**Supplemental Digital Content**

**Multiple regression model development steps for all infant (<1 year old) heart transplant recipients studied (Table 1) and for only those who survived >30 days after transplant (Table 2).**

Notes: Initial univariate analyses were conducted to evaluate the relationships between RBC transfusion volume, Log LOS and the secondary outcomes.

Identified significant confounding variables were subjected to multiple regression analysis to evaluate the effects of confounding factors on LOS in a stepwise manner. 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.

The analysis was performed using SAS/STAT software, Version 9.4 of the SAS System for Windows, SAS Institute Inc, Cary, NC, USA.

Postoperative major adverse events were defined as cardiac arrest, primary open chest (open sternum at conclusion of primary operation), reoperation (additional postoperative surgical intervention), new dialysis, or new onset of seizures.

Abbreviations used: LOS = postoperative length of stay; corr = correlation; RBC = intraoperative red blood cell transfusion volume

**Table 1**: Multiple regression model development steps for all infant heart transplant recipients studied (N = 307)

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Variable** | **Parameter Estimate** | **Confidence Interval** | **p-value** |
| **0** | Intercept | 2.934 | (2.733, 3.136) | <.0001 |
|  | RBC 100 ml/kg | 0.004 | (-0.154, 0.162) | 0.960 |

|  |
| --- |
| Univariate analysis of each possible predictor and Log LOS was used to determine which variables to use in the multiple regression model building process. This is documentation of the decision of adding those variables into our final multiple regression model. |

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Variable** | **Parameter** | **Confidence Interval** | **p-value** | **Variance** | **Adjusted R2** | **% change** |
| **Model** | **Estimate** | **Inflation** |
| **1** | Intercept | 2.847 | (2.581, 3.116) | <.0001 | 0 | -0.0034 | 11 |
|  | RBC (100 ml/kg) | 0.048 | (-0.133, 0.229) | 0.604 | 1.306 |  |  |
|  | 1995-2012 vs. 1985-1994 | 0.093 | (-0.093, 0.280) | 0.326 | 1.306 |  |  |

|  |
| --- |
| We investigated the effect of year of transplant on Log LOS. Based on a practice change introduced in 1995 (implementation of selective cerebral perfusion), we chose to dichotomize year of treatment. This seems to be a confounding variable to RBC because the beta coefficient in Model 1 has changed by more than 10% compared to Model 0. |

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Adding Age to Model 1 (N = 307)** | | | | | | | |
| **2** | Intercept | 3.823 | (3.348, 4.300) | <.0001 | 0 | 0.0646 | 3.8333 |
|  | RBC (100 ml/kg) | -0.136 | (-0.326, 0.054) | 0.16 | 1.549 |  |  |
|  | 1995-2012 vs. 1985-1994 | 0.109 | (-0.071, 0.289) | 0.236 | 1.308 |  |  |
|  | Log Age at transplant (days) | -0.198 | (-0.280, -0.117) | **<.0001** | 1.264 |  |  |

|  |
| --- |
| Age is very heavily right skewed (Mean = 77.67 days versus Median = 50 days). There is a significant inverse linear correlation between Log Age and Log LOS (corr = -0.24; p<0.0001). Age is a significant predictor of Log LOS when added to Model 1. The log transformation of age better approximated normality of the residuals when compared to the model of the untransformed age. |

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Adding Days Postoperative ventilator support to Model 2 (N = 307)** | | | | | | | |
| **3** | Intercept | 3.221 | (2.785, 3.658) | <.0001 | 0 | 0.2786 | 0.544 |
|  | RBC (100 ml/kg) | -0.21 | (-0.378, -0.042) | **0.014** | 1.562 |  |  |
|  | 1995-2012 vs. 1985-1994 | 0.108 | (-0.050, 0.267) | 0.181 | 1.308 |  |  |
|  | Log Age at transplant (days) | -0.122 | (-0.196, -0.050) | **0.001** | 1.325 |  |  |
|  | Log Days postoperative ventilator support | 0.346 | (0.274, 0.417) | **<.0001** | 1.1 |  |  |

|  |
| --- |
| Days of postoperative ventilator support is very heavily right skewed (Mean = 7.12 versus Median = 3.00). There is a significant linear correlation between log days of postoperative ventilator support and Log LOS (corr = 0.49; p<0.0001). Log days of postoperative ventilator support is a significant predictor of Log LOS when added to model 2. The log transformation of days of postoperative ventilator support drastically improved the model fit when compared to the model with untransformed days of postoperative ventilator support. |

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Adding Days postoperative vasoactive support to Model 3 (N = 306)** | | | | | | | |
| **4** | Intercept | 3.057 | (2.616, 3.500) | <.0001 | 0 | 0.2983 | 0.0762 |
|  | RBC (100 ml/kg) | -0.226 | (-0.392, -0.059) | **0.008** | 1.572 |  |  |
|  | 1995-2012 vs. 1985-1994 | 0.173 | (0.012, 0.335) | **0.035** | 1.384 |  |  |
|  | log Age at transplant (days) | -0.124 | (-0.196, -0.051) | **0.001** | 1.324 |  |  |
|  | Log Days postoperative ventilator support | 0.278 | (0.195, 0.361) | **<.0001** | 1.497 |  |  |
|  | Log Days postoperative vasoactive support | 0.179 | (0.068, 0.290) | **0.002** | 1.561 |  |  |

|  |
| --- |
| One subject was lost due to missing data. Days of postoperative vasoactive support is very heavily right skewed (Mean = 5.15 versus Median = 4.00). There is a significant linear correlation between Log days of postoperative vasoactive support and Log LOS (corr = 0.36; p<0.0001). Log days of postoperative vasoactive support is a significant predictor of Log LOS. The log transformation of Days of postoperative vasoactive infusion greatly improved the influence of potential outliers compared to the model with untransformed days of postoperative vasoactive support (Cooks D dropped from 2.00 to 0.12). |

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Adding Intubated at transplant to Model 4 (N = 306)** | | | | | | | | |
| **5** | Intercept | 3.025 | (2.575, 3.465) | <.0001 | 0 | 0.308 | -0.062 |  |
|  | RBC (100 ml/kg) | -0.212 | (-0.378, -0.047) | **0.012** | 1.58 |  |  |  |
|  | 1995-2012 vs. 1985-1994 | 0.183 | (0.022, 0.343) | **0.026** | 1.387 |  |  |  |
|  | Log Age at transplant (days) | -0.124 | (-0.195, -0.052) | **0.001** | 1.324 |  |  |  |
|  | Log Days postoperative ventilator support | 0.246 | (0.160, 0.333) | **<.0001** | 1.658 |  |  |  |
|  | Log Days postoperative vasoactive support | 0.173 | (0.062, 0.283) | **0.002** | 1.565 |  |  |  |
|  | Intubated prior to transplant | 0.179 | (0.025, 0.334) | **0.023** | 1.19 |  |  |  |

|  |
| --- |
| There were 99 (32.25%) patients who were intubated prior to transplant and 208 (67.75%) who were not. In an Independent T-Test, intubated prior to transplant was significantly related to Log LOS (p<0.0001). In the multiple regression model, intubated prior to transplant is a significant predictor of Log LOS (p = 0.02) and will be kept in the model. |

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Adding Repeat Sternotomy to Model 5 (N = 306)** | | | | | | | |
| **6** | Intercept | 2.896 | (2.448, 3.344) | <.0001 | 0 | 0.3195 | -0.118 |
|  | RBC (100 ml/kg) | -0.187 | (-0.352, -0.022) | **0.027** | 1.604 |  |  |
|  | 1995-2012 vs. 1985-1994 | 0.212 | (0.051, 0.373) | **0.01** | 1.418 |  |  |
|  | Log Age at transplant (days) | -0.093 | (-0.168, -0.017) | **0.016** | 1.486 |  |  |
|  | Log Days postoperative ventilator support | 0.246 | (0.160, 0.332) | **<.0001** | 1.658 |  |  |
|  | Log Days postoperative vasoactive support | 0.171 | (0.061, 0.280) | **0.002** | 1.565 |  |  |
|  | Intubated prior to transplant | 0.201 | (0.047, 0.355) | **0.011** | 1.205 |  |  |
|  | Repeat Sternotomy | -0.251 | (-0.453, -0.050) | **0.015** | 1.177 |  |  |

|  |
| --- |
| There were 45 (14.66%) patients who had a prior sternotomy. In an Independent T-Test, repeat sternotomy was significantly related to Log LOS (p = 0.02). In the multiple regression model, repeat sternotomy is a significant predictor of Log LOS (p = 0.01) and will be kept in the model. We needed to carefully consider the inclusion of this variable in our model because there is a significant correlation of Repeat Sternotomy with Age (corr = 0.34; p<0.0001). |

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Adding Major Adverse Events to Model 6 (N = 306)** | | | | | | | |
| **7** | Intercept | 3.102 | (2.652, 3.552) | <.0001 | 0 | 0.35 | 0.048 |
|  | RBC (100 ml/kg) | -0.196 | (-0.358, -0.034) | **0.018** | 1.605 |  |  |
|  | 1995-2012 vs. 1985-1994 | 0.226 | (0.069, 0.384) | **0.005** | 1.421 |  |  |
|  | Log Age at transplant (days) | -0.123 | (-0.198, -0.047) | **0.002** | 1.55 |  |  |
|  | Log Days postoperative ventilator support | 0.286 | (0.199, 0.372) | **<.0001** | 1.752 |  |  |
|  | Log Days postoperative vasoactive support | 0.169 | (0.062, 0.276) | **0.002** | 1.565 |  |  |
|  | Intubated prior to transplant | 0.154 | (0.001, 0.307) | **0.048** | 1.235 |  |  |
|  | Repeat Sternotomy | -0.288 | (-0.486, -0.090) | **0.005** | 1.187 |  |  |
|  | Major Adverse Event | -0.286 | (-0.431, -0.141) | **0.0001** | 1.194 |  |  |

|  |
| --- |
| There were 115 (37.4%) patients who had at least one major adverse event following transplant. In an Independent T-Test, major adverse event was not a significant predictor of Log LOS (p = 0.94). We added major adverse event to model 6 to evaluate possible confounding effect on RBC. The addition of major adverse event to the model did not significantly change the beta estimate of RBC, however, it was a significant predictor in the presence of the other covariates and will be kept in the model. |

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Adding Preoperative hemoglobin to Model 7 (N = 300)** | | | | | | | |
| **8** | Intercept | 2.729 | (2.097, 3.361) | <.0001 | 0 | 0.3549 | 0.0443 |
|  | RBC (100 ml/kg) | -0.205 | (-0.368, -0.042) | **0.014** | 1.636 |  |  |
|  | 1995-2012 vs. 1985-1994 | 0.225 | (0.065, 0.384) | **0.006** | 1.438 |  |  |
|  | Log Age at transplant (days) | -0.108 | (-0.185, -0.031) | **0.006** | 1.568 |  |  |
|  | Log Days postoperative ventilator support | 0.293 | (0.206, 0.380) | **<.0001** | 1.768 |  |  |
|  | Log Days postoperative vasoactive support | 0.153 | (0.044, 0.262) | **0.006** | 1.611 |  |  |
|  | Intubated prior to transplant | 0.156 | (0.002, 0.310) | **0.048** | 1.249 |  |  |
|  | Repeat Sternotomy | -0.307 | (-0.457, -0.108) | **0.003** | 1.2 |  |  |
|  | Major Adverse Event | -0.311 | (-0.457, -0.165) | **<.0001** | 1.185 |  |  |
|  | Preoperative hemoglobin | 0.026 | (-0.007, 0.059) | 0.123 | 1.066 |  |  |

|  |
| --- |
| We are missing 6 observations from preoperative hemoglobin (Hb). Preoperative Hb is normally distributed (Mean = 13.14 versus Median = 13.00; KS: D = 0.04; p >0.150). Preoperative Hb is not significantly linearly correlated with Log LOS (corr = 0.10; p = 0.10). In the univariate linear regression, Preoperative Hb was not a significant predictor of Log LOS (p = 0.10). In the multiple regression setting, Preoperative Hb was not a significant predictor of Log LOS and did not significantly change the beta coefficient of RBC. |

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Adding 30 Day Mortality to Model 7 (N = 306)** | | | | | | | | |
| **9** | Intercept | 2.862 | (2.449, 3.276) | <.0001 | 0 | 0.4632 | -0.463 |  |
|  | RBC (100 ml/kg) | -0.11 | (-0.258, 0.039) | 0.148 | 1.639 |  |  |  |
|  | 1995-2012 vs. 1985-1994 | 0.178 | (0.035, 0.322) | **0.015** | 1.431 |  |  |  |
|  | Log Age at transplant (days) | -0.073 | (-0.143, -0.004) | **0.039** | 1.599 |  |  |  |
|  | Log Days postoperative ventilator support | 0.268 | (0.190, 0.347) | **<.0001** | 1.757 |  |  |  |
|  | Log Days postoperative vasoactive support | 0.146 | (0.049, 0.243) | **0.003** | 1.571 |  |  |  |
|  | Intubated prior to transplant | 0.158 | (0.019, 0.296) | **0.026** | 1.235 |  |  |  |
|  | Repeat Sternotomy | -0.23 | (-0.410, -0.050) | **0.013** | 1.195 |  |  |  |
|  | Major Adverse Event | -0.059 | (-0.203, 0.084) | 0.418 | 1.409 |  |  |  |
|  | 30 Day Mortality | -0.956 | (-1.192, -0.720) | **<.0001** | 1.222 |  |  |  |

|  |
| --- |
| There are 25 (8.14%) subjects who died in 30 days. In the Independent T-Test, 30-day mortality was significantly associated with shorter Log LOS, as we would expect (p<0.0001). The addition of 30-day mortality significantly altered the beta coefficient for RBC by more than 10% and is a significant predictor of Log LOS, in the presence of these other variables (p<0.0001). After adding death within 30 days, RBC is no longer a significant predictor of Log LOS and neither is Major Adverse Events. Since RBC is our variable of interest, we will keep this in the model and drop major Adverse Events to observe the change of our model with and without this variable. |

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Dropping Major Adverse Events from Model 9 (N = 306)** | | | | | | | |
| **10** | Intercept | 2.817 | (2.419, 3.215) | <.0001 | 0 | 0.4638 | -0.055 |
|  | RBC (100 ml/kg) | -0.104 | (-0.252, 0.043) | 0.166 | 1.628 |  |  |
|  | 1995-2012 vs. 1985-1994 | 0.174 | (0.031, 0.317) | **0.017** | 1.423 |  |  |
|  | Log Age at transplant (days) | -0.066 | (-0.133, 0.001) | 0.055 | 1.497 |  |  |
|  | Log Days postoperative ventilator support | 0.261 | (0.184, 0.337) | **<.0001** | 1.661 |  |  |
|  | Log Days postoperative vasoactive support | 0.145 | (0.048, 0.243) | **0.004** | 1.57 |  |  |
|  | Intubated prior to transplant | 0.166 | (0.029, 0.303) | **0.018** | 1.209 |  |  |
|  | Repeat sternotomy | -0.221 | (-0.400, -0.042) | **0.016** | 1.179 |  |  |
|  | Died within 30 days | -0.994 | (-1.21, -0.777) | **<.0001** | 1.036 |  |  |

|  |
| --- |
| We dropped Major Adverse Events from Model 9. There was about 5% decrease in the beta coefficient for RBC. Since Major Adverse Event was not significant, after the inclusion of the other covariates, and the beta coefficient is not largely affected by the inclusion or exclusion of this variable, we decided to drop this variable from our model. Additionally, the amount of variation in Log LOS accounted for is nearly identical with and without Major Adverse Event in the model and actually increases without Major Adverse Event in the model (R2 = 0.4632 versus R2 = 0.4638). |

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Adding Preoperative Inotrope Score > 0 to Model 10** | | | | | | | |
| **11** | Intercept | 2.818 | (2.419, 3.22) | <.0001 | 0 | 0.462 | 0.058 |
|  | RBC (100 ml/kg) | -0.11 | (-0.256, 0.043) | 0.163 | 1.659 |  |  |
|  | 1995-2012 vs. 1985-1994 | 0.179 | (0.026, 0.332) | **0.022** | 1.617 |  |  |
|  | Log Age at transplant (days) | -0.066 | (-0.133, 0.002) | 0.056 | 1.5 |  |  |
|  | Log Days postoperative ventilator support | 0.26 | (0.184, 0.337) | **<.0001** | 1.665 |  |  |
|  | Log Days postoperative vasoactive support | 0.146 | (0.048, 0.243) | **0.004** | 1.573 |  |  |
|  | Intubated prior to transplant | 0.169 | (0.028, 0.309) | **0.019** | 1.266 |  |  |
|  | Repeat sternotomy | -0.221 | (-0.400, -0.042) | **0.016** | 1.18 |  |  |
|  | Died within 30 days | -0.993 | (-1.210, -0.775) | **<.0001** | 1.04 |  |  |
|  | Preoperative Inotrope Score | -0.017 | (-0.196, 0.162) | 0.852 | 1.358 |  |  |

|  |
| --- |
| There are 54 (17.59%) patients with a Preoperative Inotrope Score >0. The Independent T-Test resulted in a non-significant association between Preoperative Inotrope Score (0 versus >=1) (p=0.5952) and Log LOS. We added this variable to Model 10 to check for any possible confounding effects. There was nearly no change in the beta coefficient for RBC after including Preoperative Inotrope Score in the model. We decided to drop this variable from our model. |

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Dropping Repeat Sternotomy from Model 10 (Final Model) (N = 306)** | | | | | | | |
| **12** | Intercept | 2.929 | (2.538, 3.320) | <.0001 | 0 | 0.4549 | 0.2038 |
|  | RBC (100 ml/kg) | -0.126 | (-0.274, 0.022) | 0.096 | 1.606 |  |  |
|  | 1995-2012 vs. 1985-1994 | 0.148 | (0.005, 0.290) | **0.043** | 1.391 |  |  |
|  | Log Age at transplant (days) | -0.093 | (-0.157, -0.0289) | **0.005** | 1.338 |  |  |
|  | Log Days postoperative ventilator support | 0.261 | (0.184, 0.338) | **<.0001** | 1.661 |  |  |
|  | Log Days postoperative vasoactive support | 0.147 | (0.049, 0.245) | **0.004** | 1.57 |  |  |
|  | Intubated prior to transplant | 0.147 | (0.009, 0.284) | **0.037** | 1.193 |  |  |
|  | Died within 30 days | -1.004 | (-1.222, -0.785) | **<.0001** | 1.035 |  |  |

|  |
| --- |
| We evaluated dropping repeat sternotomy from the model. While it is a significant predictor of Log LOS, there is a significant correlation with Age. The VIF of repeat sternotomy in the model is low, however we considered dropping this variable because it does not change the adjusted R square by much (0.4638 versus 0.4549 which is a 2% change). This variable does change the beta estimate of RBC by about 20% when dropped from model 10. This is our final model. It seems reasonable since this is our most parsimonious model. |

**Correlations to be wary of during multiple regression model building:**

* Age is highly correlated with transfused RBC volume (ml/kg): -0.45831; p-value < 0.0001
* Major Adverse Events is highly correlated with Death: -0.30; p-value < 0.0001 (however, dropped from the model)
* Age is highly correlated with Preoperative Inotrope Score: 0.52; p-value < 0.0001 (however, dropped from the model)
* Age is correlated with Repeat Sternotomy: 0.34; p-value < 0.0001 (However, dropped from the model)

Multiple regression model development steps for all infant heart transplant recipients studied (N = 307). Volume of red blood cell transfusion (RBC) was inversely related to length of stay (LOS) after heart transplantation, but was a small effect when other confounding variables were considered. LOS was log transformed to better approximate a normal distribution. Further modeling used RBC 100 ml/kg as a relevant transfusion volume.

**Table 2**: Multiple regression model development steps for infant heart transplant recipients who survived >30 days after transplant (N = 282)

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **Variable** | **Parameter** | **Confidence** | **P-value** | **Variance** |
|  | **Estimate** | **Interval** | **Inflation** |
|  | Intercept | 2.8855 | (2.7087, 3.0623) | **<.0001** | 0 |
|  | RBC (100 ml/kg) | 0.1240 | (-0.0179, 0.2660) | 0.0865 | 1.3082 |

|  |
| --- |
| Assessed linearity with visual inspection of the residual plots as well as partial regression plots. |
|

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Variable** | **Parameter** | **Confidence** | **P-value** | **Variance** | **Adjusted R2** | **% change** |
| **Model** | **Estimate** | **Interval** | **Inflation** |
| **1** | Intercept | 2.8267 | (2.5917, 3.0618) | **<.0001** | 0 | 0.2419 | 0.2419 |
|  | RBC (100 ml/kg) | 0.1540 | (-0.0085, 0.3165) | 0.0632 | 1.3082 |  |  |
|  | 1995-2012 vs. 1985-1994 | 0.0607 | (-0.0992, 0.2207) | 0.4553 | 1.3082 |  |  |

|  |
| --- |
| Based on a practice change introduced in 1995 (implementation of selective cerebral perfusion), we chose to dichotomize year of treatment. Independent T-Test showed no significant difference in mean Log LOS between the 2 categories of year of treatment (p = 0.86). While year of transplant is not a significant predictor of Log LOS it seems to be a confounding variable to RBC because the beta coefficient in Model 1 has changed by more than 10% compared to Model 0. |

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Adding Age to Model 1 (N = 282)** | | | | | | | |
| **2** | Intercept | 3.6311 | (3.2078, 4.0543) | **<.0001** | 0 | 0.0678 | -1.0844 |
|  | RBC (100 ml/kg) | -0.013 | (-0.1869, 0.1609) | 0.8831 | 1.5984 |  |  |
|  | 1995-2012 vs. 1985-1994 | 0.0638 | (-0.0910, 0.2187) | 0.4178 | 1.3083 |  |  |
|  | Log Age at transplant (days) | -0.1593 | (-0.2300, -0.0886) | **<.0001** | 1.2956 |  |  |

|  |
| --- |
| Age is very heavily right skewed (Mean = 77.30 days versus Median = 49.00 days). There is a significant inverse linear correlation between Log Age and Log LOS (corr = -0.27; p<0.0001). Age is a significant predictor of Log LOS when added to Model 1. The log transformation of age better approximated normality of the residuals when compared to the model of the untransformed age. |

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Adding Days postoperative ventilator support to Model 2 (N = 282)** | | | | | | | |
| **3** | Intercept | 3.0922 | (2.7253, 3.4591) | **<.0001** | 0 | 0.3479 | 5.5923 |
|  | RBC (100 ml/kg) | -0.0857 | (-0.2317, 0.060) | 0.2489 | 1.6112 |  |  |
|  | 1995-2012 vs. 1985-1994 | 0.0666 | (-0.0629, -0.1961) | 0.3124 | 1.3083 |  |  |
|  | Log Age at transplant (days) | -0.0953 | (-0.1555, -0.0350) | **0.002** | 1.345 |  |  |
|  | Log Days postoperative ventilator support | 0.3262 | (0.2676, 0.3847) | **<.0001** | 1.0867 |  |  |

|  |
| --- |
| Days on postoperative ventilator support is very heavily right skewed (Mean = 7.33 versus Median = 3.00). There is a significant linear correlation between Log Days postoperative ventilator support and Log LOS (corr = 0.58; p<0.0001). Log Days postoperative ventilator support is a significant predictor of Log LOS when added to model 2. The log transformation of ventilator days drastically improved the model fit when compared to the model with untransformed ventilator days (normality of residuals and equal variance improved). |

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Adding Days postoperative Vasoactive Support to Model 3 (N = 281)** | | | | | | | |
| **4** | Intercept | 3.0095 | (2.6351, 3.3838) | **<.0001** | 0 | 0.3566 | 0.0782 |
|  | RBC (100 ml/kg) | -0.0924 | (-0.2384, 0.0535) | 0.2135 | 1.6244 |  |  |
|  | 1995-2012 vs. 1985-1994 | 0.1055 | (-0.0281, 0.2914) | 0.1213 | 1.3999 |  |  |
|  | Log Age at transplant (days) | -0.0970 | (-0.1570, -0.0371) | **0.0016** | 1.3429 |  |  |
|  | Log Days postoperative ventilator support | 0.2970 | (0.2304, 0.3637) | **<.0001** | 1.4201 |  |  |
|  | Log Days postoperative vasoactive support | 0.0876 | (-0.0048, 0.1800) | 0.0629 | 1.5126 |  |  |

|  |
| --- |
| We are missing one observation from Days of postoperative vasoactive support and that subject is deleted from analysis. Days of postoperative vasoactive support is very heavily right skewed (Mean = 5.15 versus Median = 4.00). There is a significant linear correlation between Log Days postoperative vasoactive support and Log LOS (corr = 0.35; p<0.0001). Days of postoperative vasoactive support was log transformed to meet assumptions of equal variance in the residuals. Log Days postoperative vasoactive support is not a significant predictor of Log LOS, in the presence of other variables. We decided to drop Days postoperative vasoactive support from the model as it does not change the beta estimate by more than 10% and is not independently significant. |

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Adding Intubated prior to transplant to Model 3 (N = 281)** | | | | | | | |
| **5** | Intercept | 3.0695 | (2.7057, 3.4334) | **<.0001** | 0 | 0.3604 | -0.1223 |
|  | RBC (100 ml/kg) | -0.0811 | (-0.2258, 0.0635) | 0.2706 | 1.6122 |  |  |
|  | 1995-2012 vs. 1985-1994 | 0.0756 | (-0.0528, 0.2041) | 0.2475 | 1.3123 |  |  |
|  | Log Age at transplant (days) | -0.0967 | (-0.1563, -0.037) | **0.0016** | 1.3449 |  |  |
|  | Log Days postoperative ventilator support | 0.2962 | (0.2337, 0.3586) | **<.0001** | 1.2638 |  |  |
|  | Intubated prior to transplant | 0.1627 | (0.0359, 0.2894) | **0.0121** | 1.1759 |  |  |

|  |
| --- |
| There were 93 (32.98%) patients who were intubated prior to transplant and 189 (67.02%) who were not. In an Independent T-Test, intubated was significantly related to Log LOS (p<0.0001). In the multiple regression model, intubated prior to transplant is a significant predictor of Log LOS (p = 0.012) and will be kept in the model. **\*\*This is the suggested final model.** |

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Adding Repeat Sternotomy to Model 5 (N = 281)** | | | | | | | |
| **6** | Intercept | 2.9715 | (2.5974, 3.3560) | **<.0001** | 0 | 0.3675 | -0.2429 |
|  | RBC (100 ml/kg) | -0.0614 | (-0.2065, 0.0838) | 0.4058 | 1.6408 |  |  |
|  | 1995-2012 vs. 1985-1994 | 0.1035 | (-0.0271, 0.2341) | 0.1198 | 1.3711 |  |  |
|  | Log Age at transplant (days) | -0.0748 | (-0.1378, -0.0118) | **0.0201** | 1.5167 |  |  |
|  | Log Days postoperative ventilator support | 0.2970 | (0.2348, 0.3591) | **<.0001** | 1.264 |  |  |
|  | Intubated prior to transplant | 0.1750 | (0.0484, 0.3016) | **0.0069** | 1.1865 |  |  |
|  | Repeat Sternotomy | -0.1769 | (-0.3485, -0.0053) | **0.0434** | 1.2007 |  |  |

|  |
| --- |
| There were 40 (14.18%) patients who had a prior sternotomy and survived 30 days. In an Independent T-Test, repeat sternotomy was significantly related to Log LOS (p = 0.02). There is a significant correlation with Log LOS (corr = -0.14; p = 0.02). There is also a significant correlation with RBC (corr = -0.12; p = 0.04). In the multiple regression model, repeat sternotomy is a significant predictor of Log LOS (p = 0.04). We need to carefully consider the inclusion of this variable in our model because there is a significant correlation of Repeat Sternotomy with Age (corr = 0.34; p<0.0001). We will drop this variable from our model. |

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Adding Major Adverse Events to Model 5 (N = 282)** | | | | | | | |
| **7** | Intercept | 3.0558 | (2.6720, 3.4396) | **<.0001** | 0 | 0.3582 | 0.2948 |
|  | RBC (100 ml/kg) | -0.0795 | (-0.2251, 0.0662) | 0.2836 | 1.6282 |  |  |
|  | 1995-2012 vs. 1985-1994 | 0.0747 | (-0.0543, 0.2036) | 0.2554 | 1.3179 |  |  |
|  | Log Age at transplant (days) | -0.0943 | (-0.1575, -0.0312) | **0.0036** | 1.5026 |  |  |
|  | Log Days postoperative ventilator support | 0.2940 | (0.2287, 0.3594) | **<.0001** | 1.3767 |  |  |
|  | Intubated prior to transplant | 0.1650 | (0.0364, 0.2935) | **0.0121** | 1.2051 |  |  |
|  | Major Adverse Event | 0.0150 | (-0.1171, 0.1471) | 0.8229 | 1.2656 |  |  |

|  |
| --- |
| There were 92 (32.62%) patients who had one or more major adverse event and survived 30 days. In an Independent T-Test, major adverse event was a significant predictor of Log LOS (p = 0.003). The addition of major adverse event to the model did not significantly change the beta estimate of RBC. It was not a significant predictor in the presence of the other covariates and will be excluded from the final model. |

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Adding Preoperative hemoglobin to Model 5 (N = 276)** | | | | | | | |
| **8** | Intercept | 2.8315 | (2.3128, 3.3502) | **<.0001** | 0 | 0.3563 | 0.1497 |
|  | RBC (100 ml/kg) | -0.0914 | (-0.2390, 0.0561) | 0.2236 | 1.6603 |  |  |
|  | 1995-2012 vs. 1985-1994 | 0.0768 | (-0.0533, 0.2069) | 0.246 | 1.3208 |  |  |
|  | Log Age at transplant (days) | -0.0873 | (-0.1483, -0.0263) | **0.0052** | 1.3557 |  |  |
|  | Log Days postoperative ventilator support | 0.2934 | (0.2301, 0.3566) | **<.0001** | 1.2802 |  |  |
|  | Intubated prior to transplant | 0.1670 | (0.0383, 0.2958) | **0.0112** | 1.1899 |  |  |
|  | Preoperative hemoglobin g/dl | 0.0158 | (-0.0120, 0.0436) | 0.2633 | 1.0313 |  |  |

|  |
| --- |
| We are missing 5 observations from Preoperative hemoglobin. Preoperative hemoglobin is not quite normally distributed (Mean = 13.18 versus Median = 13.00; KS: D = 0.05; p = 0.046). Preoperative hemoglobin is symmetrical and will be left untransformed for the linear regression analysis. Preoperative hemoglobin is not significantly linearly correlated with Log LOS (corr = 0.08; p = 0.20). Preoperative hemoglobin is significantly correlated with RBC (corr = 0.16; p = 0.008). In the univariate linear regression, Preoperative hemoglobin was not a significant predictor of Log LOS (p = 0.20). In the multiple regression setting, Preoperative hemoglobin was not a significant predictor of Log LOS, however, it did change the beta coefficient of RBC by about 15%. Of note, the adjusted R Square decreased, this leads us to believe this variable does not improve our ability to explain the variability in Log LOS and will be excluded from our model. |

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Adding Preoperative Inotrope Score >0 to Model 5 (N = 282)** | | | | | | | |
| **9** | Intercept | 3.084 | (2.7199, 3.448) | **<.0001** | 0 | 0.3619 | 0.0405 |
|  | RBC (100 ml/kg) | -0.0951 | (-0.2412, 0.0509) | 0.2008 | 1.6473 |  |  |
|  | 1995-2012 vs. 1985-1994 | 0.1047 | (-0.0310, 0.2404) | 0.13 | 1.4682 |  |  |
|  | Log Age at transplant (days) | -0.0955 | (-0.1551, -0.0358) | **0.0018** | 1.3462 |  |  |
|  | Log Days postoperative ventilator support | 0.2945 | (0.2320, 0.3584) | **<.0001** | 1.2659 |  |  |
|  | Intubated prior to transplant | 0.1826 | (0.0524, 0.3127) | **0.0061** | 1.2431 |  |  |
|  | Preoperative Inotrope Score >0 | -0.1085 | (-0.2737, 0.0566) | 0.1969 | 1.3207 |  |  |

|  |
| --- |
| There are 50 (17.73%) patients with a Preoperative Inotrope Score >0. The Independent T-Test resulted in a non-significant difference in mean Log LOS between Preoperative Inotrope Score (No versus Yes) (p=0.5960). We added this variable to Model 5 to check for any possible confounding effects. We must also note there is a relationship between RBC and Preoperative Inotrope Score (corr = -0.34; p < 0.0001). There is less than 10% change in the beta estimate with the inclusion of Preoperative Inotrope Score. Based on the correlation with RBC, as well as the non-significant relationship between preoperative inotrope score as Log LOS, we have decided to not include this variable in the final model. |

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Adding Preoperative hemoglobin to Model 6 (N = 276)** | | | | | | | |
| **10** | Intercept | 2.6747 | (2.1409, 3.2085) | <.0001 | 0 | 0.3654 | 0.1401 |
|  | RBC (100 ml/kg) | -0.0700 | (-0.2178, 0.0778) | 0.3517 | 1.6887 |  |  |
|  | 1995-2012 vs. 1985-1994 | 0.1088 | (-0.0235, 0.2411) | 0.1065 | 1.3857 |  |  |
|  | Log Age at transplant (days) | -0.0621 | (-0.1267, 0.0025) | 0.0593 | 1.5431 |  |  |
|  | Log Days postoperative ventilator support | 0.2943 | (0.2315, 0.3571) | <.0001 | 1.2804 |  |  |
|  | Intubated prior to transplant | 0.1802 | (0.0518, 0.3086) | 0.0061 | 1.1999 |  |  |
|  | Repeat Sternotomy | -0.1933 | (-0.3663, -0.0203) | 0.0286 | 1.221 |  |  |
|  | Preoperative hemoglobin | 0.0192 | (-0.0085, 0.0469) | 0.1741 | 1.0438 |  |  |

|  |
| --- |
| Adding preoperative hemoglobin to model 6 to investigate the change if we choose to keep repeat sternotomy in the model (we may drop based on relationship with age as well as the fact that inclusion is a small change in adjusted R square). Preoperative hemoglobincontinues to be a non-significant predictor of Log LOS. The inclusion of this variable results in a 14% change in the beta estimate for RBC. We may consider including this in our final model as a possible confounder to RBC. |

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Adding Preoperative Inotrope Score to Model 6 (N = 276)** | | | | | | | |
| **11** | Intercept | 2.9885 | (2.6135, 3.3635) | <.0001 | 0 | 0.3683 | 0.2166 |
|  | RBC (100 ml/kg) | -0.0747 | (-0.2215, 0.0721) | 0.3176 | 1.6811 |  |  |
|  | 1995-2012 vs. 1985-1994 | 0.1281 | (-0.0090, 0.2652) | 0.0669 | 1.5138 |  |  |
|  | Log Age at transplant (days) | -0.0747 | (-0.1376, -0.0117) | 0.0203 | 1.5167 |  |  |
|  | Log Days postoperative ventilator support | 0.2955 | (0.2333, 0.3576) | <.0001 | 1.2662 |  |  |
|  | Intubated | 0.1922 | (0.0623, 0.3220) | 0.0039 | 1.2502 |  |  |
|  | Repeat Sternotomy | -0.1694 | (-0.3414, 0.0026) | 0.0535 | 1.2075 |  |  |
|  | Preoperative Inotrope Score >0 | -0.0964 | (-0.2612, 0.0684) | 0.2506 | 1.3281 |  |  |

|  |
| --- |
| Adding Preoperative Inotrope Score to model 6 to evaluate the possible confounding effect of this variable on RBC. The inclusion of this variable drastically changes the beta estimate for RBC (about 20%) from model 6. We may consider including this in the final model. |

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Adding Repeat Sternotomy, Preoperative hemoglobin, and Preoperative Inotrope Score to Model 5 (N = 276)** | | | | | | | |
| **12** | Intercept | 2.6853 | (2.1516, 3.2190) | <.0001 | 0 | 0.3663 | 0.1218 |
|  | RBC (100 ml/kg) | -0.0838 | (-0.2333, 0.0656) | 0.2705 | 1.7297 |  |  |
|  | 1995-2012 vs. 1985-1994 | 0.1346 | (-0.0044, 0.2736) | 0.0577 | 1.5317 |  |  |
|  | Log Age at transplant (days) | -0.0619 | (-0.1265, 0.0026) | 0.0601 | 1.5432 |  |  |
|  | Log Days postoperative ventilator support | 0.2925 | (0.2297, 0.3553) | <.0001 | 1.2833 |  |  |
|  | Intubated prior to transplant | 0.1983 | (0.0665, 0.3300) | 0.0033 | 1.2663 |  |  |
|  | Repeat Sternotomy | -0.1864 | (-0.3597, -0.0132) | 0.035 | 1.2264 |  |  |
|  | Preoperative hemoglobin | 0.0197 | (-0.0080, 0.0474) | 0.1624 | 1.0449 |  |  |
|  | Preoperative Inotrope Score >0 | -0.0990 | (-0.2641, 0.0660) | 0.2385 | 1.3326 |  |  |

|  |
| --- |
| Because Repeat Sternotomy, Preoperative hemoglobin and Preoperative Inotrope Score >0 changed the beta coefficients by more than 10% in the previous model; we further investigated these variable as none of these were significant predictors of Log LOS. Building on model 11 and including Preoperative hemoglobin back into the model results in a change of the beta coefficient of RBC by more than 10%. This could be a final model for patients who survived 30 days; however model 5 is preferable, as the estimates for RBC are very similar and the adjusted R square is nearly identical. |

Multiple regression model development steps for infant heart transplant recipients who survived >30 days after transplant (N = 282). Volume of red blood cell transfusion (RBC) was inversely related to length of stay (LOS) after heart transplantation on univariate analysis, but was not related to LOS when other confounding variables were considered. LOS was log transformed to better approximate a normal distribution. Further modeling used RBC 100 ml/kg as a relevant transfusion volume.