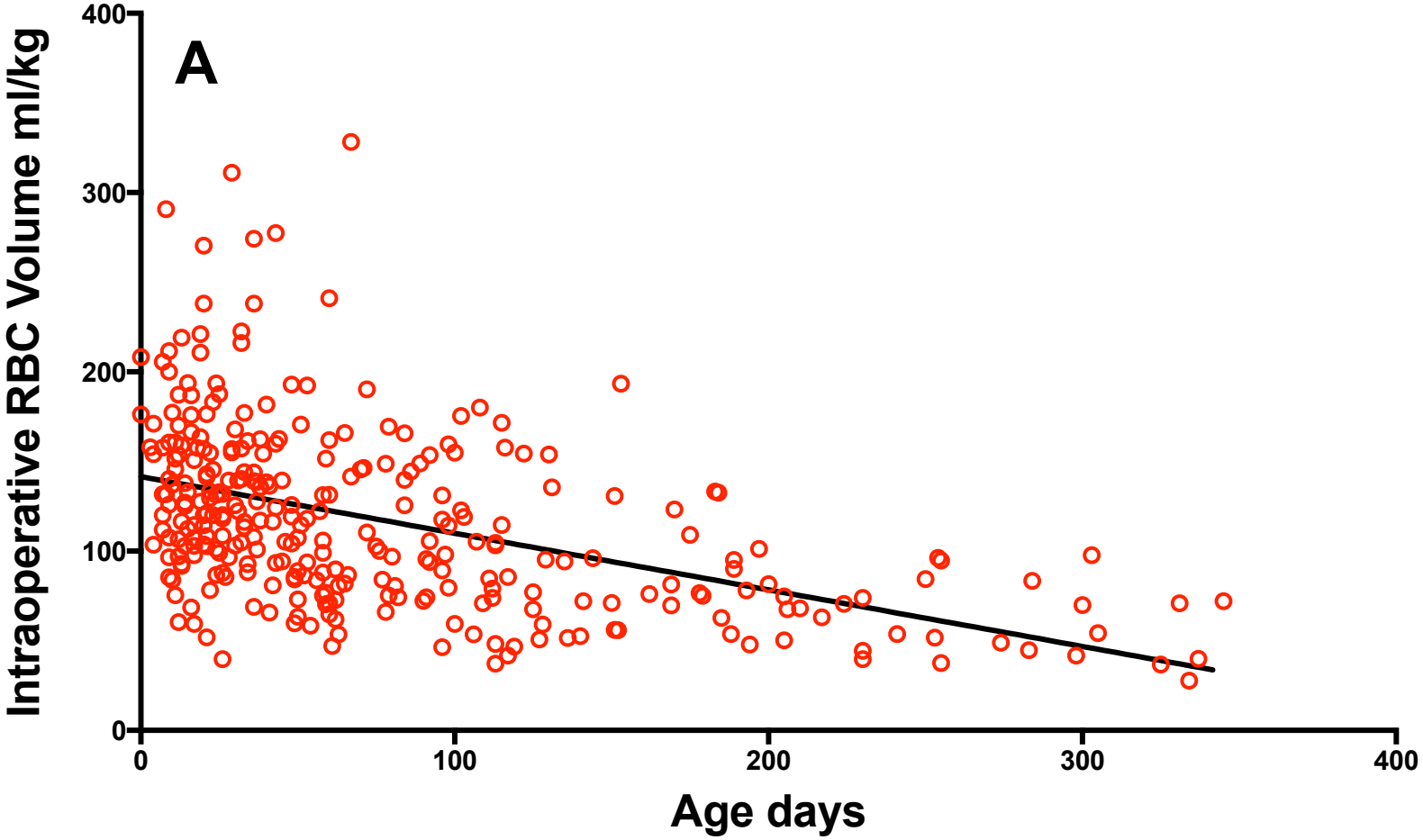
Table 7: Bivariate logistic regression modeling of variables related to 30-day mortality in 25 heart transplant recipient infants <1 year of age who died within 30 days of transplant compared to 282 who survived >30 days after transplant. One patient has missing data for time on CPB, so the analysis of CPB time contains one fewer. **Bold** indicates significance; *italic* indicates variables that do not hold well in the logistic regression analysis because of the small sample size. Log of odds was linear with the continuous independent variables. H-L Chi Square p-value: Hosmer and Lemeshow Goodness-of-fit test. Odds ratios were calculated as the odds of the outome for the first listed categorical variable compared to the odds of the outcome for the second listed categorical variable.

Figure 1

Click here to download Figure Fig 1AB.eps



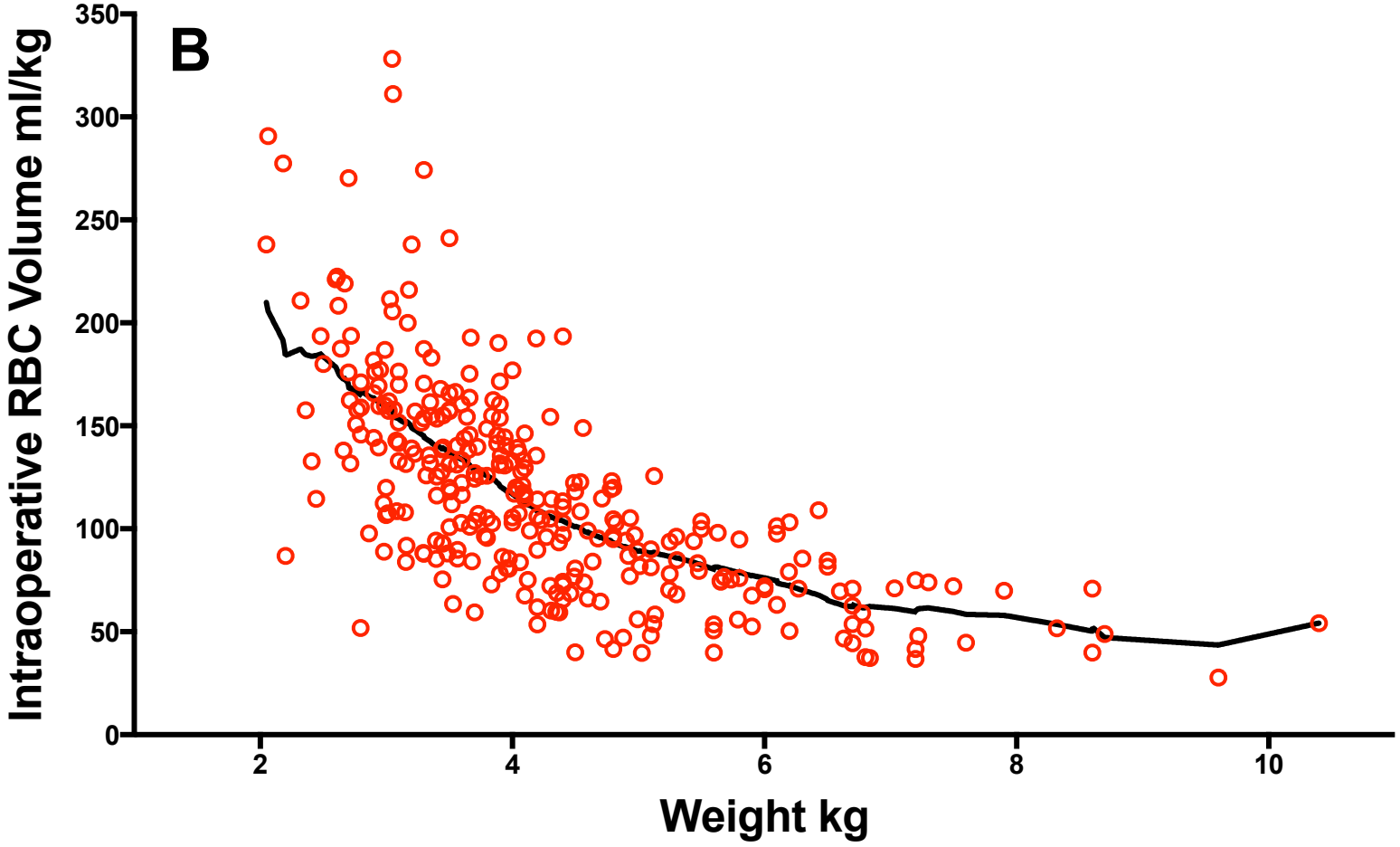


Figure 2

Click here to download Figure Fig 2 RBC on off CPB.eps

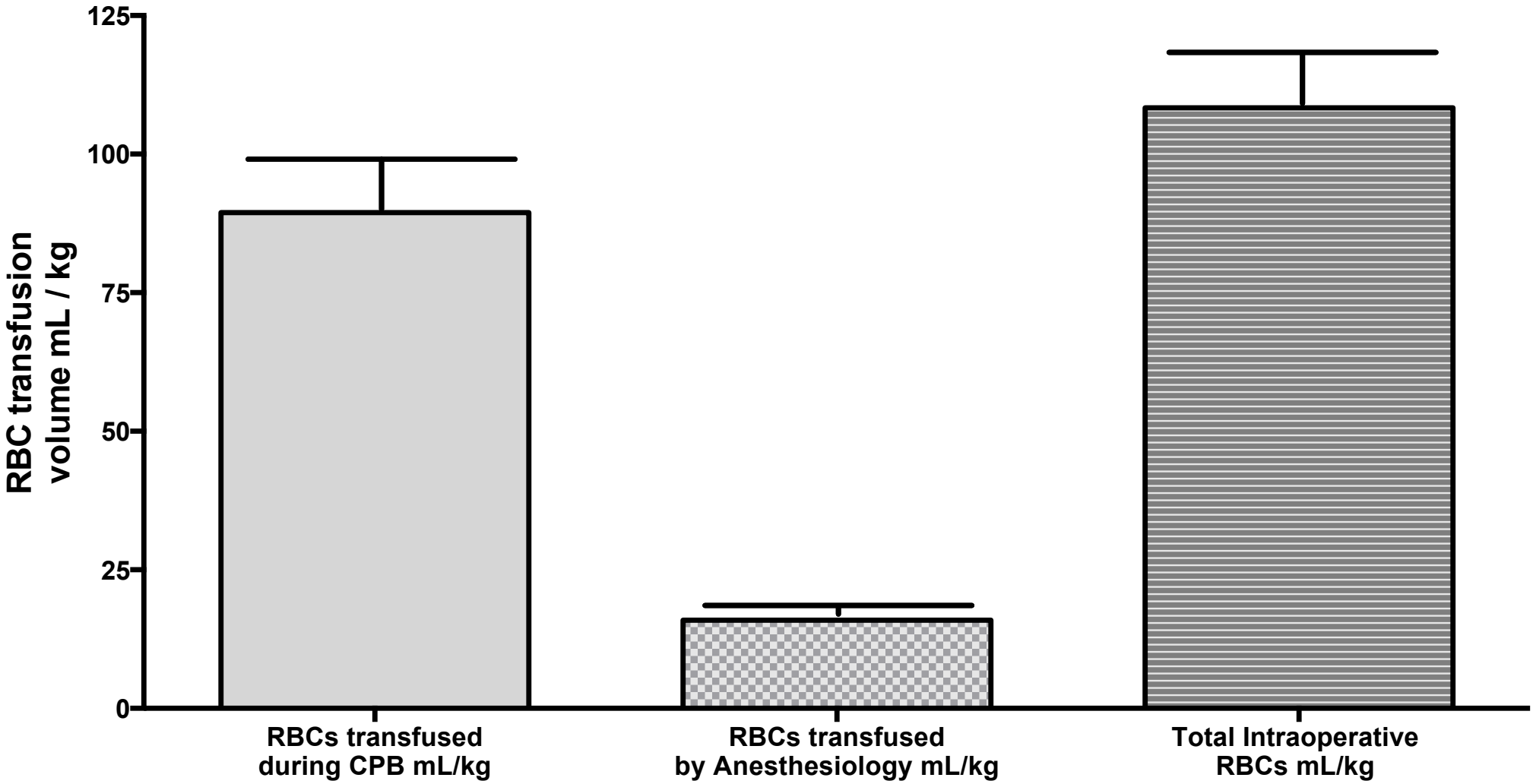


Figure 3

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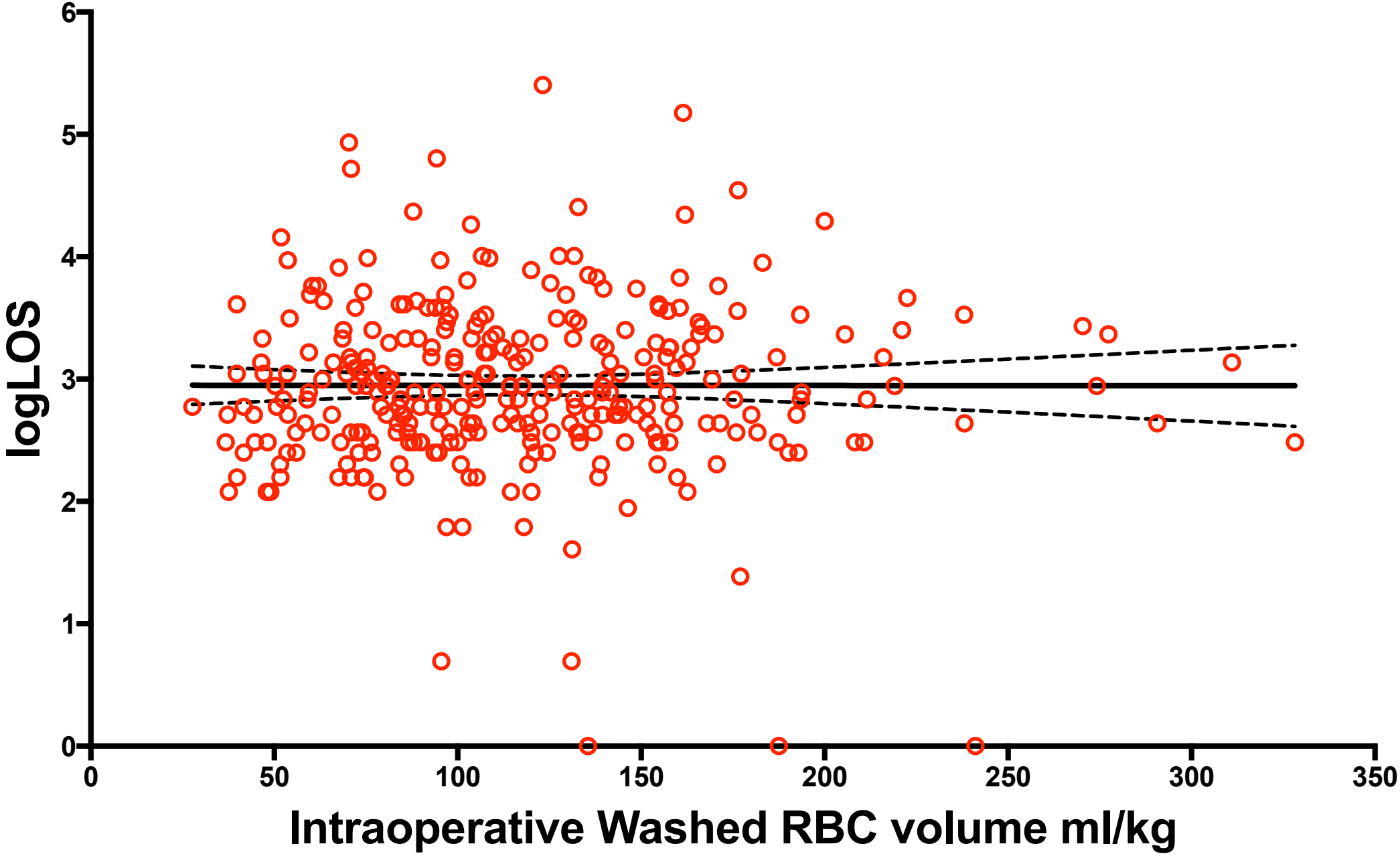

Click here to download Table Table 1 Survivor vs nonsurvivor.docx

Table 1: Characteristics of infant heart transplant recipients <1 year age who survived more than 30 days (Survivors) compared to those who died within 30 days (Non-survivors) after heart transplant

Patient Characteristics	Survivors N = 282	Non-survivors N = 25	Difference 95% CI	p-value
Gender # (%) Female	115 (40.8%)	12 (48.0%)	-7.22% -26.99% to 12.39%	0.467
Age at transplant days median; 95% CI Range	48.6; 41.3 to 56.7 0 to 345	64.8; 43.0 to 97.3 7 to 254	8.0 -12.0 to 31.0	0.450
Weight at transplant kg median; 95% CI Range	3.95; 3.80 to 4.10 2.05 to 10.40	3.97; 3.61 to 4.32 2.16 to 7.03	-0.88 -0.58 to 0.40	0.747
Cardiac defect leading to transplant # (%) Single ventricle physiology Complex Congenital Heart Disease Cardiomyopathy Other	 192 (68.1%) 44 (15.6%) 42 (14.9%) 4 (1.42%)	 19 (76.0%) 3 (12.0%) 2 (8.0%) 1 (4.0%)		0.472
Year of Transplant Group # (%) 1985 to 1994	169 (59.9%)	19 (76.0%)	-16.07%	0.111

			-31.7 to 3.27%	
Preoperative Characteristics				
Vasoactive support # (%)	50 (17.73%)	4 (16.0%)	-1.73% -14.756 to 15.878%	0.943
Ventilator support # (%)	93 (32.98%)	6 (24.0%)	-8.98% -24.59% to 10.24%	0.420
Prostaglandin infusion # (%)	192 (68.09%)	18 (72.0%)	3.92% -15.65 to 20.47%	0.793
Prior sternotomy # (%)	40 (14.18%)	5 (20.0%)	0.058% -8.42 to 23.99%	0.387
Preoperative Hemoglobin g/dl mean; CI Range g/dl	13.2; 12.9 to 13.4 7.8 to 19.5	12.7; 11.9 to 13.5 9.3 to 15.3	-0.30 -1.20 to 0.40	0.225
Intraoperative Characteristics				
Donor organ ischemic time minutes median; CI Range	270.0; 251.5 to 289.2 60 to 595	235.7; 170.8 to 309.8 90 to 539	-23.0 -81.0 to 29.0	0.393
Total cardiopulmonary bypass time minutes	95.5; 89.3 to 104.0			0.842

median; CI Range	38 to 235	99.9; 85.6 to 124.0 57 to 281	1.0 -14.0 to 16.0	
Circulatory arrest time minutes median; CI Range	43.4; 40.2 to 45.6 0 to 82	49.3; 35.6 to 54.3 0 to 110	6.0 0 to 14.0	0.076
Intraoperative Transfusion				
Red blood cell transfusion volume ml/kg median; CI Range	107.6; 101.2 to 115.9 27.7 to 311.1	126.2; 106.5 to 144.2 52.5 to 328.2	15.9 -5.41 to 37.09	0.225
Postoperative Characteristics n=307				
Length of stay days median; CI Range	19.1; 17.6 to 20.6 6 to 222	10.1; 5.6 to 14.2 0 to 30	-11.0 -14.0 to -7.0	<0.0001
Ventilator days median; CI Range	3.1; 2.7 to 3.7 0 to 423	3.5; 2.0 to 5.5 0 to 17	0.0 -1.0 to 1.0	0.928
Vasoactive support days median; CI Range	4.1; 3.8 to 4.7 0 to 129	4.2; 2.5 to 6.4 0 to 17	0.0 -1.0 to 1.0	0.994
Hemoglobin g/dl mean; CI	12.2; 12.0 to 12.5	12.5; 11.8 to 13.2	0.26	0.522

Range	7.4 to 18.1	9.6 to 16.9	-0.50 to 1.03	
Postoperative complications				
Cardiac arrest	24 (8.51%)	14 (56.0%)	-47.49% -65.78 to -27.72%	<0.000 1
Primary open chest or Reoperation	30 (10.64%)	10 (40.0%)	29.36% 10.94 to 48.71%	0.002
Reoperation	12 (4.26%)			
New dialysis	22 (7.80%)	11 (44.0%)	36.19% 17.34 to 55.36%	0.0002
New seizures	55 (19.50%)	3 (12.0%)	-7.50% -19.08 to 9.27%	0.498

Table 1: Comparison of characteristics in infants <1 year of age who survived >30 days (Survivors) compared to those who died within 30 days (Non-survivors) after heart transplant. Data were tested for normal distribution using the Shapiro Wilk test, with $p<0.05$ indicating data were not normally distributed. Normally distributed data are given as mean; 95% confidence interval (CI) and differences were tested using the t-test. Data that were not normally distributed are given as median; smoothed empirical quantiles and differences were compared using the Hodges Lehman method assuming data symmetry. Categorical data are given as number (%) and

differences were compared using the Wald test for proportions. Year of transplant was grouped based on implementation of selective cerebral perfusion during bypass starting in 1995.

Table 2: Analysis of relationship between patient characteristics and red blood cell transfusion

Linear regression analysis of continuous variables to intraoperative red blood cell transfusion 100 ml/kg			
Characteristic	slope	intercept	r^2
Log Age days	-0.216	2.0005	0.208
Log Weight kg	-1.189	2.840	0.485
Preoperative hemoglobin g/dl	0.0351	0.703	0.019
Donor organ ischemic time minutes	-0.00007	1.186	0.0003
Total cardiopulmonary bypass time minutes	-0.00265	1.457	0.051
Circulatory arrest time minutes	0.0114	0.741	0.252
Postoperative hemoglobin g/dl	0.0638	0.381	0.062
Log Postoperative ventilator support days	0.110	1.040	0.047
Log Postoperative vasoactive support days	0.189	0.915	0.080
Log Length of stay days	0.002	1.16	0.0000
Categorical variables yes vs no unless otherwise indicated compared to intraoperative red blood cell transfusion 100 ml/kg			
Variable	Hodges Lehman Difference	95% CI	p-value
Sex Female vs Male	-0.072	-0.182 to 0.038	0.197
Cardiac defect leading to transplant	0.035	0.080 to 0.152	0.532

single ventricle vs other diagnoses			
Intubated prior to transplant	-0.026	0.143 to 0.086	0.648
Prior sternotomy	0.167	0.017 to 0.315	0.032
Prostaglandin infusion	-0.358	-0.458 to -0.258	<0.0001
Postoperative cardiac arrest	-0.139	-0.287 to 0.039	0.123
Primary open chest or reoperation	-0.246	-0.494 to -0.025	0.004
New postoperative dialysis	-0.140	-0.319 to 0.040	0.118
New postoperative seizures	0.021	-0.111 to 0.149	0.790
30 day mortality	-0.162	-0.048 to 0.371	0.112

Table 2: Intraoperative red blood cell transfusion (100 ml/kg) compared to patient and perioperative characteristics. Continuous data were compared by linear regression. Differences in continuous data between categorical variables were compared by the Hodges Lehman method assuming data symmetry.

Table 3: Analysis of relationship between patient characteristics and length of stay

Linear regression analysis of continuous variables to Log length of stay			
Characteristic	slope	intercept	R^2
Log Age days	-0.1567	3.545	0.0556
Log Weight kg	-0.3240	3.395	0.0183
Year of transplant	-0.0053	13.460	0.0024
Preoperative hemoglobin g/dl	0.0338	2.485	0.0092
Donor organ ischemic time minutes	0.0003	2.846	0.0033
Total cardiopulmonary bypass time minutes	-0.0019	3.152	0.0437
Circulatory arrest time minutes	0.0003	2.928	0.0001
Red blood cell transfusion 100 ml/kg	0.0004	2.9345	0.0000
Postoperative hemoglobin g/dl	-0.0068	3.012	0.0004
Log Postoperative ventilator support days	0.3411	2.486	0.131
Postoperative vasoactive support days	0.0260	2.814	0.093
Categorical variables Yes vs No unless otherwise indicated compared to length of stay days			
Variable	Hodges Lehman Difference	95% CI	p-value
Sex Female vs Male	-0.134	-0.262 to 0.000	0.260
Cardiac defect leading to transplant single ventricle vs other diagnosis	0.000	-0.165 to 0.113	0.271
Intubated prior to transplant	-0.405	-0.547 to -0.288	<0.0001

Prior sternotomy	0.310	0.143 to 0.511	0.0054
Prostaglandin infusion	-0.241	-0.377 to -0.105	0.0186
Cardiac arrest	-0.053	-0.288 to 0.211	0.492
Primary open chest or reoperation	-0.191	-0.427 to 0.065	0.349
New postoperative dialysis	-0.192	-0.446 to 0.077	0.244
New postoperative seizures	-0.074	-0.228 to 0.080	0.355
30 day mortality	0.847	0.499 to 1.253	<0.0001

Table 3: Length of stay (LOS) compared to patient and perioperative characteristics. The log transformation of LOS better approximated normality than the untransformed LOS. Continuous data were compared to Log LOS by linear regression and differences in continuous data between categorical variables were compared by Hodges Lehman assuming data symmetry.

Table 4 Click here to download Table Table 4 final multi regression model all pts_R3.docx

Table 4: Multiple Regression Analysis of Infant Heart Transplant Recipients on Log Length of Stay

Variable	Beta	Confidence Interval	P-value
RBC (100 mL/kg)	-0.126	-0.274 to 0.022	0.098
1995-2012 vs. 1985-1994	0.148	0.005 to 0.290	**0.0425**
Log Age (days)	-0.093	-0.157 to -0.0289	**0.0046**
Intubated prior to transplant	0.147	0.009 to 0.284	**0.0367**
Log Postoperative ventilator support (days)	0.261	0.184 to 0.338	**<0.0001**
Log Postoperative vasoactive support (days)	0.147	0.049 to 0.245	**0.0035**
30 day mortality	-1.004	-1.222 to -0.785	**<0.0001**
Intercept	2.929	2.538 to 3.320	**<0.0001**
Bold indicates significance; adjusted $R^2 = 0.4549$			

Table 4: Final multiple regression model of factors influencing Log length of stay (LOS) for 307 infants <1 year undergoing cardiac transplantation included in the study. The model indicates that RBC transfusion has no impact on LOS. Year of transplant group had an effect on LOS for all patients, but not when those who died within 30 days of transplant were excluded (Table 5). For every 10% increase in age one would expect an 8.9% reduction in LOS (exp(-0.093) = 0.911). Those intubated prior to transplantation had a 15.82% increase

in LOS over those who were not intubated (exp(0.1469) = 1.158). There was a 63% decrease in LOS for those who died within 30 days (exp(-1.0038) = 0.366). For each 10% increase in days on postoperative ventilator support, one would expect a 2.52% increase in the LOS (1.1^(0.2612)=1.025) and for each 10% increase in days on postoperative vasoactive support one would expect a 15.82% increase in the LOS (1.1^(0.1468)=1.1582).

Table 5

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Table 5: Mulitiple Regression Analysis of 282 Infant Heart Transplant Recipients Who Survived >30 Days on Log Length of Stay

Variable	Beta	Confidence Interval	P-Value
RBC (100 mL/kg)	-0.081	2.706 to 3.433	0.271
1995-2012 vs. 1985-1994	0.076	-0.226 to 0.064	0.248
Log Age (days)	-0.097	-0.053 to 0.204	**0.0016**
Log Postoperative ventilator support (days)	0.296	-0.156 to -0.037	**<.0001**
Intubated prior to transplant	0.163	0.234 to 0.359	**0.012**
Intercept	3.07	0.036 to 0.289	**<0.0001**
Bold indicates significance; adjusted R^2 = 0.3604			

Table 5: Final multiple regression model of factors influencing Log length of stay (LOS) for 282 infants <1 year of age undergoing cardiac transplantation who survived >30 days postoperatively. The model indicates that there is no impact of intraoperative red blood cell transfusion (RBC) on LOS. For every 10% increase in age one would expect a 0.91% decrease in LOS. Those intubated prior to transplantation had a 17.70% increase in LOS compared to those who were not intubated (exp(0.16268) = 1.1767). For each 10% increase in days of postoperative ventilator support, one would expect a 3.44% increase in the LOS (1.1^(0.29615)=1.344).

Click here to download Table Table 6 univariate odds 30day mort final.docx

Table 6: Univariate logistic regression modeling of variables related to 30-day mortality

	Odds Ratio Estimates			Wald		H L Chi
Effect	**Point Estimate**	**95% Wald Confidence Limits**		**p-value**	**R^2**	**Square P-Value**
RBC (100 ml/kg)	2.154	1.057	4.387	**0.0346**	0.0134	0.1891
Year of transplant: 1995-2012 vs. 1985-1994	2.117	0.82	5.465	0.1210	0.0086	
Sex: Female vs Male	1.341	0.591	3.043	0.4835	0.0016	
Age at transplant days	1.001	0.996	1.006	0.7727	0.0003	0.8161
Log Age at transplant days	1.146	0.772	1.7	0.4995	0.0015	0.8413
Weight at transplant kg	0.885	0.638	1.229	0.4670	0.0018	0.0971
Log Weight at transplant kg	0.57	0.135	2.399	0.4432	0.0020	0.0921
Single Ventricle physiology: No vs Yes	1.969	0.864	4.487	0.1068	0.0083	
Indication: cardiomyopathy: Yes vs No	0.47	0.107	2.067	0.318	0.0039	
Indication: complex congenital heart disease: Yes vs No	0.527	0.152	1.821	0.3109	0.0038	
Indication: other cardiac defect: Yes vs No	2.896	0.311	26.948	0.3502	0.0023	
Preoperative hemoglobin g/dl	0.878	0.711	1.084	0.2248	0.005	0.1362

Intubated prior to transplant: Yes vs No	0.642	0.248	1.661	0.3606	0.0029	
Preoperative prostaglandin infusion No vs Yes	0.83	0.335	2.057	0.6869	0.0005	
Preoperative Inotrope Score	0.995	0.909	1.09	0.9222	0	0.7628
Repeat Sternotomy: Yes vs No	1.513	0.537	4.26	0.4335	0.0019	
Donor organ ischemic time minutes	0.999	0.995	1.002	0.476	0.0017	0.3319
Circulatory arrest time minutes	1.019	0.998	1.04	0.0732	0.0113	0.0565
Cardiopulmonary bypass time minutes	1.002	0.993	1.011	0.6856	0.0005	0.8754
Postoperative hemoglobin g/dl	1.07	0.871	1.315	0.5202	0.0014	0.1529
Postoperative ventilator support days	0.992	0.952	1.033	0.6814	0	0.5589
Log Postoperative ventilator support days	0.996	0.657	1.509	0.9853	0	0.7346
Above vs Below median Postoperative ventilator support days	1.322	0.583	2.999	0.5039	0.0015	
Postoperative vasoactive Support days	0.999	0.949	1.053	0.9846	0	0.2458
Log Postoperative vasoactive support days	0.906	0.525	1.565	0.7246	0.0004	0.2390
Above vs Below median Postoperative vasoactive support days	1.103	0.486	2.503	0.8139	0.0002	

Reoperation other than open chest closure: Yes vs No	*7.105*	*2.401*	*21.023*	**0.0004**	0.0328	
Postoperative cardiac arrest	*13.682*	*5.598*	*33.438*	**<0.0001**	0.0973	
New postoperative dialysis	*9.286*	*3.769*	*22.877*	**<0.0001**	0.0654	
New postoperative seizures	0.563	0.163	1.948	0.3643	0.0030	
Any postoperative major adverse event: Yes vs No	*23.75*	*5.482*	*102.9*	**<0.0001**	0.1106	

Table 6: Univariate Logistic Regression modeling odds of 30-day mortality in 25 heart transplant recipient infants <1 year of age who died within 30 days of transplant compared to 282 who survived >30 days after transplant. One patient has missing data for time on CPB, so the analysis of CPB time contains one fewer. **Bold** indicates significance; *italic* indicates variables that do not hold well in the logistic regression analysis because of the small sample size. Log of odds was linear with the continuous independent variables. H-L Chi Square p-value: Hosmer and Lemeshow Goodness-of-fit test. Odds ratios were calculated as the odds of the outome for the first listed categorical variable compared to the odds of the outcome for the second listed categorical variable.

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Table 7: Bivariate logistic regression modeling of variables related to 30-day mortality

	Odds Ratio Estimates				Wald		H L Chi
Model	**Effect**	**Point Estimate**	**95% Wald Confidence Limits**		**p-value**	**R^2**	**Square P-Value**
0	RBC (100 ml/kg)	1.08	1.006	1.159	**0.0346**	0.0134	0.1891
1	RBC (100 ml/kg) 1995-2012 vs. 1985-1994	1.867 1.533	0.837 0.54	4.166 4.348	0.1272 0.4221	0.0156	0.2256
2	RBC (100 ml/kg) Sex: Female vs Male	2.138 1.291	1.045 0.565	4.372 2.95	**0.0374** 0.5449	0.0146	0.2886
3	RBC (100 ml/kg) Age at transplant days	2.764 1.004	1.256 0.998	6.083 1.01	**0.0115** **0.1591**	0.0193	0.6326
4	RBC (100 ml/kg) Log Age at transplant days	2.875 1.493	1.332 0.931	6.205 2.395	 **0.0071**	0.0230	0.0258
5	RBC (100 ml/kg) Weight at transplant kg	2.705 1.167	1.067 0.78	6.857 1.745	**0.036** **0.4519**	0.0152	0.8544
6	RBC (100 ml/kg)	2.918	1.083	7.863	**0.0342**	0.0158	0.7332

	Log Weight at transplant kg	2.385	0.329	17.297	0.3900		
7	RBC (100 ml/kg) Single Ventricle physiology: No vs Yes	2.126 1.925	1.037 0.839	4.359 4.418	0.0394 0.122	0.0209	0.5111
8	RBC (100 ml/kg) Transplant for cardiomyopathy: Yes vs No	2.032 0.662	0.995 0.143	4.28 3.068	0.0620 0.5984	0.0144	0.9239
9	RBC (100 ml/kg) Transplant for complex congenital heart disease	2.154 0.516	1.063 0.148	4.365 1.792	**0.0332** 0.2972	0.0175	0.8644
10	RBC (100 ml/kg) Other cardiac defect leading to transplant: Yes vs No	2.225 3.729	1.088 0.388	4.551 35.799	**0.0285** 0.2541	0.0167	0.1394
11	RBC (100 ml/kg) Preoperative hemoglobin	2.398 0.845	1.155 0.682	4.981 1.047	**0.0190** 0.1233	0.0219	0.4459
12	RBC (100 ml/kg) Intubated prior to transplant: Yes vs No	2.201 0.611	1.075 0.234	4.507 1.596	**0.0309** 0.3149	0.0169	0.3875
13	RBC (100 ml/kg)	2.182	1.05	4.534	**0.0366**	0.0135	0.6282

	Preoperative prostaglandin infusion: No vs Yes	1.072	0.417	2.757	0.8857		
14	RBC (100 ml/kg) Preoperative Inotrope Score	2.283 1.025	1.088 0.941	4.789 1.116	**0.0291** 0.5726	0.0143	0.5776
15	RBC (100 ml/kg) Repeat Sternotomy: Yes vs No	1.083 1.716	1.009 0.599	1.163 4.916	**0.0275** 0.3149	0.0164	0.5122
16	RBC (100 ml/kg) Donor organ ischemic time minutes	2.142 0.999	1.052 0.995	4.362 1.002	0.0358 0.4980	0.0149	0.3319
17	RBC (100 ml/kg) Circulatory arrest time minutes	1.774 1.012	0.779 0.989	4.038 1.035	0.1720 0.3112	0.0169	0.7102
18	RBC (100 ml/kg) Cardiopulmonary bypass time minutes	2.225 1.004	1.098 0.994	4.629 1.013	**0.0267** **0.4313**	0.0151	0.8753
19	RBC (100 ml/kg) Postoperative hemoglobin g/dl	2.138 1.022	1.037 0.828	4.409 1.261	**0.0396** 0.8408	0.0142	0.3434
20	RBC (100 ml/kg) Postoperative ventilator support days	2.203 0.986	1.07 0.93	4.53 1.046	**0.0320** 0.6443	0.0151	0.5396

21	RBC (100 ml/kg) Log Postoperative ventilator support days	2.277 0.884	1.08 0.556	4.801 1.408	**0.0306** 0.6048	0.0143	0.2934
22	RBC (100 ml/kg) Above vs Below median Postoperative ventilator support days	2.112 1.096	1.014 0.468	4.40 2.565	**0.0458** 0.8331	0.0136	0.7961
23	RBC (100 ml/kg) Postoperative vasoactive support days	2.201 0.989	1.07 0.92	4.53 1.063	**0.0321** **0.7695**	0.0139	0.9312
24	RBC (100 ml/kg) Log Postoperative vasoactive support days	2.399 0.752	1.143 0.421	5.033 1.344	**0.0207** **0.3365**	0.0166	0.9917
25	RBC (100 ml/kg) Above vs Below median Postoperative vasoactive support days	2.201 0.901	1.061 0.385	4.564 2.106	**0.0340** 0.8092	0.0137	0.8866
26	RBC (100 ml/kg) Reoperation other than delayed chest closure	1.977 *6.436*	0.941 *2.138*	4.154 *19.374*	0.0720 **0.0009**	0.0423	0.5950
27	RBC (100 ml/kg)	1.983	0.897	4.47	0.0989	0.1051	0.7569

	Postoperative cardiac arrest: Yes vs No	*13.134*	*5.324*	*32.402*	**<0.0001**		
28	RBC (100 ml/kg) New postoperative dialysis	1.821 *8.575*	0.847 *3.439*	3.915 *21.384*	0.1249 **<0.0001**	0.0723	0.4158
29	RBC (100 ml/kg) New postoperative seizures	2.134 0.576	1.047 0.165	4.351 2.01	**0.0369** 0.3872	0.0161	0.2149
30	RBC (100 ml/kg) Any Major Adverse Event Yes vs No	1.793 *22.503*	0.834 *5.179*	3.854 *97.775*	0.1350 **<0.0001**	0.1168	0.7212

Table 7: Bivariate logistic regression modeling of variables related to 30-day mortality in 25 heart transplant recipient infants <1 year of age who died within 30 days of transplant compared to 282 who survived >30 days after transplant. One patient has missing data for time on CPB, so the analysis of CPB time contains one fewer. **Bold** indicates significance; *italic* indicates variables that do not hold well in the logistic regression analysis because of the small sample size. Log of odds was linear with the continuous independent variables. H-L Chi Square p-value: Hosmer and Lemeshow Goodness-of-fit test. Odds ratios were calculated as the odds of the outome for the first listed categorical variable compared to the odds of the outcome for the second listed categorical variable.