Low-weight infants are at increased mortality risk after palliative or corrective cardiac surgery

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Background: Low weight is an established risk factor for mortality after congenital cardiac surgery. Given the advances in the care of neonates and infants after surgery, we sought to examine the effect of low weight on outcomes in the current era.

Methods: From 2002 to 2012, 2051 infants aged 90 days or less underwent cardiac surgery including 534 (26.0%) with single-ventricle pathology. Regression models examined the effect of low weight (≤2.5 kg; n = 274, 13.4%) on early and late outcomes.

Results: Overall, the incidence of prematurity, associated chromosomal/extracardiac abnormalities was higher in infants who weighed 2.5 kg or less than in those who weighed more than 2.5 kg; the incidence of single-ventricle pathology was comparable between the 2 groups. In addition, infants who weighed 2.5 kg or less underwent more palliation and had a higher proportion of STAT (Society of Thoracic Surgeons—European Association for Cardio-Thoracic Surgery) risk category 4 and 5 procedures. Adjusted regression models showed that low weight (≤2.5 kg) did not increase unplanned reoperation (odds ratio [OR], 0.90; 95% confidence interval [CI], 0.48-1.67; P = .73) or extracorporeal membrane oxygenation requirement (OR, 1.23; 95% CI, 0.68-2.22; P = .49), however it was associated with significant increase in hospital mortality (OR, 2.15; 95% CI, 1.33-3.50; P = .002). In addition, there was a significant association between low weight and increased duration of postoperative mechanical ventilation and intensive care unit and hospital stays. Adjusted hazard analysis showed that weight equal to or less than 2.5 kg was associated with diminished late survival (hazard ratio, 1.89; 95% CI, 1.39-2.55; P < .001) and that was evident in all patients subgroups (P < .001 for all).

Conclusions: In a large single-center series, low weight continues to be associated with increased early mortality risk and resource utilization after palliative and corrective cardiac surgery. The hazard of death in low-weight patients continues beyond the perioperative period for at least 1 year before normalizing. Strategies to improve outcomes for this high-risk population must address perioperative care, outpatient surveillance, and management. (J Thorac Cardiovasc Surg 2014;148:2508-14)

See related commentary on pages 2515-6.

Supplemental material is available online.
In the current series, we aimed to examine the effect of low weight at the time of neonatal and infant cardiac surgery on hospital outcomes, resource utilization, and long-term survival, and to analyze the risk factors for mortality in this challenging group of patients.

PATIENTS AND METHODS

Inclusion Criteria

From 2002 to 2012, 2051 infants aged 90 days or less underwent congenital cardiac surgery at Children’s Healthcare of Atlanta, Emory University. Our patient cohort included patients who had all palliative and corrective congenital cardiac surgeries with the exception of primary ligation of a patent ductus arteriosus and primary pacemaker implantation for congenital heart block. Patients were identified using our institutional surgical database. Demographic, anatomic, clinical, operative, and hospital details were abstracted from medical records for analysis. Approval for this study was obtained from our hospital’s Institutional Review Board and requirement for individual consent was waived for this observational study.

Follow-up

Time-related outcomes were determined from recent office visits recorded in the electronic chart in the Children’s Healthcare of Atlanta system or from direct correspondence with other pediatric cardiologists outside the system. Follow-up was 89% complete. Mean follow-up duration was 5.8 ± 3.7 years and was 4.7 ± 3.6 years for patients who weighed 2.5 kg or less and 6.0 ± 3.6 years for patients who weighed more than 2.5 kg ($P < .001$).

Statistical Analysis

Data are presented as means with standard deviations, medians with interquartile ranges (IQR) or frequencies as appropriate. Comparisons between patients who weighed 2.5 kg or less and those weighed more than 2.5 kg were performed using the Fisher exact $\chi^2$ test and the Student $t$ test assuming unequal variance between groups (Sattertwaite method). Comparisons for postoperative ventilation time, postoperative intensive care unit (ICU) stay, and postoperative hospital stay were performed after natural log transformation. Linear regression models were used to determine the effect of weight equal to or less than 2.5 kg on mortality in different subgroups of patients was assessed using the parametric hazard regression modelling described earlier (without adjustment) and the hazard ratio with the 95% confidence interval for weight equal to or less than 2.5 kg in each subgroup is presented in a forest plot. Mean imputation was used instead of missing values for multivariable regression models. All statistical analyses were performed using SAS v9.3 (SAS Institute, Inc, Cary, NC).

RESULTS

Patient Characteristics

Between 2002 and 2012, 2051 infants aged 90 days or less underwent congenital cardiac surgery at our institution. Of those, 1777 patients (86.6%) weighed more than 2.5 kg and 274 patients (13.4%) weighed 2.5 kg or less at the time of surgery. The median age at time of surgery was 7 days (IQR 4-32 days). Overall, 344 children (17.2%) were born prematurely (≤36 weeks’ gestation) and 468 children (22.8%) had associated chromosomal or major extracardiac anomalies. With regard to the underlying cardiac pathology, 534 patients (26.0%) had a single-ventricle malformation and 1517 patients (74.0%) had a 2-ventricle malformation.

Table 1 presents the differences in patient characteristics between those who weighed 2.5 kg or less and those who weighed more than 2.5 kg at the time of cardiac surgery. The incidence of female gender, prematurity, and chromosomal/extracardiac malformations was significantly higher in infants who weighed 2.5 kg or less than in those who weighed more than 2.5 kg.

Operative Details

Overall, 792 patients (38.6%) had palliative surgery for single- or 2-ventricle abnormalities and 1259 patients (61.4%) had primary full repair for 2-ventricle abnormalities. Overall, cardiopulmonary bypass was used in 1334 patients (65.0%). The distribution of STAT categories was as follows: category 1, n = 224 (10.9%); category 2, n = 364 (17.8%); category 3, n = 236 (11.5%); category 4, n = 897 (43.8%); category 5, n = 327 (15.9%); 3 cases (<1%) were not categorized. Table 1 presents the differences in operative details between those who weighed 2.5 kg or less and those who weighed more than 2.5 kg at the time of cardiac surgery. Infants who weighed 2.5 kg or less had more palliative surgeries and consequently less use of cardiopulmonary bypass and more STAT category 4 and 5 procedures than infants who weighed more than 2.5 kg.

Hospital Outcomes

We examined the effect of weight on 3 early clinical outcomes: unplanned cardiac reoperation, requirement for ECMO support, and hospital mortality.
Overall, unplanned cardiac reoperations were performed in 115 infants (5.6%): 15 infants weighed 2.5 kg or less (5.5%) and 100 infants weighed more than 2.5 kg (5.6%; $P = .100$). In logistic regression models, there was no significant association between weight group and unplanned reoperation (odds ratio [OR], 0.90; 95% confidence interval [CI], 0.48-1.67 for $\leq 2.5$ kg, $P = .73$; OR, 1.02 per 1 kg increase in weight; 95% CI, 0.73-1.44, $P = .90$) (Figure 1, A).

Postoperative ECMO support was needed in 113 infants (5.5%): 18 infants weighed 2.5 kg or less (6.6%) and 95 infants weighed more than 2.5 kg (5.4%; $P = .39$). In logistic regression models, there was no significant association between weight group and ECMO requirement (OR, 1.23; 95% CI, 0.68-2.22 for $\leq 2.5$ kg, $P = .49$; OR, 0.66 per 1 kg increase in weight; 95% CI, 0.46-0.95, $P = .02$) (Figure 1, B).

Overall hospital mortality was 135 infants (6.5%): 37 infants weighed 2.5 kg or less (13.5%) and 98 infants weighed more than 2.5 kg (5.5%; $P < .001$). On logistic regression models, there was a significant association between low weight and hospital mortality (OR, 2.15; 95% CI, 1.33-3.50 for $\leq 2.5$ kg, $P = .002$; OR, 0.52 per 1 kg increase in weight; 95% CI, 0.36-0.75, $P = .001$) (Figure 1, C).

In addition, we examined the effect of weight on resource utilization: postoperative ventilation requirement, ICU stay, and hospital stay (Figure 2, A).

### TABLE 1. Patient characteristics and operative details stratified by weight at surgery

<table>
<thead>
<tr>
<th></th>
<th>Weight $\leq 2.5$ kg (n = 274, 13.4%)</th>
<th>Weight $&gt;2.5$ kg (n = 1777, 86.6%)</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight, kg $\pm SD$</td>
<td>3.34 ± 0.80</td>
<td>2.21 ± 0.26</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Age, d (IQR)</td>
<td>7 (4-32)</td>
<td>8 (5-21)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Female gender, n (%)</td>
<td>836 (40.8)</td>
<td>134 (48.9)</td>
<td>.04</td>
</tr>
<tr>
<td>Prematurity $\leq 36$ wks, n (%)</td>
<td>344 (17.2)</td>
<td>159 (60.0)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Chromosomal/extracardiac anomalies, n (%)</td>
<td>468 (22.8)</td>
<td>101 (36.9)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Single ventricle, n (%)</td>
<td>534 (26.0)</td>
<td>79 (28.8)</td>
<td>.27</td>
</tr>
<tr>
<td>STAT category 4 and 5, n (%)</td>
<td>1224 (59.7)</td>
<td>192 (70.1)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Palliation (vs full repair), n (%)</td>
<td>791 (38.6)</td>
<td>135 (49.3)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Cardiopulmonary bypass use, n (%)</td>
<td>1334 (65.0)</td>
<td>142 (51.8)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

SD, Standard deviation; IQR, interquartile range; STAT, Society of Thoracic Surgeons—European Association for Cardio-Thoracic Surgery.

The overall duration of postoperative mechanical ventilation was 80 hours (IQR, 43-169 hours): 128 hours (IQR 59-266 hours) in infants who weighed 2.5 kg or less and 77 hours (IQR 37-161 hours) in infants who weighed more than 2.5 kg; \( P < .001 \). In logistic regression models, there was a significant effect of weight group on duration of postoperative ventilation (Figure 2, B).

Overall postoperative ICU stay was 132 hours (IQR 77-237 hours): 188 hours (IQR 114-313 hours) in infants who weighed 2.5 kg or less and 121 hours (IQR 75-217 hours) in infants who weighed more than 2.5 kg; \( P < .001 \). In logistic regression models, there was a significant effect of weight group on postoperative ICU stay (Figure 2, C).

Overall postoperative hospital stay was 9 days (IQR 6-17 days): 13 days (IQR 8-22 days) in infants who weighed 2.5 kg or less and 9 days (IQR 6-16 days) in infants who weighed more than 2.5 kg; \( P < .001 \). In multivariable logistic regression models, there was a significant effect of weight group on postoperative hospital stay (Figure 2, D).

**Late Outcomes**

The effect of weight group on late survival was examined. Univariable parametric survival analysis showed that

![RESOURCE UTILIZATION](image1)

**FIGURE 2.** A, Difference in postoperative ventilation, ICU and hospital stay between patients \( \leq 2.5 \) kg (in red) and \( >2.5 \) kg (in gray). B, Association between postoperative ventilation duration and weight at surgery. C, Association between postoperative ICU stay and weight at surgery. D, Association between postoperative hospital stay and weight at surgery. *ICU*, Intensive care unit.

![SURVIVAL](image2)

**FIGURE 3.** A, Parametric hazard model for survival after surgery stratified by weight group (\( \leq 2.5 \) kg and \( >2.5 \) kg). B, Hazard function for mortality stratified by weight group (\( \leq 2.5 \) kg and \( >2.5 \) kg).
weight equal to or less than 2.5 kg was a significant risk factor for mortality (hazard ratio [HR], 2.64; 95% CI, 2.04-3.41, \( P < .001 \)). Adjusted regression models that included age, gender, premature birth, chromosomal/extracardiac anomalies, single ventricle, STAT category, palliation (vs full repair), and use of cardiopulmonary bypass continued to show that weight equal to or less than 2.5 kg was a significant risk factor for mortality (HR, 1.89; 95% CI, 1.39-2.55, \( P < .001 \)).

Similarly, the effect of weight as a continuous variable on late survival was examined. Unadjusted hazard analysis showed that lower weight was a significant risk factor for mortality (HR, 0.42 per kg increase in weight; 95% CI, 0.35-0.50, \( P < .001 \)). Adjusted regression models that included age, gender, premature birth, chromosomal/extracardiac anomalies, single ventricle, STAT category, palliation (vs full repair), and use of cardiopulmonary bypass continued to show that lower weight was a significant risk factor for mortality (HR, 0.51; 95% CI, 0.41-0.64, \( P < .001 \)).

Figure 3, A, depicts the parametric model for survival after surgery stratified by weight group equal to or less than 2.5 kg and greater than 2.5 kg. The hazard function for mortality for both groups over time is depicted in Figure 3, B. The hazard function for mortality for the 2 weight groups is further stratified by the type of cardiac pathology (single vs biventricle anomaly) in Figure 4.

The effect of weight equal to or less than 2.5 kg (vs >2.5 kg) on postoperative survival among different selected patient subgroups is depicted in Figure 5 and Table E1. Weight equal to or less than 2.5 kg was found to be associated with increased hazard of mortality in all subgroups.

**DISCUSSION**

The incidence of low weight in our surgical patients was 13.4%, analogous to the incidence of 8%-18% reported in the literature.\(^1,3\) This is due to the higher incidence of prematurity and associated extracardiac congenital and genetic abnormalities in infants with congenital heart disease, and the fact that neonates with congenital heart disease are frequently small for their gestational age irrespective of prematurity or genetic syndromes.\(^1,3,15\)

Despite small size and tissue delicateness, increased experience with complex neonatal repair and improved perfusion strategies have allowed palliation or full repair in low-weight neonates with successful anatomic results comparable with their larger counterparts.\(^5,8\) The risk of unplanned reoperation for residual lesions in our current series was comparable between the 2 groups of patients, suggesting that the worst survival was not necessarily related to increased technical failures in the low-weight group. In addition, there was no significant difference between the 2 weight groups in the incidence of return to cardiopulmonary bypass for correction of residual lesions, or in duration of cardiopulmonary bypass or ischemia at the time of operation, making it less likely that these factors affected early or late outcomes.
Similarly, there was no significant difference in postoperative ECMO requirement between the different weight groups although there was in increased incidence of ECMO use in the very-low-weight patients as shown in Figure 1. B. ECMO hospital survival in our series for infants who weighed 2.5 kg or less was 33% compared with 46% in the larger patients. This trend for increased ECMO mortality is comparable with other reports demonstrating worse hospital survival in lower-weight patients requiring postoperative ECMO support.10,12 Nonetheless, despite the recent advances in preoperative stabilization, surgical technique, perfusion and myocardial protection strategies, and postoperative care, low weight at time of surgery continues to be an independent risk factor for poor outcome in series from experienced centers and larger multi-institutional registry series.8-14 Therefore, the optimal approach to low-weight patients requiring palliative or corrective surgery remains a dilemma. The theoretic advantages of delaying intervention to allow the neonate to gain weight include avoidance of the deleterious effects of cardiopulmonary bypass on the patient’s immature organs such as intracranial hemorrhage, renal failure, pulmonary dysfunction, and coagulopathy. Disadvantages of that delayed intervention approach are related to persistent abnormal physiology with resultant problems such as ventilator dependency, necrotizing enterocolitis, renal dysfunction, sepsis, and neurologic complications.3,5,16,17 Moreover, adequate weight gain is infrequently achieved leading to unnecessary prolonged delays in surgical treatment and emergence of complications.3,5,16,17 In a study by Chang and colleagues examining outcomes of 100 neonates weighing 2.5 kg or less, early intervention (repair or palliation) was found to be associated with higher survival than delayed intervention and they suggested that prolonged medical therapy to achieve further weight gain did not seem to improve survival. Moreover, in a study by Reddy and colleagues examining the results of surgical repair in 102 infants weighing 2.5 kg or less, hospital survival was 90% and 5-year survival was 82%; they recommended early primary repair. Hickey and colleagues compared outcomes in neonates with very low weight (≤2.0 kg) who received usual or delayed intervention. They found that survival in children weighing less than 2.0 kg and receiving either usual or delayed care was identical and concluded that imposed delays in intervention neither compromised nor improved survival. Our institutional policy has been to offer early intervention, repair or palliation, in low-weight neonates and infants, and to defer surgery only in those with serious coexisting medical conditions such as sepsis, severe pulmonary infection, necrotizing enterocolitis, intracranial hemorrhage, coagulopathy, severe end-organ injury, or severe associated malformations requiring intervention such as severe diaphragmatic hernia. As a result, our study is not equipped to answer the question about early versus delayed intervention in low-weight infants. However, an interesting finding from this study is that although low weight was associated with increased mortality hazard in all age groups, this increased mortality hazard was most pronounced in patients older than 31 days, indicating that significant delays in surgery in low-weight patients might have a negative effect on survival, especially in those who fail to gain weight.

Multistage palliation is the mainstay of management of patients with single-ventricle pathologies. Initial palliation of single-ventricle neonates depends on the individual anatomy and physiology, and might include a pulmonary artery band, aortopulmonary shunt, or a Norwood-type palliation. Each of these palliative procedures is challenging to complete in small babies because of issues with small size of the cardiac structures, pulmonary hypertension, pulmonary dysfunction, prematurity, and so forth. Low weight has persistently been demonstrated to be a risk factor for mortality after the Norwood operation, even in contemporary series from experienced institutions.19 Similarly, low weight has been associated with increased mortality risk after aortopulmonary shunts as a result of shunt complications related to the small-sized shunts or systemic steal due to excessive pulmonary blood flow, which is likely more common in smaller infants.20,21 In a recent review of the Society of Thoracic Surgeons database, weight less than 3 kg at surgery was an independent risk factor for hospital mortality after aortopulmonary shunt.20 In addition to early death, low weight at time of first palliative surgery in patients with a single ventricle seems to have an adverse effect on progression through subsequent palliative stages and late survival.19,22 In our current series, the hazard of death was more pronounced and more prolonged in infants who weighed 2.5 kg or less, especially those with a single ventricle, indicating the need for extra monitoring and special care in these high-risk babies. After this series, an ongoing study at our institution was initiated to examine the effect of low weight on the progression of patients with a single ventricle through subsequent palliative stages (Glenn and Fontan) after first stage palliation. The preliminary analysis suggests that, in addition to higher hospital mortality, low-weight patients were more likely to have interstage mortality and less likely to progress to the Glenn operation. After Glenn, both weight groups seem to have comparable progression to the Fontan final palliation stage.

On the other hand, many patients with 2-ventricle physiology can be treated with primary repair versus palliation. The advantage of primary palliation includes avoidance of exposure to cardiopulmonary bypass and potentially shorter hospital stay. Nonetheless, palliation with a shunt or a pulmonary artery band in small babies is challenging and associated with higher mortality as
discussed earlier. In a recent series examining the effect of low weight on hospital survival from the Society of Thoracic Surgeons database, weight less than 2.5 kg was strongly associated with death in many palliative and corrective surgical categories. Similarly, in our current series, low weight was associated with increased death hazard in both palliative and repair procedures, although the death hazard was slightly more pronounced in the primary repair group. In the same way, low weight was associated with increased death hazard in all procedures including those with or without the use of cardiopulmonary bypass. Therefore, we believe that the choice of initial surgery in low-weight neonates with 2-ventricle physiology should be based on institutional experience and individualized for each patient taking into consideration the complexity of intracardiac repair and associated comorbidities.

An important finding is that the hazard of death is more prolonged in low-weight patients, especially in those undergoing single-ventricle palliation. This indicates that low-weight patients continue to be exposed to mortality risk well beyond the perioperative period. Increased postoperative complications, immature organs associated with prematurity, persistent end-organ dysfunction, and associated extracardiac anomalies might all contribute to this finding. Therefore, improvement in long-term outcomes of low-weight infants after cardiac surgery might require, in addition to improved perioperative care, vigilant attention to postdischarge follow-up and monitoring, and customized care tailored to each patient, taking into consideration their unique clinical condition and comorbidities.

CONCLUSIONS

Low weight is frequently encountered in neonates and infants with congenital heart disease, and is commonly associated with other comorbid issues related to prematurity and associated extracardiac malformations. Despite recent advances in the perioperative management of neonates and infants requiring congenital heart surgery, low weight continues to be associated with increased hospital mortality and resource utilization. The hazard of death in low-weight patients is prolonged and continues for 1 to 2 years before normalizing, indicating that methods to improve outcomes on this challenging group should address both perioperative care, outpatient surveillance, and management.

References


TABLE E1. Effect of weight ≤2.5 kg (vs >2.5 kg) on postoperative survival among selected patient subgroups: hazard ratio for mortality (with 95% confidence interval) for weight ≤2.5 kg in each patient subgroup

<table>
<thead>
<tr>
<th>Effect of weight ≤2.5 kg, HR (95% CI)</th>
<th>Effect P value</th>
<th>Interaction P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight ≤2.5 kg</td>
<td>2.64 (2.04-3.41)</td>
<td>&lt;.001</td>
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<tr>
<td>Age at operation</td>
<td></td>
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<tr>
<td>1-7 d</td>
<td>2.09 (1.46-2.99)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>8-31 d</td>
<td>3.16 (1.74-5.75)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>&gt;31 d</td>
<td>4.15 (2.48-6.94)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Male</td>
<td>2.53 (1.79-3.58)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Female</td>
<td>2.91 (1.96-4.33)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Premature</td>
<td>1.90 (1.19-3.04)</td>
<td>&lt;.001</td>
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<tr>
<td>Full term</td>
<td>2.98 (2.06-4.32)</td>
<td>&lt;.001</td>
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<td>Chromosomal/extracardiac anomalies</td>
<td>2.26 (1.54-3.30)</td>
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<td>No chromosomal/extracardiac anomalies</td>
<td>2.41 (1.68-3.46)</td>
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<tr>
<td>Two ventricles</td>
<td>2.11 (1.47-3.03)</td>
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<td>3.43 (2.37-4.98)</td>
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<td>STAT category</td>
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<tr>
<td>1-3</td>
<td>4.67 (2.19-9.94)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>4-5</td>
<td>2.13 (1.62-2.81)</td>
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<tr>
<td>Palliation</td>
<td>1.98 (1.45-2.69)</td>
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</tr>
<tr>
<td>Full repair</td>
<td>3.41 (2.12-5.48)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>No cardiopulmonary bypass use</td>
<td>2.65 (1.74-4.02)</td>
<td>&lt;.001</td>
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<tr>
<td>Cardiopulmonary bypass use</td>
<td>2.81 (2.02-3.93)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

HR, Hazard ratio; CI, confidence interval; STAT, Society of Thoracic Surgeons—European Association for Cardio-Thoracic Surgery.