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Variants of significance: medical genetics and surgical outcomes in congenital heart disease

Gabrielle C. Geddes[a,b], **Leon F. Przybylowski III**[b], **Stephanie M. Ware**[a,b]

[a]Department of Medical and Molecular Genetics, Indiana University School of Medicine

[b]Riley Heart Center, Riley Hospital for Children, Indianapolis, Indiana, USA

Abstract

Purpose of review—This article reviews the current understanding and limitations in knowledge of the effect genetics and genetic diagnoses have on perioperative and postoperative surgical outcomes in patients with congenital heart disease (CHD).

Recent findings—Presence of a known genetic diagnosis seems to effect multiple significant outcome metrics in CHD surgery including length of stay, need for extracorporeal membrane oxygenation, mortality, bleeding, and heart failure. Data regarding the effects of genetics in CHD is complicated by lack of standard genetic assessment resulting in inaccurate risk stratification of patients when analyzing data. Only 30% of variation in CHD surgical outcomes are explained by currently measured variables, with 2.5% being attributed to diagnosed genetic disorders, it is thought a significant amount of the remaining outcome variation is because of unmeasured genetic factors.

Summary—Genetic diagnoses clearly have a significant effect on surgical outcomes in patients with CHD. Our current understanding is limited by lack of consistent genetic evaluation and assessment as well as evolving knowledge and discovery regarding the genetics of CHD. Standardizing genetic assessment of patients with CHD will allow for the best risk stratification and ultimate understanding of these effects.

Keywords

congenital heart disease; congenital heart surgery; genetic testing; genetics; surgical outcomes

INTRODUCTION

The genetics basis of congenital heart disease (CHD) is simultaneously extremely well studied and very poorly understood [1,2]. The largely stable and geographically consistent incidence of CHD suggests that genetic factors are the cause for the majority of cases [3,4]. Nevertheless, despite significant investments in discover by powerful collaboratives we are currently only able to identify a genetic cause in 30–35% of cases of CHD [3–8].

Correspondence to Gabrielle C. Geddes, MD, Department of Medical and Molecular Genetics, Indiana University School of Medicine, 975 West Walnut, IB Suite 130, Room 154, Indianapolis, IN, USA. Tel: +1 317 944 3966; fax: +1 317 968 1354; egeddes@iu.edu.

Conflicts of interest

There are no conflicts of interest.

This isn't necessarily surprising, although the race of genetic discovery has been rapid, our knowledge about human genetics is still in its infancy. A chromosome was just sequenced end to end for the first time this year, approximately 20 years after the 'completion' of the Human Genome Project, the American College of Medical Genetics and Genomics only provided formal guidelines for interpretation of coding variants (covering variants across less than 1% of our genome) five years ago, and the number of genes with a known disorder listed in the Online Mendelian Inheritance in Man database as of mid-August 2020 is 3935 (which accounts for less than a quarter of our genes) [9–12]. As remarkable as the technical achievement of sequencing the human genome was, the ability to interpret its data is markedly more complex. As a result, the potential for new causes for CHD in structural variation, coding and noncoding variants alone is significant, not to mention oligogenic effects, combinatorial interactions, genetic regulation, and epigenetics [13–15].

Even with so much more to learn, it is clear that surgical outcomes in patients with CHD are affected by genetic diagnoses, both syndromic and nonsyndromic [16–22]. However, clinically many patients with critical CHD do not undergo a standard genetic or molecular evaluation for the disorders we can routinely diagnose [23–25,26▪]. Further complicating our ability to understand and identify patterns, databases designed to look for factors associated with differences in outcomes for patients with CHD, for example, the Society for Thoracic Surgeons (STS) database and the Pediatric Cardiac Critical Care Consortium (PC^4), are (understandably) not designed to accommodate the rapidly changing, complex nuances of modern genetics, limiting our ability to gain insight into this arena although active attempts to improve this gap are ongoing [27–30].

Practice variation and lack of standardized genetic evaluation create challenges in case identification. For example, among centers participating in the STS Database, the rate of genetic anomalies in infants who underwent cardiac procedures in the first 30 days of life between 2010 and 2013 was 14% (2369/15 376) [31]. Similar rates of genetic diagnoses were found at two of the participating institutions during that time period, but closer investigation revealed 30–40% of these patients had no genetic testing completed [23,32]. At one of these institutions, we were able to demonstrate that the diagnosis rate of genetic conditions rose 10% simply by implementing a standard genetic testing protocol and another 10% by implementing a program where every infant was evaluated by a cardiovascular geneticist [23,33].

In addition to the listed limitations and complexities of genetic evaluation, factors affecting surgical outcomes have their own elaborate tangle of data to decipher. Determining factors influencing perioperative, postoperative, intermediate, and long-term outcomes is a field filled with its own nuances, metrics, temporal and technologic evolutions, and commentaries. Despite this complex web of factors, reviews of modern PC^4 datasets showed current CHD surgery risk models were only able to explain 30% of variation in surgical outcomes, with 2.5% of variation directly attributable to diagnosed genetic disorders [34▪▪]. The article's authors, none of whom are medical geneticists, eloquently hypothesize that currently unmeasured genetic factors likely account for a significant amount of the remaining outcome variation and propose that better integration of genetic (and other) factors needs to be incorporated into datasets on surgical outcomes in CHD [34▪▪].

This review will focus on the current understanding of the impact of genetics on perioperative and postoperative outcomes in CHD and the potential role of medical geneticists in risk stratification. An excellent recent review by Landis *et al.* [17] focuses on surgical outcomes by diagnosis; therefore, we will concentrate on major perioperative and postoperative complications including effects that may not be diagnosis specific.

GENERAL TRENDS

Patients with diverse genetic conditions are frequently grouped together as a matter of simplicity and/or power of analysis. There are common themes associated with a genetic diagnosis: higher likelihood of extracardiac disease, longer length of length of stay, higher tendency for growth and feeding concerns, and higher rates of neurodevelopmental delays [17,21,35,36].

An evaluation of the impact of copy number variants (CNVs) on patients undergoing single ventricle palliation at 14 months found patients with rare, novel, gene containing CNVs over 300 kb had decreased linear growth (average length *Z*-score of −1.65) compared with those without CNVs (average length *Z*-score of −1.00) at 14 months [21]. Patients with known CNVs had an average mental developmental index that was significantly lower (79.8) than patients without CNVs (91.4) [21]. Using the same definition for significance of CNVs, patients with isolated CHD (as defined by geneticist examination as well as blinded geneticist chart review) was associated with a 2.55 increased likelihood of death or cardiac transplantation compared with those without CNVs [22].

These types of more generalized observations on CNVs may be somewhat practically helpful to risk-stratify patients, but they do not help us discuss the implications with families or lead to further insight as to why these risks are present or how to prevent them.

LENGTH OF STAY AND READMISSION

Length of stay (LOS) and rate of readmission have classically been thought to be indicators of quality care and follow-up [37,38]. It has been previously proposed that LOS directly correlated with quality of cardiac repair given it is also associated with need for surgical revision and thus a good metric of center outcomes [37]. There is an element of truth to this, but in high performing centers, longer LOS may be a reflection of intrinsic patient risk factors as well. A summary of the considerations is discussed in Table 1.

Patients with Trisomy 21 overall seem to have comparable or even decreased LOS compared with their peers [17,39,40]. Furlong-Dillard *et al.* [40] found overall the median LOS in patients with Trisomy 21 was the same as patients without a diagnosed genetic condition at seven days. Comparing patients who ultimately died, the median LOS diverges, but not to a statistically significant level, with Trisomy 21 patients at 36 days as compared with 29 days in those without a diagnosis [40]. Patients with Trisomy 21 do not seem to have an increased risk of readmission [38].

Patients with Trisomy 13 or Trisomy 18, 22qDS, Turner Syndrome or ‘other’ genetic conditions all have a significantly longer LOS as compared with those without a diagnosis.

Patients with 22qDS or Trisomy 13 or Trisomy 18 had the longest median LOS at 18 days and 17 days, respectively [40]. Patients with 'other' genetic conditions or Turner Syndrome had a median LOS of 11 days and 10 days respectively [40]. Readmission data was only available for 22qDS, but there was not an appreciated increased risk of readmission [38].

A large study of readmissions recorded in the STS database showed that readmission was more common in patients with 'any noncardiac or genetic abnormalities or syndromes' with 15% (2647/18 166) of patients being readmitted compared with 9% (3548/38 055) of patients not in this category [41]. The lack of specificity in noncardiac phenotyping limits conclusions that can be drawn from this type of study.

EXTRACORPOREAL MEMBRANE OXYGENATION

Furlong-Dillard *et al.* [42] specifically evaluated utilization of extracorporeal membrane oxygenation (ECMO) in patients with genetic conditions and compared those with Trisomy 21, Trisomy 13 or 18, 22qDS, 'other' genetic conditions, and those without a diagnosed genetic condition. It is worth noting they reported an identified genetic diagnosis in 15% of the study population [42]. A summary of the considerations is discussed in Table 1.

Only 1% (134/9473) of patients with Trisomy 21 had ECMO support compared with 3% (2353/80540) of patients without an identified genetic diagnosis [42]. Of children with Trisomy 21 who were supported with ECMO 49% (66/134) died which was similar to the 46% (1092/1353) of patients without an identified genetic diagnosis who died [42].

Patients with Trisomy 13 or Trisomy 18 had ECMO support 3% (5/156) of the time with mortality among all five patients who underwent ECMO support [42]. It is worth noting the average age at surgery for patients with Trisomy 13 and Trisomy 18 was 3.5 months and 53% (82/156) of the patients had a Risk Adjustment in Congenital Heart Surgery score of 1 or 2 (least complex) suggesting a potential bias for older age and low complexity making these results overly favorable and unlikely to be generalizable to most patients with diagnosis of Trisomy 13 or Trisomy 18 [42–45].

Patients with 22qDS underwent ECMO support in 3% (21/715) of cases with 76% (16/21) mortality [42]. After risk adjustment, there was a statistically significant increased risk for mortality with ECMO in patients with 22qDS compared with those without a diagnosed genetic condition.

Patients with 'other' genetic conditions were composed of 4370 patients with multiple congenital anomalies (53%, 2305), single gene defects (27%, 1171), CNVs excluding 22qDS (5%, 248), and sex chromosome disorders (15%, 646) [42]. This group required ECMO at a significantly higher rate of 4% (167/4370) than those without a diagnosed genetic condition and had a higher risk of death with ECMO at 52% (87/167) which was because of a higher rate of mortality in infants with sex chromosome disorders [42]. The same dataset was analyzed for resource utilization and demonstrated that Turner Syndrome patients who underwent ECMO support had a 63% (10/16) mortality [40,42]. Although the risk of death with ECMO was specific to the sex chromosome anomalies group, all patients within the 'other' category had a higher rate of in-hospital death which ultimately was

double (6%, 274/4370) that of patients without a diagnosed genetic condition (3%, 2344/80 540) [42].

CARDIAC ARREST, MORTALITY, AND COST OF HOSPITALIZATION

As alluded above, cardiac arrest and mortality following cardiac surgery in patients with genetic diagnoses are generally more common with the exception of patients with Trisomy 21. These data are also summarized in Table 1.

The Furlong-Dillard *et al.* [40,42] dataset showed a rate of cardiac arrest in patients with Trisomy 21 of 2% (163/9473) compared with 3% (2100/80 540) in patients without a diagnosed genetic condition. Patients with Trisomy 21 had an in-hospital mortality of 2% (193/9473) which was similar to patients without a known genetic diagnosis at 3% (2344/80 540). [40,42]. Patients with Trisomy 21 also had similar median costs of hospitalization to patients without a known genetic diagnosis among patients that survived ($44 000 versus $48 500) and those who did not ($257 500 versus $255 600) [40].

Patients with Trisomy 13 and Trisomy 18 had higher rates of cardiac arrest and in-hospital mortality than all other groups in the study. Their rate of cardiac arrest was twice that of patients without a known genetic diagnosis at 6% (10/156) [40,42]. Their in-hospital mortality was also high at 13% (20/156) [40,42]. Their median cost of hospitalization for survivors was much higher than patients without a known genetic diagnosis at $85 700 instead of $48 500 [40].

Patients with 22qDS have cardiac arrests at the same time rate as patients with Trisomy 21 or patients without diagnosed genetic conditions at 3% (24/715) [40,42]. Their rate of in-hospital death was 5% (33/715). [40,42]. Their median costs for hospitalizations were highest of all groups for survivors at $99 700 and second highest for mortalities at $337 200 [40].

Patients with Turner Syndrome had a rate of cardiac arrest of 4% (13/347) [40,42]. Their in-hospital mortality was twice that of those without known genetic conditions at 6% (20/347) [40,42]. The median cost per hospitalization was moderately elevated at $56 900 for survivors and was the highest of any group for mortalities at $351 200 [40].

Patients with ‘other’ genetic conditions had a rate of cardiac arrest of 5% (186/4023) and as previously stated also had an in-hospital mortality that was double that at 6% (274/4370, 254/4023) with and without inclusion of the Turner Syndrome group [40,42]. Their median cost per hospitalization was moderately elevated at $67 200 for survivors and $286 600 for mortalities [40].

BLEEDING AND BLOOD PRODUCTS

Patients with 22qDS have larger platelets and lower platelet counts compared with their peers without 22qDS [46,47]. This is thought to be because of haploinsufficiency of *GP1BB* which ultimately has the downstream effect of impairment of platelet adherence to von Willebrand factor [46,47]. Patients with 22qDS have been shown to have increased

likelihood of excessive bleeding characterized by chest tube output in the first 12 h after surgery as well as increased requirement for transfusions of packed red blood cells in the first 24 h after surgery [46]. An evaluation of postoperative resource utilization for CHD found a significant increase in intraventricular hemorrhage which was observed in 2.8% (20/715) of patients with 22qDS compared with 1.3% (1064/80 540) of patients without a diagnosed genetic condition although they did not find differences in rates of pulmonary hemorrhage or intracranial hemorrhage [40]. Additionally, blood products are processed with calcium-binding agents to prevent coagulation and transfusions can result in hypocalcemia even in patients without the genetic predisposition that patients with 22qDS have [48–50]. Patients with 22qDS who have hypocalcemia or hypocalcemic seizures in the perioperative period have a significantly increased rate and severity of intellectual disability [50].

Jacobsen Syndrome is because of large contiguous deletions of 11q23.3 and is associated with thrombocytopenia and platelet dysfunction called the Paris–Trousseau bleeding disorder [51,52]. Six patients with Jacobsen Syndrome have been reported to have brain hemorrhages, which is theorized to be a result of a combination of a predisposition to bleeding and a predisposition to aneurysm formation although a brain aneurysm was only found in one of the six patients [53]. Based on this, it is suggested patients with Jacobsen Syndrome should undergo a screening magnetic resonance angiography for brain aneurysms [53]. Half of patients with Jacobsen Syndrome have CHD with a tendency to left-sided lesions, and up to 5% of patients can present with hypoplastic left heart syndrome [17,51]. This is of particular note as one of the reported patients having died of a brain hemorrhage after undergoing a Norwood palliation [53].

Approximately 40–65% of patients with Noonan Syndrome can have significant bleeding diathesis because of a number of anomalies in the clotting cascade including deficiency of multiple clotting factors, von Willebrand deficiency, platelet dysfunction, and thrombocytopenia in isolation or combination which can change over time [54–57]. This makes evaluation complex as a significant number of labs need to be drawn for a comprehensive coagulation evaluation and sometimes the blood volume is limiting in infants [58]. The turnaround time for testing requires forethought to have results prior to an intervention. If confronted with patient with Noonan Syndrome who requires intervention that does not have, or cannot have, a recent (in the last three months) comprehensive coagulopathy evaluation it is best to treat the patient presumptively as high risk for bleeding due to a complex bleeding diathesis. Given the complexities of the evaluation it may even be reasonable to always treat every patient with Noonan Syndrome this way. Outcomes from cardiac transplantation in Noonan Syndrome demonstrate issues with bleeding in three of the 18 patients. One patient had known von Willebrand disease, another had severe thrombocytopenia which was associated with extramedullary hematopoiesis requiring splenectomy, and one patient ultimately died posttransplant with a portal vein thrombosis and ischemic bowel [55]. It is recommended that patients with Noonan Syndrome with known coagulopathy be treated as high-risk transplant candidates with surveillance for both bleeding and thrombosis [55]. Underlying all of this is the fact that Noonan Syndrome is underdiagnosed in CHD as it molecularly requires specific suspicion and specific molecular testing [57].

HEART FAILURE AND TRANSPLANT

From a genetics perspective heart failure in CHD resulting in cardiac transplantation is an area of evolving knowledge outside of a few discrete syndromes and genes known to overlap between cardiomyopathy and CHD (e.g., *ACTC1, MYBPC3, MYH6, MYH7,* and *TNNI3*) [59]. There is interesting work suggesting that patients with hypoplastic left heart syndrome with rare *MYH6* variants, which may be 10% of cases, have decreased transplant-free survival compared with their peers [16]. This potential functional effect of the *MYH6* variant was demonstrated in induced pluripotent stem cell-derived cardiomyocytes [16,60]. Interestingly, the patients and the parent from whom the variant was inherited both showed disorganized sarcomeres, suggesting a potential mechanism for dysfunction in the context of CHD in the patient [16,60]. This observed sarcomere disorganization was correctable or inducible after clustered regularly interspaced short palindromic repeats (CRISPR) gene editing to knock in or knock out the *MYH6* variant [60]. The ability to edit and create normalized cardiomyocytes in patients with CHD is exciting in the context of the recent creation of a complete (but not functional) heart from adipose tissue samples with three-dimensional printing [61]. This begins to paint a potential therapeutic future with personalized grafts, edited to be heart healthy, with lower risk of rejection when their Fontan inevitably fails, although this clearly is still a dream quite distant from clinical utilization [61–63].

RASopathies, the most common of which is being Noonan Syndrome, have significant risk for cardiomyopathy, but thankfully cardiac transplantation seems to be rare and generally not due to congenital structural cardiac concerns [55].

1p36 deletion is a known cause of both CHD and left ventricular noncompaction cardiomyopathy [64,65]. Specific outcomes are not clearly available, but 50% (20/40) of adolescents and adults with 1p36 deletion had a CHD (majority minor, nonsurgical lesions) as compared with 75% of infants suggesting a significant survival bias against infants with CHD due to 1p36 deletion [66,67]. Cardiomyopathy is reported in 23–31% of patients with 1p36 deletion, but only 5% (2/40) of adults and adolescents had cardiomyopathy [66,67]. This again suggests a significant survival bias against infants with CHD and/or cardiomyopathy due to 1p36 deletion despite lack of clear, specific outcomes data.

LIMITATIONS AND FUTURE DIRECTIONS

Even though there is an identifiable genetic cause in 30–35% of patients with CHD, the number of patients with a genetic diagnosis in most of our surgical outcomes studies is consistently around 15%. This suggests we are routinely missing up to half of readily identifiable genetic syndromes in the CHD population. The largest impact occurs in missed opportunities to personalize care in these patients. These missed diagnoses are also confounders in outcome analyses as it is extremely difficult to accurately measure or understand the effect of something if half of the target comparison group is consistently included in the wrong category. This is unfortunately an understandable problem given the shortage of medical geneticists, poor progress in leveraging electronic medical record systems to communicate phenotypes and record genetic testing results, and the significant

level of complexity and nuances in molecular testing interpretation [24,68–71]. Until we can accurately and accessibly document and disseminate genetic information clinically it will remain extremely difficult to make this easily translatable into clinical outcomes databases. There also remains the issue that genetic testing alone currently cannot provide a diagnosis for all clearly syndromic patients [72].

With this in mind, we recently reviewed data to determine if clinical examination by a medical geneticist alone could provide insight into outcomes in infants with critical CHD requiring Norwood palliation. Thirty-five patients who underwent Norwood palliation who were examined in infancy by a medical geneticist (G.C.G.) were split into syndromic versus nonsyndromic groups based on the presence of dysmorphic facial features. Data from the STS and PC^4 databases were then reviewed for trends or differences between groups. A brief summary of our findings is in Table 2.

This is a small sample size with a simple statistical analysis limiting our ability to draw concrete conclusions, but these data are worth discussion as support that further investigation into if facial features can help risk-stratify patient is needed. We classified 13 patients as syndromic (including two patients in this group with heterotaxy) and 22 patients as nonsyndromic. There were two statistically significant differences between groups. Patients classified as syndromic were five times more likely to have a diagnosis of a genetic disease and were intubated postoperatively on average twice the duration of nonsyndromic patients. Interesting trends that did not reach significance include that syndromic patients required an average of 100 more hours of vasopressor medications, a month longer LOS, and had an apparently increased incidence of mortality, although this could be a reflection of the increased risk of death in heterotaxy. There did not seem to be differences in need for cardiac transplantation, bleeding complications, or need for ECMO.

At first blush, this may seem like a highly impractical exercise given most centers have limited access to medical geneticists (let alone cardiovascular geneticists). Cardiovascular geneticists could be remotely utilized to risk stratify patients by review of patient pictures. An interesting area of discovery is that the standardization of facial feature assessment is advancing rapidly thanks to the incorporation of facial recognition software [73,74]. Adding standard facial pictures into outcome databases could not only allow geneticists to ‘train’ facial recognition software what patterns they are detecting but incorporating outcomes data with the software could allow machine-based learning to identify patterns of facial features not currently appreciated. This software then could be routinely utilized by clinical teams at the bedside, independent of medical geneticist access, as a potentially powerful risk stratification tool.

CONCLUSION

Novel methods to risk stratify patients are critical, but there is the much more immediate concern of utilizing the clinical and molecular tools we have available. Standardization of clinical genetic and molecular assessments of patients with CHD, which is ultimately the first step in downstream understanding of the effects of these issues on outcomes, needs to be a priority at all major CHD centers [24,26▪]. We strongly recommend implementation

of protocols of molecular testing for, at a minimum, copy number variants [23,24,26▪]. Additionally, collaboration to include more specific genetic and genomic information in outcomes databases is also a high priority [29,30,34▪▪]. There is work to consolidate outcomes information into a comprehensive Cardiac Networks United Database which would encompass the entirety of current databases and reduce the need for redundant data collection, hopefully allowing more time and resources to be spent on data analysis and accelerating the translation of data into changes in care [30].

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KEY POINTS

- At least 10% of patients with congenital heart disease that have an identifiable genetic diagnosis are not being diagnosed because of lack of standardized evaluation.
- Currently measured variables only explain 30% of variation in congenital heart disease surgical outcomes.
- Geneticist assessment of facial features and phenotypic differences may be a valuable risk stratification method independent of genetic testing.
- Further understanding of the effects of genetics on congenital heart disease surgical outcomes requires standardized genetic assessment of all patients, better incorporation into the electronic medical record, and more specific inclusion into studies based on outcomes databases.

Table 1.

Summary of outcomes by genetic diagnosis or category

	No identified genetic diagnosis	Trisomy 21	Trisomy 13 and Trisomy 18	22q11.2 deletion syndrome	Turner Syndrome	'Other' genetic conditions
Median length of stay [40]	7 days	7 days	17 days	18 days	10 days	11 days
Cardiac arrest [40]	3% (2100/80 540)	2% (163/9473)	6% (10/156)	3% (24/715)	4% (13/347)	5% (186/4023)
ECMO [42]	3% (2353/80 540)	1% (134/9473)	3% (5/156)	3% (21/715)	5% (16/347) [40]	4% (167/4370)
ECMO mortality [42]	46% (1092/2353)	49% (66/134)	100% (5/5)	76% (16/21)	63% (10/16) [40]	52% (87/167)
In-hospital death [42]	3% (2344/80 540)	2% (194/9473)	13% (20/156)	5% (33/715)	6% (20/347) [40]	6% (274/4370)
Median length of stay for survivors [40]	7 days	7 days	16 days	17 days	9 days	11 days
Median length of stay for ECMO patients	37 days	33 days	29 days	34 days	48 days	37 days
Median length of stay for mortalities [40]	29 days	36 days	29 days	34 days	43 days	40 days
Readmission within 30 days [38]	11%[a] (876/7674)	9% (61/690)		14% (30/221)		
Median cost of hospitalization for survivors [40]	$48 500	$44 000	$85 700	$99 700	$56 900	$67 200
Median cost of hospitalization for mortalities [40]	$255 600	$257 500	$245 200	$337 200	$351 200	$286 600

This table summarizes what is known regarding the effects of genetic diagnoses on length of stay, cardiac arrest, extracorporeal membrane oxygenation (ECMO), mortality, readmission, and cost of hospitalization.

[a]As Trisomy 21 and 22qDS were the only listed genetic diagnoses there certainly are patients with genetic diagnoses included in this total although no other diagnoses were listed/specified.

Table 2.

Data summary of Norwood palliation outcomes based on whether they were perceived to have dysmorphic facial features by a cardiovascular geneticist at initial assessment

	Syndromic	Nonsyndromic	*P* value*
n	13	22	
Female	7 (54%)	8 (36%)	0.7341
Mean postoperative length of stay (days)	114.8	81.8	0.1735
Number of premature births	4 (31%)	2 (9%)	0.1662
Mean birth weight (g)	3110	3171	0.7104
Number with genetic diagnosis	6 (46%)	2 (9%)	0.0321
Mean length of postoperative mechanical ventilation (h)	337	169	0.0456
Mean postoperative vasopressor medications (h)	873	770	0.6680
Mortalities	4 (31%)	1 (5%)	0.0524
Number of transplants	2 (15%)	1 (5%)	0.5412
Number with bleeding requiring reoperation	2 (15%)	5 (23%)	0.6889
Number placed on ECMO in OR	1 (8%)	1 (5%)	1
Number with postoperative chylothorax	4 (31%)	2 (9%)	0.1662
Number with postoperative NEC	1 (7%)	5 (23%)	0.3771
Number with postoperative sepsis	3 (23%)	6 (27%)	1

This table summarizes findings from a small study looking at outcomes of Norwood palliation by whether a patient was determined to have dysmorphic facial features or not by a cardiovascular geneticist after birth. A statistically significant difference was found between groups for likelihood of genetic diagnosis and mean length of postoperative mechanical ventilation. Other trends between groups that are worth further investigation include postoperative vasopressor medication use, postoperative length of stay, and mortality.

**P* values are based on Fisher's exact testing for group comparisons or *t*-test for continuous values.