Genetic and Extracardiac Anomalies Are Associated With Inferior Single Ventricle Palliation Outcomes

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Background. We examined the effect of genetic syndromes and extracardiac (GS/EC) anomalies on single-ventricle (SV) palliation with focus on hospital and interstage death and progression toward subsequent palliation stages.

Methods. First-stage palliation was performed in 530 neonates with SV: Norwood in 284 (53%), shunt in 173 (33%), and band in 73 (14%). Outcomes were compared between those with GS/EC anomalies (121 [23%]) and without GS/EC anomalies (409 [77%]). Regression analyses were adjusted for other risk factors (age, sex, prematurity, weight, SV anomaly, and first-stage palliation operation).

Results. GS/EC anomalies varied among SV defects (range, 3% for double-inlet left ventricle to 100% for atrial isomerism). Patients with GS/EC anomalies required significantly longer durations of mechanical ventilation and intensive care unit and hospital stay. Although patients had comparable rates of extracorporeal membrane oxygenation (13% vs 11%, \( p = 0.552 \)) and unplanned reoperation (16% vs 11%, \( p = 0.189 \)), hospital mortality was higher in patients with GS/EC anomalies (24% vs 12%, \( p = 0.0008 \)). After discharge, patients with GS/EC anomalies had higher interstage death, with lower progression to Glenn (60% vs 77%, \( p = 0.002 \)) and lower 10-year survival (56% vs 76%, \( p < 0.001 \)). After adjustment for other risk factors, GS/EC anomalies significantly affected survival in almost all subgroups of patients.

Conclusions. The presence of GS/EC anomalies varies among SV anomalies and is associated with additional risk factors such as prematurity and low weight. After adjusting for other risk factors, GS/EC anomalies are associated with prolonged recovery after first-stage palliation and increased hospital and interstage death, with subsequently fewer patients progressing toward Glenn shunt. The increased death risk in those patients is highest in the first 6 months and persists for 2 to 3 years after first-stage palliation, suggesting the need for more vigilant monitoring and outpatient care in these high-risk patients.


The reported incidence of genetic syndromes and major extracardiac (GS/EC) anomalies in neonates with congenital heart disease is 20% to 30% [1–5]. GS/EC anomalies are associated with prolonged recovery and worse outcomes after neonatal cardiac operations [3, 4, 6–8]. In addition, neonates with GS/EC anomalies often have associated risk factors such as prematurity, low birth weight, and poor clinical condition [4]. GS/EC anomalies might subsequently affect timing of a surgical intervention and complicate perioperative care and home management. [3, 4, 6–8]. Although GS/EC anomalies have been identified to be associated with poor hospital survival in patients with various single-ventricle (SV) anomalies, the effect of GS/EC anomalies on progression toward subsequent palliative stages has not been well studied [4, 9–14].

We aimed to examine the prevalence of GS/EC anomalies in neonates with SV anomalies undergoing first-stage palliation, to report associated risk factors, and to assess the effect of GS/EC anomalies on hospital outcomes, resource utilization, progression toward Glenn and later Fontan operations, and midterm survival.

Patients and Methods

Inclusion Criteria

From 2002 to 2012, 530 neonates born with SV anomalies underwent first-stage palliation at Children’s Healthcare of Atlanta, Emory University. Patients were identified using our institutional surgical database. Demographic, anatomic, clinical, operative, and hospital details were abstracted from medical records for analysis. The hospital’s Institutional Review Board approved this study and
waived the requirement for individual consent for this observational study.

Screening for GS/EC Anomalies

Neonates who are admitted to the cardiac intensive care unit at our institution undergo chromosomal analysis if they have cardiac defects commonly associated with genetic anomalies (eg, conotruncal lesions, complete atroventricular septal defect), hypoplastic left heart syndrome, extracardiac malformations (eg, imperforate anus, tracheoesophageal fistula), or any dysmorphic features. During the course of this current study, the type of chromosomal analysis changed. In the earlier phase, those neonates underwent standard metaphase karyotype chromosomal analysis (450 to 550 bands), high-resolution banding (600 to 850 bands), and fluorescent in situ hybridization studies; in the later phase starting in 2010, chromosomal microarray testing became the standard study for chromosomal analysis in our unit.

Follow-Up

Time-related outcomes were determined from recent office visits documented in our electronic record system or from direct correspondence with other pediatric cardiologists outside the system. Mean follow-up duration was 5.9 ± 4.1 years and was 91% complete.

Statistical Analysis

Statistical significance was evaluated at the 0.05 level, and data analyses were performed using SAS 9.4 software (SAS Institute, Inc, Cary, NC). Patient demographic and clinical characteristics were evaluated using means and SDs or medians and ranges for continuous variables, or counts and percentages for categoric variables. Differences between the study groups (GS/EC anomalies present vs absent) were assessed using t tests for continuous variables and χ² tests for categoric variables. In situations of nonnormality, the t test was replaced by a nonparametric equivalent (Mann-Whitney U test or Kolmogorov-Smirnov test); likewise, an exact form of the Pearson χ² test was implemented when expected frequency counts were low (<5). Continuous outcomes of interest included durations of ventilation and intensive care unit and postoperative hospital stay; concurrently, hospital death, need for extracorporeal membrane oxygenation (ECMO), and unplanned reoperation were evaluated. Continuous outcomes were log-transformed before statistical modeling.

General linear regression and binary logistic regression models were used to evaluate the effect of GS/EC anomalies on continuous and binary outcomes, respectively. Unadjusted and adjusted estimates are reported with associated 95% confidence intervals (CIs). In the adjusted analyses, estimates were controlled for weight, age, sex, prematurity, underlying SV anomaly, and type of first-stage palliative operation (Norwood, shunt, band).

Time until death after the initial operation was modeled using a parametric survival model. Parametric probability estimates for time-dependent outcomes (ie, death) were based on models using multiple, overlapping phases of risk from PROC HAZARD. The HAZARD procedure uses maximum likelihood estimates to resolve risk distribution of time-to-event data in up to three phases of risk (early, constant, and late hazard). Nonlinear optimization-based algorithms were used to iteratively calculate maximum likelihood estimates. Smoothed survival curves were generated using the HAZPRED procedure.

Competing risk analysis was performed to model the probability over time of each of the following two mutually exclusive end points after first-stage palliation: death or transplantation and survival to Glenn, with the remaining patients being alive without Glenn. After Glenn, mutually exclusive end points were death or transplantation and survival to Fontan, with the remaining patients being alive awaiting Fontan.

The overall risk for death, our primary outcome, was strongest in the first 6 months after the initial operation. Given this trend, an early-phase model was most appropriate for these data. The effect of study group (GS/EC present vs absent) on early-phase death was examined parametrically among subsets of patients. Effects of study group on the probability of death are given as hazard ratios with 95% CIs.

Results

Patients’ Characteristics

Between 2002 and 2012, 530 neonates with SV underwent first-stage palliation. Of those, 121 (23%) had GS/EC anomalies and 409 (77%) did not.

Chromosomal abnormalities were identified in 107 neonates and included Down syndrome (n = 6), 22q11.2 deletion syndrome (n = 4), laterality sequences (ie, heterotaxy syndrome; n = 58), sex chromosome–related syndromes (ie, Turner, Klinefelter, XY; n = 6), chromosomal abnormalities involving various mutations (ie, CHARGE [coloboma, heart defect, atresia choanae, retarded growth and development, genital abnormality, and ear abnormality], Dandy-Walker, cat eye, Pfeiffer; n = 8), chromosomal abnormalities involving various monosomies, trisomies, deletions, or duplications (ie, cri du chat, Jacobsen; n = 10), single gene abnormalities (ie, sickle cell, CHILD [congenital hemidysplasia with ichthyosiform erythroderma and limb defects], Mowat-Wilson; n = 4), multifactorial syndromes associated with genetic origins (ie, VACTREL [vertebral defects, anal atresia, cardiac defects, tracheoesophageal fistula, renal anomalies, and limb abnormalities]; n = 2), and severe dysmorphia without an identified chromosomal abnormality (n = 9). In addition, the GS/EC anomalies group included 14 neonates who had major extracardiac anomalies without genetic syndromes (ie, tracheoesophageal fistula, intestinal atresia, imperforate anus, Hirschsprung disease, and omphalocoe).

Median age was 6 days (interquartile range [IQR], 4 to 10 days), and median weight was 3.1 kg (IQR, 2.8 to 3.5 kg) with 77 (15%) weighing 2.5 kg or less. Overall, 78 (14%)
were born prematurely at 36 weeks’ or less gestation. The distribution of underlying SV anomalies is summarized in Table 1. Of note, the incidence of prematurity and weight of 2.5 kg or less was significantly higher in neonates with GS/EC anomalies. Neonates with GS/EC anomalies were more likely to receive a modified Blalock-Taussig shunt, and those without GS/EC anomalies were more likely to receive a Norwood.

Hospital Outcomes
We examined the effect of GS/EC anomalies on three hospital outcomes: unplanned cardiac reoperation, ECMO support, and hospital mortality. The unadjusted differences between neonates with and without GS/EC anomalies are presented in Table 1.

Unplanned cardiac reoperations included surgical revisions and did not include delayed sternal closure, mediastinal explorations, ECMO procedures, or procedures to treat noncardiac complications such as diaphragmatic plication or thoracic duct ligation. Overall, unplanned cardiac reoperations were performed in 65 neonates (12%), including 19 (16%) with GS/EC anomalies and 46 (11%) without GS/EC anomalies ($p = 0.1893$). Multiple logistic regression results indicated no significant association between GS/EC anomalies and unplanned reoperation after controlling for confounders (odds ratio, 1.1; 95% CI, 0.6 to 2.2; $p = 0.7749$; Fig 1).

Postoperative ECMO support was needed in 62 neonates (12%), including 16 (13%) with GS/EC anomalies and 46 (11%) without GS/EC anomalies ($p = 0.5524$). Multiple logistic regression results demonstrated no significant association between GS/EC anomalies and ECMO requirement after controlling for confounders (odds ratio, 0.9; 95% CI, 0.4 to 1.9; $p = 0.849$; Fig 1).

Hospital mortality occurred in 77 neonates (5%), including 29 (24%) with GS/EC anomalies and 48 (12%) without GS/EC anomalies ($p = 0.008$). Multiple logistic regression results demonstrated a trend for higher hospital mortality in patients with GS/EC anomalies after controlling for confounders (odds ratio, 1.7; 95% CI, 1.0 to 3.5; $p = 0.0706$; Fig 1).

We also examined the effect of GS/EC anomalies on resource utilization, including postoperative ventilation requirement and intensive care unit and hospital stays. The unadjusted differences between neonates with and without GS/EC anomalies are presented in Table 1.

Postoperative mechanical ventilation duration was a median 124 hours (IQR, 70 to 276 hours) in all patients, 208 hours (IQR, 89 to 384 hours) in neonates with GS/EC anomalies, and 120 hours (IQR, 65 to 240) in those without GS/EC anomalies ($p = 0.0003$). Multiple linear regression models showed a significant effect of GS/EC on postoperative ventilation duration, with neonates with GS/EC requiring longer ventilation duration relative to neonates without GS/EC after controlling for confounders (mean, 182 vs 116 hours; $p < 0.0001$; Fig 2).

Postoperative intensive care unit stay was a median 193 hours (IQR, 117 to 368 hours) in all patients, 287 hours (IQR, 145 to 574 hours) in neonates with GS/EC anomalies, and 186 hours (IQR, 110 to 333 hours) in those without GS/EC anomalies ($p = 0.0001$). Multiple linear regression models showed a significant effect of GS/EC anomalies on postoperative intensive care unit stay, with neonates with GS/EC anomalies requiring a longer intensive care unit stay relative to neonates without GS/EC anomalies after controlling for confounders (mean, 280 vs 177 hours; $p < 0.0001$; Fig 2).

The events after first-stage palliation are depicted in Figure 3. Among hospital survivors after first-stage palliation, 15 patients (16%) with GS/EC anomalies died or received heart transplantation before Glenn compared with 38 (11%) with no GS/EC anomalies ($p = 0.124$). Overall, when hospital mortality is included, 44 patients (40%) with GS/EC anomalies died or received heart transplantation before Glenn compared with 86 (23%) with no GS/EC anomalies ($p = 0.002$). After Glenn, 10 patients (13%) with GS/EC anomalies died or received heart transplantation before Fontan compared with 28 (9%) with no GS/EC anomalies ($p = 0.595$).

Competing risk models showed that the proportion of patients who underwent Glenn started to rise at approximately 3 months and peaked at approximately 5 months after first-stage palliation. The hazard function for death or transplantation before Glenn was characterized by the presence of an early hazard phase during the initial 3 months after first-stage palliation that significantly decreased after that period. Competing risk analysis showed that at 6 months after first-stage palliation, 22% of patients had died or received transplantation, 55% had undergone Glenn, and 23% were alive without Glenn. At 2 years after first-stage palliation, 25% of patients had died or received transplantation, 75% had undergone Glenn, and less than 1% were alive without Glenn.

Figure 4 depicts the difference in the competing risk models after first-stage palliation between patients with and without GS/EC anomalies. At 6 months after the first palliation, the proportion of patients who had died or received transplantation was 32% in those with GS/EC anomalies and 20% in those without GS/EC anomalies ($p = 0.002$). Consequently, the proportion of patients who had progressed to Glenn was 36% in those with GS/EC anomalies and 64% in those without GS/EC anomalies ($p = 0.002$).
Table 1. Patient Characteristics, Operative Details, and Hospital Data Stratified by the Presence or Absence of Genetic Syndromes/Extracardiac Anomalies

<table>
<thead>
<tr>
<th>Variable</th>
<th>All Patients (n = 530)</th>
<th>GS/EC Anomalies</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Absent (n = 409)</td>
<td>Present (n = 121)</td>
<td></td>
</tr>
<tr>
<td>Patient characteristics</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Age at procedure, days</td>
<td>6 (4–10)</td>
<td>7 (4–16)</td>
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<tr>
<td>Male sex</td>
<td>318 (60.0)</td>
<td>247 (60.4)</td>
<td>71 (58.7)</td>
</tr>
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<td>Premature birth</td>
<td>78 (14.7)</td>
<td>47 (11.5)</td>
<td>31 (25.6)</td>
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<tr>
<td>Weight, kg</td>
<td>3.1 (2.8–3.5)</td>
<td>3.2 (2.8–3.5)</td>
<td>3.0 (2.6–3.4)</td>
</tr>
<tr>
<td>Weight ≤2.5 kg</td>
<td>77 (14.5)</td>
<td>48 (11.7)</td>
<td>29 (24.0)</td>
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<tr>
<td>Underlying single ventricle anomaly</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Double-inlet left ventricle</td>
<td>34 (6.2)</td>
<td>31 (7.6)</td>
<td>3 (2.5)</td>
</tr>
<tr>
<td>Double-outlet right ventricle</td>
<td>29 (5.5)</td>
<td>25 (6.1)</td>
<td>4 (3.3)</td>
</tr>
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<td>Hypoplastic left heart syndrome</td>
<td>219 (41.3)</td>
<td>199 (48.7)</td>
<td>20 (16.5)</td>
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<td>Atrial isomerism</td>
<td>58 (10.9)</td>
<td>0 (0)</td>
<td>58 (47.9)</td>
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<td>Mitral atresia</td>
<td>15 (2.8)</td>
<td>11 (2.7)</td>
<td>4 (3.3)</td>
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<td>Pulmonary atresia with intact ventricular septum</td>
<td>53 (10)</td>
<td>49 (12)</td>
<td>4 (3.3)</td>
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<tr>
<td>Tricuspid atresia</td>
<td>80 (15.1)</td>
<td>65 (15.9)</td>
<td>15 (12.4)</td>
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<td>Unbalanced atrioventricular septal defect</td>
<td>21 (4.0)</td>
<td>12 (2.9)</td>
<td>9 (7.4)</td>
</tr>
<tr>
<td>Other</td>
<td>21 (4.0)</td>
<td>17 (4.2)</td>
<td>4 (3.3)</td>
</tr>
<tr>
<td>First-stage palliation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Modified Blalock-Taussig shunt</td>
<td>173 (32.6)</td>
<td>112 (27.4)</td>
<td>61 (50.4)</td>
</tr>
<tr>
<td>Norwood</td>
<td>284 (53.6)</td>
<td>245 (59.9)</td>
<td>39 (32.2)</td>
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<td>Pulmonary artery band</td>
<td>73 (13.8)</td>
<td>52 (12.7)</td>
<td>21 (17.4)</td>
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<td>Use of cardiopulmonary bypass</td>
<td>333 (62.8)</td>
<td>266 (65.0)</td>
<td>67 (55.4)</td>
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<tr>
<td>Early results</td>
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<td></td>
<td></td>
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<tr>
<td>Ventilation time, hours</td>
<td>124 (70–275)</td>
<td>120 (65–240)</td>
<td>208 (89–384)</td>
</tr>
<tr>
<td>Intensive care unit stay, hours</td>
<td>193 (117–368)</td>
<td>186 (110–333)</td>
<td>287 (145–574)</td>
</tr>
<tr>
<td>Postoperative hospital stay, days</td>
<td>18 (12–32)</td>
<td>17 (12–28)</td>
<td>23 (14–42)</td>
</tr>
<tr>
<td>Unplanned reoperation</td>
<td>65 (12.3)</td>
<td>46 (11.3)</td>
<td>19 (15.7)</td>
</tr>
<tr>
<td>Extracorporeal membrane oxygenation use</td>
<td>62 (11.7)</td>
<td>46 (11.3)</td>
<td>16 (13.2)</td>
</tr>
<tr>
<td>Hospital death</td>
<td>77 (14.5)</td>
<td>48 (11.7)</td>
<td>29 (24.0)</td>
</tr>
</tbody>
</table>

*Continuous data are presented as median (interquartile range) and categoric data as number (%).

GS/EC = genetic syndromes/extracardiac.

Fig 1. Model-based probability estimates for hospital death, extracorporeal membrane oxygenation (ECMO) requirement, and unplanned reoperation in patients with and without genetic syndromes/extracardiac anomalies. The range bars indicate the 95% confidence interval.
Late Survival

The hazard of death after first-stage palliation was characterized as a high early phase within the first 6 months after the operation, a lower constant phase that persisted for 1 to 3 years after first-stage palliation, and a low late phase thereafter. When stratified by the presence or absence of GS/EC anomalies, the hazard of death after first-stage palliation showed a higher early phase and a higher and more prolonged constant phase in neonates with GS/EC anomalies (Fig 5). Parametric survival estimates at 10 years after first-stage palliation were 56% in neonates with GS/EC anomalies compared with 76% in those without GS/EC anomalies ($p < 0.001$; Fig 5).

The effect of the presence of GS/EC anomalies on postoperative survival among different selected patient subgroups is depicted in Figure 6. GS/EC anomalies were associated with an increased hazard of death in almost all subgroups of patients.

Comment

On one hand, the incidence of GS/EC anomalies in neonates with SV undergoing first-stage palliation in this series was 23%, comparable to the 20% in neonates undergoing operations for biventricular cardiac anomalies at our institution and parallel to other reported series [1–5]. On the other hand, the incidence of GS/EC anomalies varied among different SV anomalies and was the lowest in those with double-inlet left ventricle (3%) and highest in those with atrial isomerism (100%). Multistage SV
palliation outcomes vary among different SV anomalies, and those disparities in outcomes might be partly explained by the diverse incidence of GS/EC anomalies [15]. For example, reported survival is highest in patients with double-inlet left ventricle and tricuspid atresia (both have a low incidence of GS/EC anomalies, at 3% and 9%, respectively), and lowest in patients with atrial isomerism and unbalanced atrioventricular septal defect (both have a high incidence of GS/EC anomalies, at 100% and 45%, respectively) [15–19]. Although those poor outcomes might be due to the frequent presence of associated cardiac lesions (eg, total anomalous pulmonary venous connection, common atrioventricular valve regurgitation, pulmonary atresia, and heart block associated with atrial isomerism, or atrioventricular valve regurgitation associated with unbalanced atrioventricular septal defect), the presence of extracardiac lesions in those patients, such as airway obstruction, ciliary dysfunction, and gastrointestinal obstruction, unquestionably contributes to morbidity and mortality in those patients [15, 18–22]. Even in SV anomalies that have low association with GS/EC anomalies, such as hypoplastic left heart syndrome and tricuspid atresia (incidence of GS/EC anomalies is almost 9% in each), the presence of GS/EC anomalies has been identified as an independent and significant factor associated with poorer outcomes [9–11, 14, 16].

As expected, neonates with GS/EC anomalies have high incidence of associated risk factors such as prematurity and low birth weight, both well-recognized factors for poor outcomes after cardiac operations [4, 23–26]. Those inferior outcomes are likely not related to poor technical results or tissue friability but rather to physiologic challenges in the very small neonates. Those physiologic challenges are due to metabolic immaturity associated with prematurity, such as autonomic dysfunction and deficiency of coagulation factors, and to immature organs with subsequent increased incidence of pulmonary, gastrointestinal, and neurologic complications, all affecting recovery after cardiac operations, increasing hospital mortality and decreasing hospital intermediate survival even after hospital discharge [23–26]. Although the incidence of low weight and prematurity in our series was higher in neonates with GS/EC anomalies, the presence of GS/EC anomalies was a significant risk factor for inferior results even in the adjusted analysis, suggesting that GS/EC anomalies independently affected outcomes even in neonates.

Our finding of poor survival after first-stage palliation in neonates with GS/EC anomalies is similar to other recent reports examining outcomes after SV palliation [4, 8–14, 16]. A recent study showed that GS/EC anomalies were associated with increased operative death and hospital stay in neonates who underwent the Norwood operation, as recorded in The Society of Thoracic Surgeons database, in addition to increased early hazard of death and decreased 10-year survival in neonates who underwent...
the Norwood operation as noted in the Congenital Heart Surgeons’ Society database [10]. In addition, reports from the Single Ventricle Reconstruction (SVR) trial showed that GS/EC anomalies were associated with higher hospital and constant-phase mortality after the Norwood operation [11, 14]. Interestingly, 72% of deaths in our study were cardiac in nature, with the remaining deaths being noncardiac. Both groups of patients had comparable distribution of the mode of death, with most patients in the GS/EC anomalies group also having cardiac death. However, the cause of death was directly related to the associated GS/EC anomaly in at least 6 patients: liver failure from biliary atresia (n = 1), sepsis after a complicated abdominal operation to correct coexisting gastrointestinal anomalies (n = 1), neurologic injury related to sickle cell anemia (n = 1), excessive fluid sequestration due to lymphatic vessel hypoplasia in a patient with Turner syndrome after Norwood (n = 1), and cardiac arrest in 2 patients who were not candidates for ECMO due to coexisting anomalies.

Our study clearly demonstrated that GS/EC anomalies independently and significantly affected postoperative recovery, hospital death, and late survival after first-stage SV palliation. Therefore, GS/EC anomalies should be taken into consideration in the preoperative assessment of neonates born with SV anomalies. Many of the existing risk-stratification models in congenital cardiac surgery are based on the surgical procedure and therefore often inaccurately predict operative risk and expected survival for individual patients with additional risk factors, specifically those with significant GS/EC anomalies [27, 28].

Our findings suggest that GS/EC anomalies should be accounted for in those risk-stratification models. To achieve that, multiinstitutional efforts are necessary to allow collection of a large number of patients that would permit analysis of the effect of those GS/EC anomalies on early and late outcomes and subsequently design risk-stratification models that accurately estimate survival for individual patients. The efforts from The Society of Thoracic Surgeons to expand the database and include more granular data on specific GS/EC anomalies would confidently provide a valuable insight on the effect of those GS/EC anomalies on outcomes and, hopefully, allow examination of the effect of specific genetic syndromes on survival rather than lumping all of those GS/EC anomalies together. In our current analysis, we are statistically limited and therefore unable to identify any specific GS/EC anomalies in which SV palliation is futile. Collaborative efforts and registry studies would expectantly permit such an analysis and consequently provide valuable knowledge that will aid physicians in their decision making in the future.

Importantly, in addition to hospital death, we found that the hazard of death is higher and also more prolonged in SV neonates with GS/EC anomalies, and extends for 2 to 3 years beyond first-stage palliation. That indicates that those patients continue to be exposed to risk of death well beyond the perioperative period. Increased postoperative complications, immature organs associated with prematurity, persistent end-organ dysfunction, and associated extracardiac malformations likely all contribute to this finding. Improvement of long-term outcomes in those neonates after cardiac operations might therefore 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 his or her unique clinical condition and comorbidities.

Moreover, those findings suggest that our existing databases should be modified to allow collection of longitudinal follow-up as opposed to short-term follow-up that
is limited to the initial hospital stay or 30 days. Additional efforts to link The Society of Thoracic Surgeons database (which is limited to early outcomes) with other databases with longer follow-up, if successful, might prove valuable with this regard. Interestingly, survival after Fontan was comparable between the two groups of patients. This might be likely due to natural selection, with most of the higher-risk patients dying during the early highest risk period.

Conclusion
The incidence of GS/EC anomalies in neonates with SV anomalies in our series was 23% and varied among different SV anomalies. Those neonates with GS/EC anomalies commonly have associated risk factors for morbidity and mortality, such as prematurity and low weight. After adjusting for those confounding factors, GS/EC anomalies are independently and significantly associated with prolonged postoperative recovery after first-stage palliation and consequently increased resource utilization.

In addition, GS/EC anomalies are associated with increased hospital and interstage death, with a subsequently smaller number of patients progressing toward subsequent SV palliation stages. Importantly, the hazard of death in those neonates is higher and more prolonged beyond the perioperative period for 2 to 3 years after first-stage palliation. GS/EC anomalies are independent factors associated with decreased survival in many subgroups of patients with various underlying SV anomalies undergoing different first-stage palliative operations (Norwood, modified Blalock-Taussig shunt, and pulmonary artery band). Our findings show that the presence of GS/EC anomalies should be emphasized during parent counseling and decision making and underscore the need to explore strategies to improve outcomes for this high-risk population that must address perioperative care, outpatient surveillance, and management.

References
INVITED COMMENTARY

We congratulate Alsoufi and colleagues [1] for another important contribution in assessment of the outcomes associated with pediatric and congenital cardiac surgery. Their single-institution analysis studied 530 neonates with functionally univentricular hearts who underwent first-stage palliation. The analysis demonstrated that “after adjustment for other risk factors, genetic syndromes (GS) and extra-cardiac anomalies (EC) significantly affected survival in almost all subgroups of patients.” Alsoufi and colleagues [1] concluded: “The presence of GS/EC varies between single ventricle anomalies and is associated with additional risk factors such as prematurity and low weight. After adjusting for other risk factors, GS/EC are associated with prolonged recovery following first-stage palliation and increased hospital and interstage mortality, with subsequently fewer patients progressing towards Glenn shunt. The increased death risk in those patients persists for 1 to 2 years following first-stage palliation, suggesting the need for more vigilant monitoring and outpatient care in those high-risk patients.”

Multinstitutional analyses of both The Society of Thoracic Surgeons (STS) Congenital Heart Surgery Database (CHSD) and the Congenital Heart Surgeons’ Society (CHSS) database have also examined the important relationship between congenital cardiac disease and both genetic abnormalities and noncardiac abnormalities [2,3]. Using the STS CHSD and the CHSS Database, Patel and colleagues [2] demonstrated that survival in patients with hypoplastic left heart syndrome is strongly influenced by the presence of noncardiac abnormalities. In-hospital mortality, mean postoperative length of stay, and prevalence of postoperative complications were all significantly worse in infants with noncardiac abnormalities or genetic defects [2]. In a follow-up analysis using STS CHSD, Patel and colleagues [3] demonstrated that the prevalence of noncardiac congenital anatomic abnormalities, genetic abnormalities, and syndromes varies widely across diagnostic groups of patients with congenital cardiac disease. In the Comment section of the paper by Alsoufi and colleagues [1], the authors state: “The efforts from the STS to expand the database and include more granular data on specific GS/EC anomalies would confidently provide a valuable insight on the impact of those GS/EC on outcomes, and hopefully allow examination of the effect of specific genetic syndromes on survival rather than lumping all those GS/EC together.” This statement forewarns an ongoing research project of the STS CHSD: An analysis of noncardiac congenital anatomic abnormalities (NCAA), chromosomal abnormalities (CA), and syndromes (S) in the STS CHSD has recently been completed. Data generated from this project will be used to inform refinement of the STS CHSD Mortality Risk Model that is used for outcomes reporting in the feedback reports to STS CHSD participants and in voluntary public reporting. The current model [4,5] accounts for the presence or absence of any one or more abnormalities within each of these three categories (CA, S, NCAA), but without individual adjustment for the specific conditions. In the proposed refined version of the model that is currently being developed, commonly occurring NCAA are considered individually, rather than categorically as “any or none.” Individual CA and S are stratified into groups based on within-group homogeneity with respect to associated incremental risk of mortality. The stratification includes consideration of interaction with age group, as well as specific procedure and age group for several individual conditions (eg, trisomy 21, with reference to single-ventricle palliation versus other procedures). For each of these covariates, specific coefficients are derived from the robust multiinstitutional dataset of the STS CHSD.

The current STS CHSD Mortality Risk Model adjusts for patient-related factors, including the binary presence or absence of CA, S, or NCAA. STS will soon update its CHSD Mortality Risk Model and refine its case mix adjustment by adding more granular adjustment for individual CA, S, and NCAA, on the basis of the concept that associated mortality risk differs among individual CA, S, and NCAA. This refinement of the STS CHSD Mortality Risk Model is another step in the ongoing evolution of risk adjustment for pediatric and congenital cardiac surgery, a refinement supported by this important article from Alsoufi and colleagues [1].

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