Genetic abnormalities/syndromes significantly impact perioperative outcomes of conotruncal heart defects

Subhrajit Lahiri[1], Wernovsky Gil[2], Salyakina Daria[3], Gruber Joshua[3], Jayakar Parul[3], Burke Redmond[3], Welch Elizabeth[3]

[1]Pediatric Cardiology, Texas Children's Hospital, Houston, Texas, USA, [2]Pediatric Cardiology, Children's National Health System, Washington, DC, USA, [3]Heart Center, Nicklaus Children's Hospital, Miami, Florida, USA

ABSTRACT

Objectives : **The main objective of the study is to characterize the effects of genetic abnormalities/syndromes (GA/S) on perioperative outcomes of cardiac surgeries involving repair of conotruncal heart defects (CTHD).**

Design : **The study involves a single-center retrospective analysis of patients who underwent complete repair of CTHDs (tetralogy of Fallot [TOF], truncus arteriosus, interrupted aortic arch, and ventricular septal defect with coarctation) between January 2000 and December 2015. The primary outcome was the post operative length of stay (PLOS). The secondary outcomes were mortality, cardiac complications, hematologic complications, infections, and number of medications-at-discharge.**

Setting : **Cardiac intensive care unit in a tertiary pediatric hospital in South Florida that performs around 300 open-heart surgeries a year.**

Subjects : **A total of 177 patients with CTHDs who underwent cardiac surgeries in the stated time period were included in the final study cohort.**

Measurements and Main Results : **Majority of patients had TOF (72.5%) and 46 (26%) had GA/S. The most common GA/S was 22q11 deletion (37%). PLOS was significantly increased in patients with GA/S ($P < 0.05$). Patients with GA/S were 4.5 times more likely to have a postoperative cardiac complication, 4.2 times more likely to have a postoperative infection, and received 1.6 times more medications at discharge than those without GA/S. However, GA/S was not associated with increased perioperative mortality. Black patients were three times more likely to have a longer PLOS than White patients.**

Conclusions : **Perioperative outcomes in patients with GA/S suggested an increased residual cardiovascular disease and increased resource usage. Notably, this is the first study demonstrating the effect of race and ethnicity on PLOS in CTHD patients.**

Keywords : 22q11, congenital, conotruncal, ethnicity, genetic, race, syndrome

INTRODUCTION

Conotruncal heart defects (CTHDs) comprise 20% of prenatally diagnosed congenital heart diseases (CHDs).[1] In particular, four diagnoses of CTHDs, i.e., tetralogy of Fallot (TOF) (including forms of double-outlet right ventricle), truncus arteriosus, interrupted aortic arch,

Access this article online

Quick Response Code:

Website: www.annalspc.com

DOI: 10.4103/apc.APC_51_19

How to cite this article: Lahiri S, Gil W, Daria S, Joshua G, Parul J, Redmond B, *et al.* Genetic abnormalities/syndromes significantly impact perioperative outcomes of conotruncal heart defects. Ann Pediatr Card 2020;13:38-45.

Address for correspondence: Dr. Subhrajit Lahiri, 6621 Fannin Street, MC: 19345-C, Houston, Texas 77030, USA. E-mail: subhrajit.lahiri@gmail.com

Received: 15-04-2019 **Revised:** 05-06-2019 **Accepted:** 23-07-2019 **Published:** 09-10-2019

and posterior malalignment ventricular septal defect with coarctation of aorta, have been associated with a high rate of genetic abnormalities/syndromes (GA/S).[1,2] Frequently, mutations in TBX5, NKX2, FGF10 genes, and 22q11locus have been associated with these CHDs.[2] These genes play significant roles in the embryonic development of aortic arches, cardiac outflow tract, and the conotruncal part of the heart.[3-5] Compared with other types of CHDs, CTHDs are more frequently associated with GA/S.[3,6] The most frequent GA/S in CTHDs is 22q11 deletion, followed by trisomy 21.[7] Other GA/Ss associated with CTHDs are VACTERL, Noonan, Alagille, and Cantrell syndrome.[8]

The current literature suggests that the presence of GA/S impacts perioperative morbidity, patient's neurodevelopment, and quality of life.[9-11] Studies have shown increased mortality, cross-clamp time, risk of cardiac complications, impaired response to vasopressors, increased risk of infections, and hypocalcemia in CTHD patients with GA/S.[7,11-14] Other studies reported perioperative outcomes of the index and staged surgeries focused on patient populations with 22q11 deletion, which is one of the many GA/S related to CTHDs. Hence, the results of those studies, though significant, could not be incorporated in the entire spectrum of GA/S associated with CTHDs. Genotype frequencies and prevalence of GA/S differ among various races and ethnicities, and there is a racial disparity in infant mortality rate due to CHDs.[15,16] Most of the prior studies were conducted in homogenous Caucasian populations, and only a few studies described perioperative outcomes in other races and ethnicities.[11-14] In contrast, only a few other studies included a unique racial and ethnic composition, i.e., nearly 68% Hispanic and 14% White non-Hispanic population.[17,18]

Our study attempts to improve on the previous literature by characterizing the effects of GA/S as well as race and ethnicity on perioperative outcomes of index cardiac surgeries for the complete repair of CTHDs. We hypothesize that patients with GA/S will have lower postoperative survival, longer hospital stay, and more perioperative complications than those without GA/S . We also hypothesize that there would be no effect of racial or ethnic differences in outcomes. The results of this study suggest better risk stratification of future patients for more tailored counseling and ancillary care and improve resource allocation.

METHODS

Patient population

A retrospective single institution review of patients with (ToF) (including double outlet right ventricle with ToF) truncus arteriosus, interrupted aortic arch, and ventricular septal defect with coarctation of aorta who underwent cardiac surgery between 2000 and 2015 at our institution were included. Patients who had any prior cardiac surgery, interventional catheterization, or univentricular palliation were excluded from the study. Investigators confirmed CTHD diagnosis by reviewing the preoperative transthoracic echocardiogram and the operative reports. A total of 177 patients with confirmed CTHDs underwent cardiac surgery and comprised the final study cohort [Figure 1].

Clinical data

Patient demographics (age, gender, weight, race, and ethnicity) and pre- and post-operative variables were collected from existing medical records. Race was divided into White, Black and others. Ethnicity was divided into Hispanic and non-Hispanic. The non-Hispanic group comprised of non-Hispanic Black, White, and Native Americans. The primary outcome variable was postoperative length of stay (PLOS). The secondary outcome variables included length of hospital stay prior to surgery, perioperative morbidity including aortic cross-clamp time, cardiac complications, infections, hematologic events, hypocalcemia, Vasoactive-Inotropic Score (VIS) at arrival, and total number of medications at discharge.[19] Cardiac complications included cardiac arrest, use of extracorporeal membrane oxygenator, supraventricular tachycardia requiring therapy, complete heart block requiring pacing (including temporary pacing), bradycardia, ventricular tachycardia or junctional rhythm requiring therapy, cardioversion, pacing, pericardial effusion requiring therapy, central venous line placement in unit, unexplained cardiac catheterization, mediastinal exploration, and unplanned reoperation. Infectious complications included any infection that required >3 days of intravenous antibiotics. Hematologic complications included any complication that required a blood transfusion. The chromosomal microarray was conducted to determine GA/S using Affymetrix Cytoscan™ HD Array, which features 2.6 million genetic markers including around 750,000

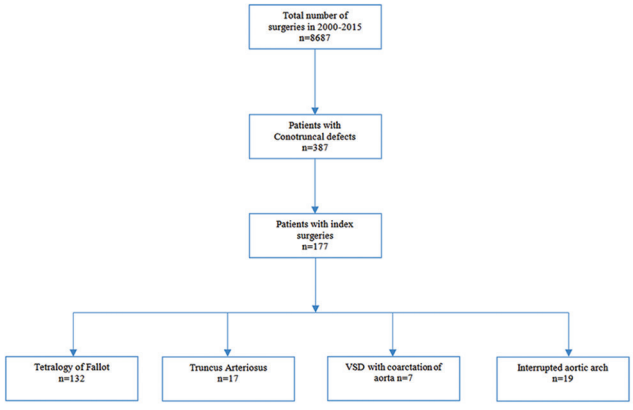

Figure 1: Flowchart of participants in the study from the Society of Thoracic Surgeons database of our institute between 2000 and 2015

single-nucleotide polymorphisms and 1.9 million nonpolymorphic probes genotyped for detecting copy number variation, loss of heterozygosity, uniparental isodisomy, regions indicated by descent, as well as measurements of low-level mosaicism and heterogeneity. Prior to 2011, fluorescent *in situ* hybridization (FISH) was carried out to confirm the clinical suspicion of 22q11 deletion. Patients were considered to have a GA/S if they had an abnormal karyotype, chromosomal microarray or FISH, or had clinical genetic syndrome previously described in the literature.

Statistical analysis

To assess the differences in demographic characteristics among the patients with and without the genetic syndrome, the Mann–Whitney U-test was conducted for nonparametric continuous variables. The Fisher's exact test and Chi-squared test of independence were used for categorical variables. Continuous data were presented as median with interquartile range. Categorical data were presented as frequencies and percentages. Multivariate logistic regression was used to understand the relationship between GA/S and various pre- and post-operative measures while accounting for demographic covariates. In particular, race and ethnicity were included in the models as both separate and combined variables to understand any racial/ethnic differences. Length of stay outcomes was analyzed using zero-truncated negative binomial regression to account for the fact that the length of stay can never be zero. Variables that were not significant were removed from the regression models. Odds ratios (ORs) and incidence rate ratios (IRR) were also calculated. McFadden's pseudo-R^2 was used to compare the overall model fit. The statistical analysis was conducted using RStudio version 1.0.143. (Rstudio, Boston, Massachusetts, USA).

RESULTS

The final study sample included 177 patients (55% male) with index cardiac surgery who met the inclusion criteria; of them, 51% were Caucasian and 15% were Black [Table 1]. All other races (Asian, Hawaiian or Pacific Islander, Native American or Alaskan Native, and mixed) comprised 14% of the study cohort and were grouped together as "Other." Approximately 20% of cases did not have a documented race. In terms of ethnicity, Hispanic and non-Hispanic patients were equally represented in this study (41% and 45%, respectively). The majority of the patients had a primary diagnosis of TOF (75%), followed by interrupted aortic arch (11%), truncus arteriosus (10%), and ventricular septal defect with coarctation of the aorta (4.0%) [Table 1 and Figure 2].

One-quarter of patients (26%) had a GA/S, and there was even distribution between sexes – 20 males and 26 females. The median age at the time of surgery was 77 days (range: 0–510 days). Those with and without a GA/S diagnosis did not differ in age (P = 0.286), weight (P = 0.103), or VIS at arrival (P = 0.280). The most common mutation among patients in the study population with GA/S was 22q11 deletion (37%), followed by trisomy 21 (17%). The other GA/S included Wolf–Hirschhorn syndrome, PHACES, tetrasomy 9, Koolen-de Vries syndrome, Goldenhar syndrome, heterotaxy syndrome, and VATER complex [Table 2].

PLOS, the primary outcome, was significantly increased in patients with GA/S (P < 0.001) [Table 1]. Multivariable analysis indicated that patients with GA/S stayed three times longer in the hospital after surgery than patients without GA/S [Table 3]. Further analysis revealed that patients with GA/S frequently had stays of 4 weeks or longer (P = 0.001) [Figure 3]. There were also differences in PLOS

Table 1: Demographic characteristics of 177 patients with conotruncal heart defects included in this study by the presence of genetic abnormalities/syndromes

Demographic characteristics	Overall (*n*=177), *n* (%)	GA/S (*n*=46), *n* (%)	No GA/S (*n*=131), *n* (%)	*P**
Gender				
Male	97 (54.8)	20 (11.3)	77 (43.5)	0.105
Female	80 (45.2)	26 (14.7)	54 (30.5)	
Race				
Caucasian	91 (51.4)	22 (12.4)	69 (39.0)	0.607
African-American	26 (14.7)	5 (2.8)	21 (11.9)	
Other	24 (13.6)	8 (4.5)	16 (9.1)	
Unknown	36 (20.3)	11 (6.2)	25 (14.1)	
Ethnicity				
Hispanic	73 (41.2)	20 (11.3)	53 (29.9)	0.815
Non-Hispanic	80 (45.2)	21 (11.9)	59 (33.3)	
Unknown	24 (13.6)	5 (2.8)	19 (10.7)	
Primary diagnosis				
Tetralogy of fallot	132 (74.6)	26 (14.7)	106 (59.9)	0.002
Truncus arteriosus	17 (9.6)	9 (5.1)	7 (4.0)	
Interrupted aortic arch	19 (10.7)	7 (4.0)	12 (6.8)	
VSD with CoA	7 (4.0)	4 (2.3)	3 (1.7)	

**P*-values were obtained from Fisher's exact test or Chi-square test of association. GA/S: Genetic abnormalities/syndrome, VSD: Ventricular septal defect, CoA: Coarctation of the aorta

Table 2: Clinical characteristics of 177 patients with conotruncal heart defects included in this study by the presence of genetic abnormalities/syndromes

Clinical characteristic	*n*	Overall (*n*=177)	GA/S (*n*=46)	No GA/S (*n*=131)	*P**
Age at surgery (days), median (IQR)	177	77.0 (133)	39.0 (180)	75.5 (123)	0.286
Weight at surgery (kg), median (IQR)	176	4.9 (3)	3.8 (4)	5.0 (3)	0.103
PLOS (days), median (IQR)	176	8.0 (9)	11.0 (15)	7.0 (5)	<0.001
VIS score at arrival, median (IQR)	126	10.0 (5)	7.0 (5)	10.0 (5)	0.280
LOSPS (days), median (IQR)	176	1.0 (6)	4.0 (8)	1.0 (5)	0.018
Total number of medications, median (IQR)	138	4.0 (3)	4.0 (6)	4.0 (4)	0.036
Cross-clamp time (min), mean (SD)	173	77.94 (31.6)	75.93 (32.2)	78.63 (31.4)	0.631
Cardiac complications, *n* (%)					
Yes		38 (21.5)	17 (9.6)	21 (11.9)	0.019
No		109 (61.6)	25 (14.1)	84 (47.5)	
Missing		30 (16.9)	4 (2.3)	26 (14.7)	
Infections, *n* (%)					
Yes		38 (21.5)	17 (9.6)	21 (11.9)	0.028
No		108 (61.0)	26 (14.7)	82 (46.3)	
Missing		31 (17.5)	3 (1.7)	28 (15.8)	
Hematologic events, *n* (%)					
Yes		30 (16.9)	12 (6.8)	18 (10.2)	0.237
No		112 (63.2)	30 (16.9)	82 (46.3)	
Missing		35 (19.8)	4 (2.3)	31 (17.5)	
Hypocalcemia, *n* (%)					
Yes		44 (24.9)	19 (10.7)	25 (14.1)	0.028
No		102 (57.6)	24 (13.6)	78 (44.1)	
Missing		31 (17.5)	3 (1.7)	27 (15.8)	
In hospital mortality, *n* (%)					
Yes		4 (2.3)	2 (1.1)	2 (1.1)	0.275
No		170 (75.1)	43 (19.8)	127 (71.8)	
Missing		3 (1.7)	1 (0.6)	2 (1.1)	

*Student's *t*-test and Mann-Whitney U-test were conducted for continuous variables while Fisher's exact test and Chi-squared test for categorical variables. PLOS: Postoperative length of stay, IQR: Interquartile range, SD: Standard deviation, LOSPS: Length of stay prior to surgery, GA/S: Genetic abnormalities/syndrome, VIS: Vasoactive-inotropic score

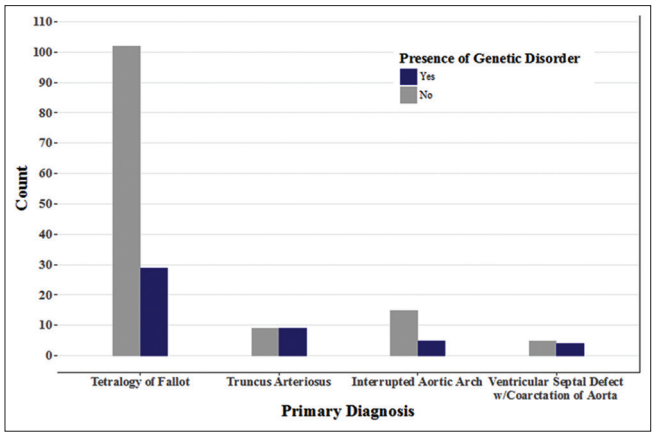

Figure 2: The frequency of each primary diagnosis stratified by the presence of genetic abnormality/syndrome

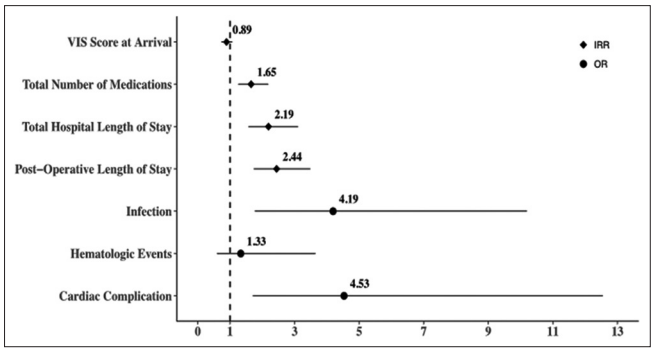

Figure 3: Genetic abnormality/syndrome as a predictor of various postoperative measures

associated with the race [Table 4]. There was no difference in outcomes when adjusted for individual pathologies. When combining race and ethnicity, non-Hispanic Blacks stayed 2.6 and 1.6 times longer postoperatively than both White non-Hispanics and White Hispanics, respectively (OR = 2.58, 95% confidence interval [CI]: 1.66–4.06, $P < 0.001$; OR = 1.61, 95% CI: 1.05–2.51, $P < 0.029$).

No differences were found in in-hospital mortality between the groups with and without GA/S. In the cardiac intensive care unit (CICU), 38/177 (22%) had a cardiac complication, 38 (22%) had an infection, 44 (25%) patients suffered from hypocalcemia, and 30 (17%) had at least one hematologic event [Table 1]. Unplanned cardiac catheterization was the most common cardiac complication, followed by mediastinal reexploration and junction rhythm [Table 5]. Patients with GA/S were 3.1 times more likely to have a postoperative cardiac complication ($P = 0.014$), 2.4 times more likely to have a postoperative infection ($P = 0.031$), 2.4 times more likely to be hypocalcemic ($P = 0.044$), and were given 1.6 times more medications at discharge ($P < 0.001$) [Table 3]. The patients with interrupted aortic arch and ventricular septal defect with coarctation of aorta received 3.7 and 1.7 times fewer medications at discharge, respectively, than those

Table 3: Associations between genetic abnormalities/syndromes and various pre-/postoperative measure

Pre-/postoperative measures	*n*	Adjusted OR or IRR (95% CI)*	*P*
Cardiac complication (Ref=no)[a]	146	3.07 (1.25-7.60)	0.014
Infection (Ref=no)[b]	146	2.44 (1.08-5.52)	<0.031
Hematologic events (Ref=no)[c]	141	1.81 (0.74-4.37)	0.188
Hypocalcemia (Ref=no)[c]	146	2.40 (1.03-5.68)	0.044
In-hospital mortality (Ref=no)[g]	174	2.95 (0.35-25.23)	0.286
LOSPS (days)[h]	172	2.28 (1.28-4.26)	0.004
PLOS (days)[d]	176	2.98 (2.24-4.01)	<0.001
VIS score at arrival[e]	123	0.83 (0.70-0.99)	0.043
Total number of medications[f]	137	1.59 (1.21-2.08)	<0.001

*ORs were calculated from binary outcomes and were modeled using logistic regression. IRRs were calculated from continuous outcomes and were modeled using negative binomial regression. Length of stay variables used zero-truncated negative binomial regression, [a]Model adjusted for age and primary diagnosis, [b]Model adjusted for age and weight at time of surgery, [c]Model adjusted for weight at time of surgery, [d]Model adjusted for age, race, [e]Model adjusted for primary diagnosis, cross-clamp time, [f]Model adjusted for primary diagnosis, [g]Model unadjusted, [h]Model adjusted for age, cross- clamp time. Ref: Reference group, PLOS: Postoperative length of stay, LOSPS: Length of stay prior to surgery, ORs: Odds ratios, IRRs: Incidence rate ratios, CI: Confidence interval

Table 4: Association between genetic abnormality/syndrome and postoperative length of stay and demographics while adjusting for covariates

Model fit (Pseudo R^2=0.362*)			
Covariates	***n***	**Adjusted IRR (95% CI)**	***P***
GA/S no (Ref)	131		
Yes	45	2.98 (2.24-4.01)	<0.001
Operation age (days)	176	1.00 (1.00-1.00)	<0.001
Race			
Caucasian (Ref)	91		
African-American	26	1.53 (1.06-2.27)	<0.001
Other	24	0.80 (0.55-1.20)	0.807
Unknown	35	0.66 (0.47-0.94)	0.017

*Calculated using McFadden's Pseudo- R^2 formula. IRR: Incidence rate ratio, CI: Confidence interval, Ref: Reference group, GA/S: Genetic abnormalities/syndrome

Table 5: Number and type of cardiac complications for patients with genetic syndromes/abnormalities

Cardiac complication	GA/S (*n*=47), *n* (%)	No GA/S (*n*=131), *n* (%)
Unplanned cardiac catheterization	34 (16)	0
Mediastinal exploration	20 (10)	8 (11)
Bradycardia	14 (7)	1.5 (2)
Cardiac arrest in CICU requiring resuscitation	10 (5)	1.5 (2)
Cardioversion	10 (5)	0.7 (1)
SVT requiring therapy	8 (4)	0
ECMO/bypass in CICU	7 (8)	2.2 (3)
Unplanned reoperation	6 (3)	0
Complete heart block	4 (2)	0
Junctional rhythm	2 (1)	5.3 (7)
Pericardial effusion requiring drainage	2 (1)	0.7 (1)

CICU: Cardiac intensive care unit, SVT: Supraventricular tachycardia, ECMO: Extracorporeal membrane oxygenation, GA/S: Genetic abnormalities/syndrome

with TOF (IRR = 3.70, 95% CI: 1.64–9.09, P = 0.002; IRR = 1.67, 95% CI: 1.08–2.63, P < 0.023).

DISCUSSION

In this study we characterized the effects of GA/S, race, and ethnicity on the pre and post operative length of stay of patients with CTHDs undergoing cardiac surgeries involving complete repair of heart defects.

Our primary outcome, PLOS, is an easily quantifiable outcome and is a surrogate for hospital characteristics such as hospital policy, team decisions, and patient characteristics. Overall, our results indicated that the presence of GA/S in patients with CTHD was associated with longer PLOS, increased perioperative complications, and more medications at discharge. Furthermore, non-Hispanic Black patients had significantly longer postoperative stays than any other racial and ethnic combination. The frequent cardiac complications in patients with GA/S included pericardial tamponade, unplanned reoperations, arrhythmias, use of extracorporeal membrane oxygenator, hypocalcemia, and others. Furthermore, infectious complications, such as postoperative urinary tract infections, pneumonia, and septic shock, were significantly more in patients with GA/S. The requirement of antibiotics for infectious complications added to PLOS.

Studies comparing the surgical outcome of CTHDs between patients with and without GA/S have found that GA/S is similarly associated with increased PLOS and various perioperative complications.[10,11,13,14,20] For instance, neonates with GA/S had increased arrhythmias, unexpected reoperation, and pericardial effusions.[21] O'Byrne *et al.* also found increased cardiac events in patients with 22q11 deletion.[14] Michielon *et al.* studied a cohort of 800 patients with CTHD between 1992 and 2007 and reported that GA/S, except 22q11 deletion and trisomy 21, was associated with increased hospital mortality and prolonged intensive care stay.[8] Most prior studies have reported an increase in the incidence of infection with 22q11 deletion. In their analysis of the Society of Thoracic Surgeons Congenital Surgery Database, Patel *et al.* reported the prevalence of GA/S in CTHD; this finding is similar to that of our study.[22] However, in contrast to our report, Momma found that as many as 62% patients having TOF with pulmonary atresia and multiple aortopulmonary collaterals had GA/S, a significantly higher incidence than in our cohort.[23] 22q11 deletion syndromes have often been shown to be associated with hypocalcemia and increased mortality and morbidity secondary to hypocalcemia.[20] In a recent study, Alsou *et al.* showed that non-22q11 deletion syndrome was associated with worse postoperative outcomes, including mortality in patients with CTHD.[24] There are scarce data on the

influence of race and ethnicity on outcomes of children with CHD with GA/S.[16,25]

Our results outline the similarities and differences across various cohorts. Similarities include a longer postoperative course with more complications that are consistent across many different centers, demographics, and time periods. However, there is most likely an effect of epigenetics, sociodemographic, and other yet-to-be-described variables that are unique to each cohort. For example, in our cohort, there was a significant negative influence of Black, non-Hispanic race. Although larger studies have shown similar racial disparities in surgical care and outcomes and on survival after cardiac arrest in adult patients, no previous study has explored how race and ethnicity are related to outcomes in patients with GA/S. Previous studies have included non-Hispanic Caucasian population, and only a few studies focused on the effects of race and ethnicity on perioperative outcomes. Unlike previous literature on GA/S, this study uniquely addressed this question given that Nicklaus Children's Hospital is in a racially and ethnically diverse South Florida Community. The outlook of patients with CTHD may be moderated by the presence of GA/S or ethnicity and race, specifically for PLOS. The postoperative morbidities that contribute to increased PLOS in our study are congruent to that in literature. We did not find an increased frequency of hypocalcemia with 22q11 deletion in comparison to other GA/S, unlike many other studies. These complications of 22q11 deletion are not a constant association and have widely different incidences reported in different studies. Non-22q11 genetic syndromes were associated with increased cardiac, hematologic, and neurologic complications. However, their numbers were small and did not reach statistical significance.

We did not find increased mortality with GA/S, as found in some earlier studies. Advancement in surgical techniques, early diagnosis, and improved CICU management may have increased survival among all CHD patients.[26] Like other studies, 17% of patients with GA/S had 22q11 deletion in our study.[5,21,27] Our study reported the prevalence of GA/S may be underestimated due to changes in genetic evaluation procedures over time. Prior to 2011, chromosomal microarray/FISH tests were performed in our institution based on clinical suspicion; thus, the actual prevalence of 22q11 deletion may be higher than reported.

The unique finding of our study is that race and ethnicity are associated with PLOS in patients, independent of the presence of GA/S. Better understanding and awareness of disparities of outcomes between different racial/ethnic groups will help clinicians and public health professionals develop culturally sensitive interventions, prevention programs, and services specifically targeted toward risk burdens in each of these populations. Furthermore, GA/S comes with multisystem involvement, which needs close attention and disorder-specific care. This multisystem involvement increases postoperative complications, which translate to an increased length of stay. It has been suggested that the complexity of cardiac anatomy in combination with GA/S may lead to increased cardiac complications, and hence, prolonged PLOS.[6] In fact, Graham *et al.* showed that the more complex the individual surgical anatomy, the higher the chances of cardiac complications following surgery, irrespective of GA/S.[7] A reflection of this probability is seen in our study where truncus arteriosus, for example, was associated with poor repair outcomes independent of GA/S. Postoperative hypocalcemia found in CTHD has been related to worse postoperative morbidity in prior studies.[20] Therefore, close monitoring, prevention of these complications, and sensitization of CVICU staff to these may be recommended to decrease postoperative morbidity.

Data were collected over 15 years when there were major changes in surgical techniques and CICU management. Race and ethnicity of the population were based on documentation in the electronic medical records, which may have been biased as a result of the hospital staff helping families to fill up the registration form. Routine genetic testing on cardiac patients has been only recently implemented. Most genetic tests prior to 2011 were based on clinical suspicion, thereby underestimating the incidence of GA/S in our population. Finally, it must not be assumed that all congenital heart teams are equal. Therefore, these results might be unique to our team, our expertise, and our philosophy of care.

Multicenter studies and prospective studies on individual GA/S and individual lesions are required to further characterize the postoperative and long-term outcomes after index cardiac surgeries. In a study published in 2018, Mercer-Rosa *et al.* showed 22q11.2 deletion syndrome was not associated with adverse perioperative outcomes in patients with TOF, pulmonary atresia, and major aortopulmonary collateral arteries when compared to those without 22q11.2 deletion syndrome.[27] Based on these studies, guidelines for early screening of complications should be established for GA/S specific management strategies in intensive care unit.

CONCLUSION

GA/S was found to be associated with increased cardiac complications and consequent prolonged PLOS, infectious complications, and a higher number of medications at discharge. This suggests an increased burden of cardiovascular complications, other comorbidities, and increased resource usage for index complete repairs. However, GA/S was not associated with increased

perioperative mortality. Outcomes of patients with GA/S were influenced by race and ethnicity. These findings suggest that GA/S should be considered as a part of preoperative risk assessment and counseling.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Long J, Ramadhani T, Mitchell LE. Epidemiology of nonsyndromic conotruncal heart defects in Texas, 1999-2004. Birth Defects Res A Clin Mol Teratol 2010;88:971-9.
2. El Malti R, Liu H, Doray B, Thauvin C, Maltret A, Dauphin C, *et al.* A systematic variant screening in familial cases of congenital heart defects demonstrates the usefulness of molecular genetics in this field. Eur J Hum Genet 2016;24:228-36.
3. Ahrens-Nicklas RC, Khan S, Garbarini J, Woyciechowski S, D'Alessandro L, Zackai EH, *et al.* Utility of genetic evaluation in infants with congenital heart defects admitted to the cardiac intensive care unit. Am J Med Genet A 2016;170:3090-7.
4. Van Mierop LH, Kutsche LM. Cardiovascular anomalies in DiGeorge syndrome and importance of neural crest as a possible pathogenetic factor. Am J Cardiol 1986;58:133-7.
5. Buckingham M, Meilhac S, Zaffran S. Building the mammalian heart from two sources of myocardial cells. Nat Rev Genet 2005;6:826-35.
6. Lammer EJ, Chak JS, Iovannisci DM, Schultz K, Osoegawa K, Yang W, *et al.* Chromosomal abnormalities among children born with conotruncal cardiac defects. Birth Defects Res A Clin Mol Teratol 2009;85:30-5.
7. Hoang TT, Goldmuntz E, Roberts AE, Chung WK, Kline JK, Deanfield JE, *et al.* The Congenital Heart Disease Genetic Network Study: Cohort description. PLoS One 2018;13:e0191319.
8. Michielon G, Marino B, Oricchio G, Digilio MC, Iorio F, Filippelli S, *et al.* Impact of DEL22q11, trisomy 21, and other genetic syndromes on surgical outcome of conotruncal heart defects. J Thorac Cardiovasc Surg 2009;138:565-70.
9. Gunn JK, Beca J, Hunt RW, Goldsworthy M, Brizard CP, Finucane K, *et al.* Perioperative risk factors for impaired neurodevelopment after cardiac surgery in early infancy. Arch Dis Child 2016;101:1010-6.
10. Wernovsky G, Licht DJ. Neurodevelopmental outcomes in children with congenital heart disease-what can we impact? Pediatr Crit Care Med 2016;17:S232-42.
11. Landis BJ, Cooper DS, Hinton RB. CHD associated with syndromic diagnoses: Peri-operative risk factors and early outcomes. Cardiol Young 2016;26:30-52.
12. Anaclerio S, Di Ciommo V, Michielon G, Digilio MC, Formigari R, Picchio FM, *et al.* Conotruncal heart defects: Impact of genetic syndromes on immediate operative mortality. Ital Heart J 2004;5:624-8.
13. Boneva RS, Botto LD, Moore CA, Yang Q, Correa A, Erickson JD, *et al.* Mortality associated with congenital heart defects in the United States: Trends and racial disparities, 1979-1997. Circulation 2001;103:2376-81.
14. O'Byrne ML, Yang W, Mercer-Rosa L, Parnell AS, Oster ME, Levenbrown Y, *et al.* 22q11.2 deletion syndrome is associated with increased perioperative events and more complicated postoperative course in infants undergoing infant operative correction of truncus arteriosus communis or interrupted aortic arch. J Thorac Cardiovasc Surg 2014;148:1597-605.
15. Collins JW Jr., Soskolne G, Rankin KM, Ibrahim A, Matoba N. African-American: White disparity in infant mortality due to congenital heart disease. J Pediatr 2017;181:131-6.
16. Goldmuntz E, Driscoll DA, Emanuel BS, McDonald-McGinn D, Mei M, Zackai E, *et al.* Evaluation of potential modifiers of the cardiac phenotype in the 22q11.2 deletion syndrome. Birth Defects Res A Clin Mol Teratol 2009;85:125-9.
17. Hobbs F, Stoops NN. U.S. Census Bureau, Census 2000 Special Reports. Washington (DC): U.S. Government Printing Office; 2002.
18. Hasegawa K, Tsugawa Y, Brown DF, Camargo CA Jr. A population-based study of adults who frequently visit the emergency department for acute asthma. California and Florida, 2009-2010. Ann Am Thorac Soc 2014;11:158-66.
19. Gaies MG, Jeffries HE, Niebler RA, Pasquali SK, Donohue JE, Yu S, *et al.* Vasoactive-inotropic score is associated with outcome after infant cardiac surgery: An analysis from the pediatric cardiac critical care consortium and virtual PICU system registries. Pediatr Crit Care Med 2014;15:529-37.
20. Shen L, Gu H, Wang D, Yang C, Xu Z, Jing H, *et al.* Influence of chromosome 22q11.2 microdeletion on postoperative calcium level after cardiac-correction surgery. Pediatr Cardiol 2011;32:904-9.
21. Agergaard P, Olesen C, Østergaard JR, Christiansen M, Sørensen KM. The prevalence of chromosome 22q11.2 deletions in 2,478 children with cardiovascular malformations. A population-based study. Am J Med Genet A 2012;158A: 498-508.
22. Patel A, Costello JM, Backer CL, Pasquali SK, Hill KD, Wallace AS, *et al.* Prevalence of noncardiac and genetic abnormalities in neonates undergoing cardiac operations: Analysis of the society of thoracic surgeons congenital heart surgery database. Ann Thorac Surg 2016;102:1607-14.
23. Momma K. Cardiovascular anomalies associated with chromosome 22q11.2 deletion syndrome. Am J Cardiol 2010;105:1617-24.
24. Alsoufi B, McCracken C, Shashidharan S, Deshpande S, Kanter K, Kogon B, *et al.* The impact of 22q11.2 deletion syndrome on surgical repair outcomes of conotruncal cardiac anomalies. Ann Thorac Surg 2017;104:1597-604.

25. Garcia Guerra G, Joffe AR, Robertson CM, Atallah J, Alton G, Sauve RS, *et al.* Health-related quality of life experienced by children with chromosomal abnormalities and congenital heart defects. Pediatr Cardiol 2014;35:536-41.

26. Carotti A, Digilio MC, Piacentini G, Saffirio C, Di Donato RM, Marino B, *et al.* Cardiac defects and results of cardiac surgery in 22q11.2 deletion syndrome. Dev Disabil Res Rev 2008;14:35-42.

27. Mercer-Rosa L, Elci OU, Pinto NM, Tanel RE, Goldmuntz E. 22q11.2 deletion status and perioperative outcomes for tetralogy of Fallot with pulmonary atresia and multiple aortopulmonary collateral vessels. Pediatr Cardiol 2018;39:906-10.