Title

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

Journal

Journal of Thoracic and Cardiovascular Surgery, 148(4)

ISSN

0022-5223

Authors

O'Byrne, Michael L
Yang, Wei
Mercer-Rosa, Laura
et al.

Publication Date

2014-10-01

DOI

10.1016/j.jtcvs.2014.02.011

Peer reviewed

Published in final edited form as:
J Thorac Cardiovasc Surg. 2014 October ; 148(4): 1597–1605. doi:10.1016/j.jtcvs.2014.02.011.

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

Michael L. O'Byrne, MD[1], **Wei Yang, PhD**[2], **Laura Mercer-Rosa, MD, MSCE**[1], **Aimee S. Parnell, MD, MSCE**[3], **Matthew E Oster, MD, MPH**[4], **Yosef Levenbrown, DO**[5], **Ronn E. Tanel, MD**[6], and **Elizabeth Goldmuntz, MD**[1]

[1]Division of Cardiology Department of Pediatrics, The Children's Hospital of Philadelphia and the University of Pennsylvania Perelman School of Medicine, Philadelphia, PA

[2]Center for Clinical Epidemiology and Biostatistics, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA

[3]Division of Cardiology, Department of Pediatrics, Children's Healthcare of Mississippi, University of Mississippi Medical Center, Jackson, MS

[4]Children's Healthcare of Atlanta, Department of Pediatrics, Emory University School of Medicine, Atlanta, GA

[5]Department of Anesthesiology and Critical Care, A.I. duPont Hospital for Children, Wilmington, DE and Jefferson Medical College, Philadelphia PA

[6]Department of Pediatrics, University of California San Francisco School of Medicine, Division of Pediatric Cardiology, UCSF Benioff Children's Hospital, San Francisco, CA

Abstract

Objective—The impact of genotype on outcomes of infant cardiac operations is not well established. The purpose of this study was to investigate the impact of 22q11.2 deletion (22q11del) on infants with truncus arteriosus communis (TA) and interrupted aortic arch (IAA) undergoing operative correction during infancy.

Methods—We conducted a retrospective cohort study of all infants who underwent operative correction of TA or IAA at The Children's Hospital of Philadelphia from 1995 to 2007, comparing peri-operative outcomes (hospital length of stay, intensive care, and mechanical ventilation, risk of

Address for correspondence: Michael O'Byrne MD, Division of Cardiology, The Children's Hospital of Philadelphia, 34th Street and Civic Center Blvd., Philadelphia, PA 19104, Tel: (215) 590-1790, Fax: (215) 590-5825, obyrnem@email.chop.edu.

Authors' relationship with industry:
Dr. Tanel has previously served for St. Jude Medical, Inc. on a speaker's bureau.

cardiac and non-cardiac events, number of consultations, and number of discharge medications) by 22q11del status.

Results—A total of 104 patients were studied (55 with TA and 49 with IAA), of which 40 (38%) were 22q11del positive. 22q11del status was unknown in 9 cases (7 with TA and 2 with IAA). In patients with known deletion status, those with 22q11del had a longer hospital length of stay and duration of intensive care. Subjects with 22q11del also underwent more frequent operative re-intervention, underwent more consultations, and were prescribed more medications at discharge. There was no significant difference in method of feeding between those with and without 22q11del at discharge.

Conclusions—22q11del is associated with perioperative outcomes in infants undergoing operative correction of TA and IAA, with longer hospital stay and greater resource utilization in the perioperative period. These findings inform counseling and risk stratification and warrant further study to identify genotype specific management strategies to improve outcomes.

Keywords

Truncus Arteriosus; Interrupted Aortic Arch; Congenital Heart Surgery; DiGeorge Syndrome; 22q11.2 deletion

INTRODUCTION

Truncus arteriosus communis (TA) and interrupted aortic arch (IAA) are two conotruncal defects for which operative correction is undertaken during infancy. 22q11.2 deletion (22q11del) is frequently coincident with both, present in 48% of IAA and 36% of TA[1]. Perioperative mortality and risk of reoperation are well described for both lesions without regard to 22q11del status[2-13]. 22q11del is associated with multiple non-cardiac conditions, such as palate anomalies, hypocalcemia, and immunodeficiency, that could complicate recovery from cardiac operation[14]. Early series reported high perioperative mortality (between 60-80%) in subjects with 22q11del and cardiac disease, largely attributed to sepsis[15]. In the current era, 22q11del is not associated with a higher mortality but is still associated with prolonged hospital course in children with tetralogy of Fallot[16]. However, there have been no series describing the association of 22q11del on outcomes following infant cardiac operation. We sought to investigate the association of 22q11del on perioperative outcomes in a cohort of subjects with a diagnosis of TA or IAA, hypothesizing that 22q11del is associated with a prolonged and more complicated postoperative course.

MATERIALS AND METHODS

Study population

The Institutional Review Board of The Children's Hospital of Philadelphia approved the protocol for this study. Subjects were identified by a query of an institutional cardiothoracic surgical database. Inclusion criteria included patients undergoing primary complete operative correction of TA or IAA at The Children's Hospital of Philadelphia between January 1, 1995 and February 28, 2007. Patients with recognized genetic syndromes other than 22q11del were excluded. Diagnosis was confirmed by review of preoperative

transthoracic echocardiogram reports. Anatomic classification of IAA[17,18] and TA[19] were performed according to previously published definitions.

Data Collection

A retrospective cohort design was chosen. Data were collected through review of hospital medical records. Demographic and relevant clinical information from the index hospitalization were abstracted. Reports from preoperative transthoracic echocardiograms were reviewed to confirm diagnosis, anatomic classification, and preoperative anatomy. The cohort was divided based on 22q11del status, which was extracted from clinical and research study records, based on fluorescence *in situ* hybridization performed following standard protocols[20]. Outcomes of interest included in-hospital mortality and in those who survived to discharge: hospital length of stay (LOS), duration of intensive care, duration of mechanical ventilation, postoperative complications, utilization of consulting services, feeding methods, and prescribed medications at discharge/transfer to outside facility.

Each outcome was defined prior to data collection. Mortality was defined as death prior to hospital discharge regardless of duration of hospitalization. Other outcomes were restricted to those who survived to discharge to eliminate disproportionate skew introduced by subjects who died. LOS was determined for all subjects surviving to discharge. Because a subset of subjects was transferred to outside facilities and their outcomes following transfer were not available leading to possible missing data, LOS for all subjects and LOS for those subjects discharged to home were considered separately. Duration of intensive care was defined as the time between postoperative admission to the cardiac intensive care unit until: 1) discontinuation of mechanical ventilation, 2) removal of chest tubes and intra-cardiac lines, 3) removal of temporary pacing wires, and 4) discontinuation of any and all intravenous inotropic medications. For purposes of analysis, the rates of these events were compared both for all cardiac events and for each individual event. Cardiac events were defined as any of the following: delayed sternal closure, arrhythmias requiring medical therapy, pericardial effusions/hemopericardium drained via pericardiocentesis, cardiac catheterizations in the post-op period, operative mediastinal exploration, extracorporeal membrane oxygenation, re-operation, or cardiac arrest requiring resuscitation, all prior to hospital discharge. Non-cardiac events, including seizures confirmed by electroencephalogram, infections prompting antimicrobial treatment, long term airway management such as tracheostomy, pleural effusions requiring mechanical drainage, number of consultations requested, etc. were considered in three levels of analysis. First, all non-cardiac events were pooled and considered together. Second, non-cardiac events were divided in the following categories: neurologic, gastrointestinal, hematologic, infectious, airway/respiratory, pulmonary, renal, and other. Finally, post-hoc, additional analyses of specific events in non-cardiac systems was performed to determine if rates differed between 22q11del positive and negative subjects. Feeding status at discharge was classified into one of the following categories: parenteral nutrition, oral feedings, or feedings that involved some portion being delivered through a nasogastric tube. The number of consultations ordered for a patient was also tabulated. Multiple consultations by the same service at different times for different problems were counted separately.

Statistical Analysis

Study population demographics and clinical characteristics were described using standard summary statistics. Continuous variables were described using mean and standard deviation or median and range where appropriate. For categorical variables frequencies and percentages were reported. The cohort was divided by 22q11del status. Subjects with TA and IAA were first considered as a single cohort because the two groups share key characteristics: 1) affected infants underwent a single neonatal operation at our institution during the study period and 2) operative correction for TA and IAA have similar procedural difficulty scores, risk of perioperative mortality, length of stay, and re-intervention[13,21]. To support this analysis, subgroup analyses of TA and IAA were performed separately. For subjects whose 22q11del status was unknown, baseline characteristics were summarized, and sensitivity analyses were performed, first positing that all subjects with unknown deletion status were 22q11del positive and then positing that they all were 22q11del negative.

Differences in outcomes between 22q11del positive and negative groups were performed using Chi-squared or Fisher's exact test (with Fisher's exact test noted) for categorical variables and Wilcoxon rank sum test for continuous variables, as applicable. A p-value of < 0.05 was considered statistically significant. All analyses were performed using StataSE 12.1 (Statacorp, College Station TX).

The authors had full access to and take full responsibility for the integrity of the data. All authors have read the article and agree to the article as written.

RESULTS

Study Population

A total of 104 subjects met inclusion criteria (57 with TA and 47 with IAA) of which 38% (n=40) were 22q11del positive. Nine subjects (2 with IAA and 7 with TA) did not have 22q11del status assessed. Of those with known deletion status, the proportion of subjects with 22q11del was not significantly different between subjects with TA and subjects with IAA (35% vs. 45%, $p=0.31$). Subjects with IAA were operated on at a younger age than those with TA (2 days range: 0-8 days vs. 5 days range: 1-124 days, $p<0.0001$). Otherwise, there were no differences in the demographic and preoperative characteristics between subjects with IAA (Table 1) and TA (Table 2). In terms of the operative characteristics, cardiopulmonary bypass (CPB) time was longer in IAA patients (96 minutes range: 65-230 minutes) than in TA (81 minutes range: 57-354 minutes, $p=0.02$), deep hypothermic circulatory arrest (DHCA) was used in a greater proportion of subjects with IAA (98%) than TA (85%, $p=0.04$), and DHCA time, when required, was greater in subjects with IAA (46 minutes range: 28-100 minutes) than those with TA (37 minutes range: 3-68 minutes $p=0.008$). In subjects with IAA, DHCA time was not independently associated with 22q11del status ($p=0.8$) or presence of coronary artery anomalies ($p=0.1$). In subjects with TA, neither arch anomaly ($p=0.6$) or 22q11del status ($p=0.3$) were independently associated with DHCA time.

Effect of 22q11del on perioperative outcome

For each of the 89 subjects with known deletion status, the effect of 22q11del on postoperative course was assessed (Table 3). There was no significant difference in time spent in the hospital prior to operation between subjects with and without 22q11del (3 days range: 0-124 days vs. 3 days range: 1-58 days respectively, p=0.83). In-hospital mortality was not different between subjects with and without 22q11del (5.0% 95% CI: 0.6-16.9% vs. 7.3% 95% CI: 2.0-17.5%, Fisher's exact test p=0.5). Of the total cohort, 25% (22/89) of subjects were transferred to another facility prior to discharge at a median of 7 days post-operatively (range: 7-103 days). Further information regarding, 88% (n=18) of these 22 subjects was available, with 17 surviving to discharge and 1 dying >120 days after transfer. There were no available clinical records of 4 subjects, representing 12% of those transferred prior to discharge and 4.5% of the total cohort. To determine the maximum possible effect on rates of mortality, a sensitivity analysis was performed positing that the 4 subjects lost to follow-up all died prior to discharge. There was still no significant difference in mortality between subjects with and without 22q11del (data not shown). This was true for the entire cohort as well as in subgroup analysis looking at subjects with IAA and TA separately.

LOS in survivors was greater in 22q11del positive subjects than in 22q11del negative subjects (18 days range: 2-103 days vs. 14 days range: 17-96 days, p=0.02, Table 3). Subgroup analyses of subjects who were discharged home also demonstrated a longer LOS in 22q11del positive subjects (p=0.009), but for those transferred to another institution (rather than discharged directly home), LOS at our institution was not significantly different (p=0.32). 22q11del was associated with a longer duration of mechanical ventilation (123 hours range: 22-968 vs. 74 hours range: 26-1038, p=0.01) and longer duration of intensive care (7 days range: 3-48 days vs. 4 days range: 2-56 days p=0.02).

In addition, 22q11del positive subjects experienced more cardiac adverse events than 22q11del negative counterparts (p=0.02, Table 3) and were at greater risk for cardiac reoperation (RR: 2.7 95% CI: 1.2-6.0 p=0.01, Table 4). The total number of non-cardiac events was not increased in subjects with 22q11del (p=0.12, Table 5). When non-cardiac events were divided by system, only gastrointestinal events were more common in 22q11del positive than negative subjects (p<0.04). Post-hoc analysis of specific gastrointestinal (GI) events (necrotizing enterocolitis, GI bleeding, gastro-esophageal reflux, and radiologic studies) did not demonstrate any specific differences between 22q11del positive and negative subjects. Of note, the number of infection-related events was not significantly different between 22q11del positive and negative subjects (p=0.17).

The number of consultations performed by other specialties was greater in 22q11del positive subjects than those without (p<0.0001), with higher rates of consultation from genetics (95% versus 61%, p<0.001), immunology (82% versus 2%, p<0.001), endocrinology (37% versus 7%, p=0.001), and ophthalmology (24% versus 4%, p=0.009) in 22q11del positive versus negative subjects. Rates of consultation for neurology (24% versus 13%, p=0.2), plastic surgery (13% versus 7%, p=0.3), urology (13% versus 4%, p=0.1), feeding team (55% versus 37% p=0.09), general surgery (21% versus 9% p=0.1), and neonatology (18% versus

11% *p=0.3*) were higher in 22q11del positive subjects but the differences were not statistically significant.

The number of discharge medications was greater in 22q11del positive as compared to negative subjects (*p*=0.0005). Analysis of medications prescribed in greater than 10% of subjects demonstrated that calcium supplements (42% in 22q11del positive subjects vs. 10% of 22q11del negative subjects p<0.001) and metoclopramide (32% in 22q11del positive subjects vs. 12% of 22q11del negative subjects) were prescribed in a higher proportion of 22q11del positive than negative subjects. Ranitidine (39% in 22q11del positive subjects, 25% in 22q11del negative subjects, *p*=0.2) had a higher rate of prescription in 22q11del positive subjects but the difference was not significant. Digoxin (*p*=1.0), and furosemide (*p*=0.3) were not prescribed at different rates between the two groups. Captopril was prescribed less frequently in 22q11del positive than negative subjects though the difference was not statistically significant (8% in 22q11del positive subjects and 24% of 22q11del negative subjects *p*=0.05). The proportion of the study population receiving oral versus tube feedings was not significantly different at discharge between subjects with 22q11del and those without 22q11del (Fisher's exact test *p*=0.4).

Effect of 22q11del on outcomes in IAA subgroup

The study population included 47 subjects with IAA and known 22q11del status, of which 44% were 22q11del positive. Admission weight was lower in 22q11del positive subjects (*p*=0.03), and type B interruption was more prevalent in 22q11del positive subjects relative to 22q11del negative subjects (100% vs. 65%, *p*<0.01). No other preoperative characteristics differed between 22q11del positive and negative subjects (Table 1). CPB time was not significantly different between those with and without 22q11del (*p*=0.21). The proportion of cases in which DHCA was used was not significantly different (*p*=0.82), but among those who underwent DHCA, DHCA time was greater in 22q11del positive subjects (*p*=0.03). Otherwise, there were no differences in the characteristics of the operations performed.

No difference in mortality was measured between 22q11del positive and negative subjects (Fisher's exact test *p*=0.70). As seen in the larger cohort, LOS (*p*=0.004), LOS if discharged home (*p*=0.01), duration of mechanical ventilation (*p*=0.007), and duration of intensive care *p*=0.02) were all greater in 22q11del positive subjects than in 22q11del negative counterparts (Table 6). The number of cardiac events and non-cardiac events were not significantly different between 22q11del positive and negative subjects. In subjects with 22q11del, the number of consults (*p*=0.0002) and medications prescribed at discharge (*p*=0.04) were higher. To assess for confounding by subtype of IAA, a subgroup analysis of subjects with type B IAA was performed with no changes in the results seen in the analysis of subjects with IAA without regard to subtype (data not shown).

Effect of 22q11del on outcomes in TA subgroup

The study population included 55 subjects with TA, 12% of whom did not have known 22q11del status. Of the 48 subjects with known 22q11del status, 40% were 22q11del positive. There was no difference in the proportion of subjects with moderate or greater truncal valve stenosis or regurgitation (*p*=0.74) or interrupted aortic arch (*p*=0.14) between

deleted and non-deleted subjects. There were no differences in operative characteristics seen between groups, specifically no differences in CPB time, proportion undergoing DHCA, and amongst those undergoing DHCA, DHCA times (Table 2). A subgroup analysis was performed to assess whether DHCA times were associated with anatomic abnormalities independent of 22q11del status. For subjects with IAA, neither anatomic anomalies of arch branching (p=0.1) nor 22q11del status (p=0.8) were associated with increased DCHA time. In subjects with TA, neither anomalous coronary branching patterns (p=0.6) nor 22q11del status (p=0.3) were associated with increased DHCA time.

In hospital mortality in subjects with and without 22q11del were not significantly different (p=0.48). Although differences in LOS (p=0.19), duration of intensive care (p=0.30), and duration of mechanical ventilation(p=0.43) between 22q11del positive and negative subjects were not statistically significant in the TA subgroup, the point estimates for each were larger in subjects with 22q11del than those without (Table 7). There were a larger number of cardiac adverse events in 22q11del positive subjects relative to 22q11del negative subjects (p=0.04). The number of consultations ordered and discharge medications prescribed were greater in subjects with 22q11del those without 22q11del (p<0.0001 and p=0.004 respectively).

Sensitivity analyses for unknown 22q11del status

For the nine subjects with unknown 22q11del status, sensitivity analyses were performed, first positing that all subjects with unknown deletion status were 22q11del positive and then positing that they all were 22q11del negative. Sensitivity analyses assuming that subjects with unknown status were 22q11del positive biased analyses towards the null but did not change the numeric trends reported in complete analyses, while analyses assuming that subjects with unknown deletion status were 22q11.2 deletion negative biased results away from the null with increased statistical significance, but again without any changes in the associations reported (Data not included).

DISCUSSION

This study identifies clinically relevant differences in perioperative outcomes between 22q11del positive and negative infants undergoing operative correction of IAA and TA. 22q11del positive subjects had longer total LOS, longer duration of mechanical ventilation, and longer duration of intensive care. They also underwent more repeat cardiac operations. Moreover, in subjects with 22q11del, utilization of non-cardiac medical resources was greater, as they underwent more consultations and were discharged on more medications. There were no differences in in-hospital mortality, nor were there significant differences in number of infections or feeding practices upon discharge. Subgroup analysis of subjects with IAA who are 22q11del positive demonstrated similarly prolonged duration of mechanical ventilation, duration of intensive care, and LOS, relative to 22q11del negative subjects. Differences in LOS, mechanical ventilation, and intensive care were not significant in subjects with TA, but point estimates remained consistent with those observed in the IAA subgroup as well as the whole study cohort. 22q11del positive subjects with either anatomic lesion experienced more postoperative cardiac events, underwent more consults, and were

discharged on a larger number of medications. We conclude that, in subjects undergoing neonatal cardiac operation, 22q11del is associated with a longer and more complex postoperative course, which are not explained by the number of infections or differences in feeding practices at discharge.

Previous studies have identified associations between anatomic features of IAA and TA and risk of perioperative mortality and morbidity, but have not identified how these are related to 22q11del. In IAA, type B anatomy has been identified as a risk factor for mortality[22]. In TA dysplastic and regurgitant truncal valve [9,23] associated arch interruption [9,23], and coronary anomalies[24] have been associated with higher short-term mortality. None of these studies assessed the association of 22q11del status and mortality. The association between 22q11del and type B interruption is well documented[20,25]. Though a small case series raised the question of whether 22q11del was associated with increased risk of dysplastic truncal valve[26], a larger population-based observational study did not find an association between 22q11del and dysplasia, stenosis, or insufficiency of the truncal valve[27] and likewise found no association between 22q11del and interruption of the aortic arch in TA[27]. To our knowledge, there are no studies demonstrating an association between coronary artery anomalies in TA and 22q11del. Distinguishing the contribution of anatomic features from deletion status for mortality and perioperative morbidity is challenging and has not been performed to date.

Studies directly assessing the association of 22q11del and perioperative mortality have been limited. Most have pooled children with heterogeneous genetic syndromes and/or cardiac diagnoses to be able to examine a larger cohort[28-30], but, in doing so, the variability in cardiac phenotype and operative strategy introduced may mask differences in outcome. At the same time, dividing these cohorts for subgroup analyses by single genetic or cardiac diagnoses has to date been limited by small sample size and the resultant potential for type II error. One study of children with tetralogy of Fallot with pulmonary atresia (pulmonary atresia with ventricular septal defect) demonstrated increased five-year mortality with most deaths occurring during hospitalizations associated with one in a sequence of operations[31]. More recently, a study focusing on children who underwent complete operative correction for tetralogy of Fallot (with or without preceding aortopulmonary shunt) found that, 22q11del was associated with longer ICU care without a significant difference in perioperative mortality[16]. These studies illustrate that sufficiently powered studies of single anatomic lesions can demonstrate that 22q11del s associated with perioperative outcomes. To our knowledge no study has assessed the role of 22q11del on perioperative outcomes following operations in infancy, nor has any study assessed outcomes specifically in subjects with TA or IAA.

In this study, no difference in early mortality was observed between 22q11del positive and negative subjects, in contrast to previously reported differences in tetralogy of Fallot with pulmonary atresia, which demonstrated an association between 22q11del and five year mortality independent of PA anatomy and presence of major aortopulmonary collaterals[31]. Meanwhile, subjects with 22q11del demonstrated prolonged duration of intensive care, duration of mechanical ventilation, and LOS compared to subjects without 22q11del. The increased number of cardiac reoperations suggests an increased burden of residual anatomic

lesions and/or cardiovascular dysfunction that may explain the longer duration of each stage of care. However, other factors may also contribute to these observations, and since these periods are nested, they may be in part related to one another. Because the current study is retrospective, it is limited in its ability to explain the underlying cause(s) of the observed differences, but for each time interval (mechanical ventilation, ICU care, and total hospital stay), several potential factors can be examined.

Duration of intensive care and mechanical ventilation are the product of multiple factors. The observed differences in our study were not the result of infectious adverse events, in which there were no differences between 22q11del positive and negative subjects. This is in contrast with earlier studies that identified immunodeficiency and associated infections as a source of tremendous morbidity and mortality[15], and consistent with more recent studies that have not observed a difference in infectious complications[16,31]. Likewise, there was no difference in non-cardiac events overall between 22q11del positive and negative subjects, and specifically no significant difference in the rate of infectious events. In our cohort, the higher rate of DHCA use and longer DHCA times and higher rate of cardiac reoperation and cardiac adverse events, are consistent with possible primary cardiac issues that prolonged intensive care and mechanical ventilation. In our analysis, neither 22q11del status nor anatomic abnormalities was an independent risk factor for DHCA time, but we acknowledge that this may be the result of type II error. These factors deserve further study.

Total LOS is influenced not only by duration of intensive care but also by events that follow intensive care. Despite our intuition, feeding issues were not different between subjects with and without 22q11del and presumably did not influence LOS. There was a significant difference in gastrointestinal events in survivors, but post hoc analysis did not demonstrate differences in specific events within this category. This category includes events across a broad range of severity and risk from potentially lethal events such as GI bleeding and necrotizing enterocolitis to relatively innocuous studies such as a barium swallow. Thus, it is unclear what the effect of the difference in GI event rate had on hospital length of stay. The incidences of other non-cardiac adverse events were not different between 22q11del positive and negative subjects. 22q11del positive subjects did undergo a greater number of subspecialty consultations and were prescribed more medications on discharge than 22q11del negative subjects. This is consistent with children undergoing operative correction of tetralogy of Fallot[16] and may indirectly implicate non-cardiac causes for prolonged LOS. These issues deserve further investigation.

Subgroup analysis of subjects with IAA and TA was performed to determine if the association of 22q11del with perioperative outcome was different in the two cardiac lesions. The association between 22q11del status and LOS, mechanical ventilation, duration of intensive care, and cardiac events remained statistically significant in the IAA subgroup. In subjects with TA, point estimates of each variable pointed to a difference between 22q11del positive and negative subjects, but these differences were not statistically significant. We would argue that since differences in point estimates in the TA subgroup are similar to those in the whole cohort, that the lack of statistical significance seen in the TA subgroup is likely the result of type II error due to small sample size. Confirmation in other studies would be helpful, but we acknowledge that this is difficult with rare conditions such as TA.

There are several additional limitations to this study. First, this retrospective study spanned a period of 13 years (1995 to 2007) with results that reflect those eras. Operations were distributed evenly across the study period (as assessed by visual inspection of histograms) whether subjects were grouped together or in subgroups by 22q11del status or anatomic lesion (data not shown). Thus, we do not anticipate that any unmeasured confounders by era should have a differential effect on comparisons between subjects with and without 22q11del. Second, the 22q11del status was not known in all cases (8.6%), which is not atypical of the era. Sensitivity analyses demonstrated that the uncertainty is increased by the introduction of missing exposure data but would not change the direction of associations observed. Third, rates of mortality were expressed as rates prior to discharge or transfer instead of mortality prior to 30 days post-operatively and prior to discharge. Sensitivity analysis using the latter definition did not demonstrate a significant difference in mortality between subjects with and without 22q11del. Sensitivity analysis assessing the effect of loss to follow-up in 5 subjects transferred to other institutions also showed no effect on the conclusion that there was no difference in mortality by 22q11del status. In addition, though the primary outcomes chosen for this study (duration of mechanical ventilation, duration of intensive care, LOS, consultations, and discharge medications) are commonly used outcomes, they are dependent on clinician choice. Outcomes were clearly defined in our study design, but ICU practice was variable with no clinical protocols guiding timing of extubation and discontinuation of vasoactive support and central lines. Whether clinicians were aware of 22q11del status and what effect that potentially had on their decision-making was not ascertainable in the current study. Finally, many events (e.g. in-hospital mortality along with individual cardiac and non-cardiac adverse events) were rare and this study is likely underpowered to detect differences in these outcomes.

In conclusion, 22q11del was associated with prolonged care in 22q11del positive subjects compared to 22q11del negative subjects suggesting an increased burden of residual cardiovascular disease and other co-morbid disease, and increased resource utilization. 22q112DS was not associated with increased perioperative mortality in infants undergoing neonatal repair of TA or IAA. These findings suggest that genotype should be taken into account as part of pre-operative risk assessment and counseling. Future studies should attempt to identify modifiable risk factors to reduce these differences.

Acknowledgments

The authors acknowledge Sharon Edman who acted as a database manager for this project. This study was supported by the National Institutes of Health [P50 HL74731] and National Center for Research Resources (Grant # UL1RR024134). Dr. O'Byrne was supported by the National Institutes of Health [T32 HL007915]. The content is solely the responsibility of the authors and does not necessarily represent the official view of the National Institutes of Health or National Center for Research Resources. The supporting agencies had no role in the design, conduct, interpretation, or decision to publish the data in this manuscript.

References

1. Peyvandi S, Lupo PJ, Garbarini J, Woyciechowski S, Edman S, Emanuel BS, et al. 22q11.2 Deletions in Patients with Conotruncal Defects: Data from 1,610 Consecutive Cases. Pediatr Cardiol. 2013 Apr 21.

2. Brown JW, Ruzmetov M, Okada Y, Vijay P, Turrentine MW. Truncus arteriosus repair: outcomes, risk factors, reoperation and management. European Journal of Cardio-Thoracic Surgery. 2001 Aug; 20(2):221–7. [PubMed: 11463535]
3. Henaine R, Azarnoush K, Belli E, Capderou A, Roussin R, Planché C, et al. Fate of the truncal valve in truncus arteriosus. The Annals of Thoracic Surgery. 2008 Jan; 85(1):172–8. [PubMed: 18154803]
4. Ebert PA, Turley K, Stanger P, Hoffman JI, Heymann MA, Rudolph AM. Surgical treatment of truncus arteriosus in the first 6 months of life. Ann Surg. 1984 Oct; 200(4):451–6. [PubMed: 6237622]
5. Kaza AK, Lim H-G, DiBardino DJ, Bautista-Hernandez V, Robinson J, Allan C, et al. Long-term results of right ventricular outflow tract reconstruction in neonatal cardiac surgery: options and outcomes. The Journal of Thoracic and Cardiovascular Surgery. 2009 Oct; 138(4):911–6. [PubMed: 19660342]
6. Urban AE, Sinzobahamvya N, Brecher AM, Wetter J, Malorny S. Truncus arteriosus: ten-year experience with homograft repair in neonates and infants. ATS. 1998 Dec; 66(6 Suppl):S183–8.
7. Lacour-Gayet F, Serraf A, Komiya T, Sousa-Uva M, Bruniaux J, Touchot A, et al. Truncus arteriosus repair: influence of techniques of right ventricular outflow tract reconstruction. The Journal of Thoracic and Cardiovascular Surgery. 1996 Apr; 111(4):849–56. [PubMed: 8614146]
8. Thompson LD, McElhinney DB, Reddy M, PETROSSIAN E, Silverman NH, Hanley FL. Neonatal repair of truncus arteriosus: continuing improvement in outcomes. ATS. 2001 Aug; 72(2):391–5.
9. Rajasinghe HA, McElhinney DB, Reddy VM, Mora BN, Hanley FL. Long-term follow-up of truncus arteriosus repaired in infancy: a twenty-year experience. The Journal of Thoracic and Cardiovascular Surgery. 1997 May; 113(5):869–78. discussion878–9. [PubMed: 9159620]
10. Jacobs JP, O'Brien SM, Pasquali SK, Jacobs ML, Lacour-Gayet FG, Tchervenkov CI, et al. Variation in outcomes for benchmark operations: an analysis of the Society of Thoracic Surgeons Congenital Heart Surgery Database. The Annals of Thoracic Surgery. 2011 Dec; 92(6):2184–91. discussion2191–2. [PubMed: 22115229]
11. Curi-Curi P, Cervantes J, Soulé M, Erdmenger J, Calderón-Colmenero J, Ramírez S. Early and midterm results of an alternative procedure to homografts in primary repair of truncus arteriosus communis. Congenital heart disease. 2010 May; 5(3):262–70. [PubMed: 20576045]
12. Russell HM, Pasquali SK, Jacobs JP, Jacobs ML, O'Brien SM, Mavroudis C, et al. Outcomes of repair of common arterial trunk with truncal valve surgery: a review of the society of thoracic surgeons congenital heart surgery database. The Annals of Thoracic Surgery. 2012 Jan; 93(1):164–9. discussion169. [PubMed: 22088417]
13. Jacobs ML, O'Brien SM, Jacobs JP, Mavroudis C, Lacour-Gayet F, Pasquali SK, et al. An empirically based tool for analyzing morbidity associated with operations for congenital heart disease. The Journal of Thoracic and Cardiovascular Surgery. 2013 Apr; 145(4):1046–1057.e1. [PubMed: 22835225]
14. Kobrynski LJ, Sullivan KE. Velocardiofacial syndrome, DiGeorge syndrome: the chromosome 22q11.2 deletion syndromes. The Lancet. 2007 Oct 20; 370(9596):1443–52.
15. Marmon LM, Balsara RK, Chen R, Dunn JM. Congenital Cardiac Anomalies Associated with the DiGeorge Syndrome: A Neonatal Experience. ATS The Society of Thoracic Surgeons. 1984 Aug 1; 38(2):146–50.
16. Mercer-Rosa L, Pinto N, Yang W, Tanel R, Goldmuntz E. 22q11.2 Deletion syndrome is associated with perioperative outcome in tetralogy of Fallot. The Journal of Thoracic and Cardiovascular Surgery. 2013 Jan 10.
17. Celoria GC, Patton RB. Congenital Absence of the Aortic Arch. American Heart Journal. 1959 Sep 1; 58(3):407–13. [PubMed: 13808756]
18. Van Praagh R, Bernhard WF, Rosenthal A, Parisi LF, Fyler DC. Interrupted Aortic Arch: Surgical Treatment. The American Journal of Cardiology. 1971 Feb 1.27:200–11. [PubMed: 5100921]
19. Van Praagh R, Van Praagh S. The Anatomy of Common Aorticopulmonary Trunk (Truncus Arteriosus Communis) and Its Embryologic Implications: A Study of 57 Necropsy Cases. American Journal of Cardiology. 1965 Sep 1.16:406–25. [PubMed: 5828135]

20. Goldmuntz E, Clark BJ, Mitchell LE, Jawad AF, Cuneo BF, Reed L, et al. Frequency of 22q11 deletions in patients with conotruncal defects. JAC. 1998 Aug; 32(2):492–8.
21. O'Brien SM, Clarke DR, Jacobs JP, Jacobs ML, Lacour-Gayet FG, Pizarro C, et al. An empirically based tool for analyzing mortality associated with congenital heart surgery. The Journal of Thoracic and Cardiovascular Surgery. 2009 Nov; 138(5):1139–53. [PubMed: 19837218]
22. McCrindle BW, Tchervenkov CI, Konstantinov IE, Williams WG, Neirotti RA, Jacobs ML, et al. Risk factors associated with mortality and interventions in 472 neonates with interrupted aortic arch: a Congenital Heart Surgeons Society study. The Journal of Thoracic and Cardiovascular Surgery. 2005 Feb; 129(2):343–50. [PubMed: 15678045]
23. Hanley FL, Heinemann MK, Jonas RA, Mayer JE, Cook NR, Wessel DL, et al. Repair of truncus arteriosus in the neonate. The Journal of Thoracic and Cardiovascular Surgery. 1993 Jun; 105(6): 1047–56. [PubMed: 8501932]
24. la Cruz de MV, Cayre R, Angelini P, Noriega-Ramos N, Sadowinski S. Coronary arteries in truncus arteriosus. AJC. 1990 Dec 15; 66(20):1482–6.
25. Marino B, Digilio MC, Persiani M, Di Donato R, Toscano A, Giannotti A, et al. Deletion 22q11 in patients with interrupted aortic arch. AJC. 1999 Aug 1; 84(3):360–1. A9.
26. Marino B, Digilio MC, Dallapiccola B. Severe truncal valve dysplasia: association with DiGeorge syndrome? ATS. 1998 Sep.66(3):980.
27. McElhinney DB, Driscoll DA, Emanuel BS, Goldmuntz E. Chromosome 22q11 deletion in patients with truncus arteriosus. Pediatr Cardiol. 2003 Nov; 24(6):569–73. [PubMed: 12947506]
28. Anaclerio S, Di Commo V, Michielon G, Digilio MC, Formigiari R, Picchio FM, et al. Contruncal heart defects: impact of genetic syndromes on immediate operative mortality. Italian Heart Journal. 2004 Dec 1; 5(8):624–8. [PubMed: 15554034]
29. McDonald R, Dodgen A, Goyal S, Gossett JM, Shinkawa T, Uppu SC, et al. Impact of 22q11.2 Deletion on the Postoperative Course of Children After Cardiac Surgery. Pediatr Cardiol. 2012 Aug 3.
30. 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. The Journal of Thoracic and Cardiovascular Surgery. 2009 Sep; 138(3):565–570.e2. [PubMed: 19698836]
31. Mahle WT, Crisalli J, Coleman K, Campbell RM, Tam VK, Vincent RN, et al. Deletion of chromosome 22q11.2 and outcome in patients with pulmonary atresia and ventricular septal defect. The Annals of Thoracic Surgery. 2003 Jul 21.:567–71. [PubMed: 12902105]

Abbreviations and acronyms

22q11del	22q11.2 deletion
CI	confidence interval
CPB	cardiopulmonary bypass
DHCA	deep hypothermic circulatory arrest
GI	gastro-intestinal
IAA	interrupted aortic arch
LOS	hospital length of stay
RR	relative risk
TA	truncus arteriosus communis

Table 1

Characteristics of subjects with interrupted aortic arch

	No deletion (N=26)	22q11 deletion (N=21)	Unknown deletion status (N=2)	*p*
Sex				
Female	42% (11)	62% (13)	0% (0)	0.24
Male	58% (15)	38% (8)	100% (2)	
Age at operation (days)	2 (0-7)	2.5 (1-8)	2 (2-2)	0.73
Race				
White	77% (20)	48% (10)	100% (2)	
Black	12% (3)	33% (7)	0% (0)	0.10
Other	12% (3)	19% (4)	0% (0)	
Gestational Age				
Full term	85% (22)	86% (18)	100% (2)	1.00
Premature	15% (4)	14% (3)		
Age at diagnosis				
Prenatal	35% (9)	38% (8)	50% (1)	1.00
Postnatal	65% (17)	62% (13)	50% (1)	
Admission weight (kg)	3.1±0.8	2.7±0.5	2.7±0.5	0.03
Feeding status at admission				
Nothing by mouth	89% (23)	95% (20)	100% (2)	0.62
Oral feedings	12% (3)	5% (1)	0% (0)	
Intubated on admission	31% (8)	38% (8)	100% (2)	0.76
Anatomic subtype				
IAA type A	35% (9)	0% (0)	50% (1)	<0.01
IAA type B	65% (17)	100% (21)	50% (1)	
Aberrant subclavian artery	31% (8)	52% (11)	50% (1)	0.13
CPB time (min)	93 (65-227)	98 (75-230)	76.5 (74-79)	0.21
DHCA	96% (25)	100% (21)	100% (2)	1.00
DHCA time (min)	41 (28-100)	52 (35-88)	34.5 (28-45)	0.03

Abbreviations: CPB, cardiopulmonary bypass time; DHCA, deep hypothermic circulatory arrest, IAA interrupted aortic arch

Table 2

Characteristics of subjects with truncus arteriosus communis

	No deletion (N=29)	22q11 deletion (N=19)	Unknown deletion status (N=7)	*p*
Gender				
Female	52% (15)	58% (11)	57% (4)	0.77
Male	48% (14)	42% (8)	43% (3)	
Age at operation	4.5 (1-124)	4.5 (2-58)	20.5 (4-43)	0.78
Race				
White	69% (20)	84% (16)	29% (2)	
Black	24% (7)	11% (2)	57% (4)	0.52
Other	7% (2)	5% (1)	14% (1)	
Gestational age				
Full term	72% (21)	79% (15)	71% (5)	0.74
Premature	28% (8)	21% (4)	29% (2)	
Timing of diagnosis				
Prenatal	45% (13)	58% (11)	43% (3)	0.56
Postnatal	55% (16)	42% (8)	57% (4)	
Admission weight (kg)	3.0 ± 0.8	2.8 ± 0.6	3.0 ± 0.6	0.26
Feeding status at admission				
Nothing by mouth	69% (20)	90% (17)	57% (4)	
Tube feedings	1 (3%)	0% (0)	0% (0)	0.47
Tube and oral feedings	1 (3%)	0% (0)	0% (0)	
Oral feedings	24% (7)	11% (2)	43% (3)	
Intubated on admission	10% (3)	21% (4)	43% (3)	0.41
Anatomic subtype				
TA type 1	52% (15)	63% (12)	57% (4)	
TA type 2	28% (8)	26% (5)	43% (3)	0.33
TA type 3	0% (0)	5% (1)	0% (0)	
TA type 4	21% (6)	5% (1)	0% (0)	
Truncal valve abnormal*	14% (4)	10% (2)	0% (0)	1.0
Interrupted aortic arch	21% (6)	5% (1)	0% (0)	0.22
Coronary anomaly (n=28)	41% (7/17)	38% (3/8)	33% (1/3)	0.6
CPB time (min)	78 (60-168)	77 (57-354)	89 (75-134)	0.82
DHCA	83% (24)	84% (16)	100% (7)	1.0
DHCA time (min)	37 (26-62)	35 (3-68)	44 (31-57)	0.40

Abbreviations: CPB, cardiopulmonary bypass time; DHCA, deep hypothermic circulatory arrest, TA, truncus arteriosus

* Truncal valve abnormality defined as moderate or greater truncal valve stenosis or regurgitation on pre-operative trans-thoracic echocardiogram.

Table 3

Outcomes in truncus arteriosus and interrupted aortic arch survivors of perioperative period with known deletion status[1]

	No deletion (N=51)	22q11 deletion (N=38)	*p*
Hospital length of stay (days) (n=89)	14 (7-58)	18 (9-103)	0.004
Hospital length of stay if discharged home[2] (days) (n= 67)	14 (8-58)	18 (9-68)	0.009
Hospital length of stay if discharged to another facility[3] (days) (n=22)	17 (7-27)	17.5 (10-103)	0.3
Duration of mechanical ventilation (hours)	74 (26-1038)	123 (22-968)	0.01
Duration of intensive care (days)[4]	4 (2-56)	7 (3-78)	0.02
Number of cardiac events	1 (0-7)	2 (0-15)	0.02
Number of non-cardiac events	1 (0-9)	2 (0-19)	0.12
Number of consults	1 (0-5)	4.5 (2-12)	<0.0001
Number of discharge medications	2 (0-10)	4 (0-8)	0.0003
Feeding status at discharge			
Nothing by mouth	2% (1)	3% (1)	
Nasogastric tube feedings	43% (22)	58% (22)	*0.37
Oral feedings	55% (28)	40% (15)	

[1] In-hospital mortality was 7% (n=4) in subjects without 22q11del and 5% (n=2) in subjects with 22q11del (Fisher's exact $p = 0.5$)

[2] Of those discharged home, 39 were 22q11del negative, 28 were 22q11del positive, and 4 had unknown 22q11del status.

[3] Of those discharged to another facility, 12 were 22q11del negative, 10 were 22q11del positive, and 1 had unknown 22q11del status.

[4] The duration of intensive care was defined as the number of days a patient received any treatment that included mechanical ventilation, infusion of a vasoactive medication, temporary pacing, or retained the original perioperative chest tube.

* Fisher's exact test

Table 4

Perioperative cardiac events in survivors of the perioperative period

	No deletion (N=51)	22q11 deletion (N=38)	*p*
Cardiac Arrest	4% (2)	13% (5)	0.11
Cardiac reoperation[1]	*14% (7)*	*37% (14)*	*0.01*
Delayed sternal closure	11% (6)	12% (5)	0.84
Extracorporeal membrane oxygenation	2% (1)	3% (1)	0.83
Pericardiocentesis	6% (3)	13% (5)	0.24
Postoperative cardiac catheterization	6% (3)	18% (7%)	0.08
Postoperative heart block	8%(4)	13% (5)	0.66
Tachyarrhythmia requiring medical treatment	16% (8)	16% (6)	0.99

[1] Re-operations: thoracic duct ligation (n=2), VSD closure (n=3), pacemaker placement (n=2), conduit replacement (n=1), and truncal root replacement (n=1). The remainder were mediastinal exploration with or without wash-out.

Table 5

Non-cardiac events in survivors of the perioperative period

		No deletion (N=51)	22q11 deletion (N=38)	*p*
Gastrointestinal[1]				
	0	88% (45)	71% (27)	0.04
	≥1	12% (6)	29% (11)	
Hematologic				
	0	94% (48)	95% (36)	0.9
	≥1	6% (3)	5% (2)	
Infectious				
	0	76% (39)	63% (25)	0.17
	≥1	24% (12)	37% (15)	
Neurologic				
	0	86% (44)	79% (30)	0.36
	≥1	14% (7)	21% (8)	
Pulmonary				
	0	88% (45)	89% (34)	0.86
	≥1	12% (6)	11% (4)	
Renal				
	0	92% (47)	100% (38)	0.08
	≥1	8% (4)	0% (0)	
Respiratory/Airway				
	0	73% (37)	55% (21)	0.21
	1	14% (7)	26% (10)	
	≥2	14% (7)	18% (7)	
Other				
	0	80% (41)	76% (29)	0.64
	≥1	20% (10)	24% (9)	

[1] GI events: necrotizing enterocolitis (n=20), barium swallow (n=15), barium enema (n=3), esophageal perforation or tear (n=2), GI bleed (n=2), and nuclear medicine milk scan (n=2). Ascites, esophagram, gastroenteritis, intestinal stricture, liver infarction, omphalocele, pH probe, rectal biopsy (n=1). No difference was seen in the rate of individual GI events by 22q11del status (data not shown).

Table 6

Outcomes in survivors with interrupted aortic arch and known 22q11del status[1]

	No deletion (N=25)	22q11 deletion (N=20)	*p*
Hospital length of stay (days) (n=45)	14 (8-58)	22 (9-59)	0.004
Hospital length of stay if discharged home (days)[2] (n=34)	14 (8-58)	25 (9-59)	0.01
Hospital length of stay if discharged to another facility (days)[3] (n=11)	13.5 (9-19)	19 (10-49)	0.19
Duration of mechanical ventilation (hours)	70 (26-1038)	135 (46-635)	0.007
Duration of intensive care (days)[4]	4 (2-56)	7 (3-48)	0.02
Number of cardiac events	1 (0-7)	2 (0-9)	0.27
Number of non-cardiac events	1 (0-9)	2 (0-13)	0.28
Number of consults	2 (1-5)	4 (2-9)	0.0001
Number of discharge medications	2 (0-4)	3 (0-8)	0.04
Feeding status at discharge			
Nothing by mouth	4% (1)	0% (0)	
Nasogastric tube feedings	48% (12)	65% (13)	0.45*
Oral feedings	48% (12)	35% (7)	

[1] In-hospital mortality was 4% (n=1) in subjects without 22q11del and 5% (n=1) in subjects with 22q11del (Fisher's exact $p = 0.7$)

[2] Of those discharged home, 19 were 22q11del negative, 15 were 22q11del positive, and 1 had unknown 22q11del status.

[3] Of those discharged to another facility, 6 were 22q11del negative, 5 were 22q11del positive, and none had unknown 22q11del status.

[4] The duration of intensive care was defined as the number of days a patient received any treatment that included mechanical ventilation, infusion of a vasoactive medication, temporary pacing, or retained the original perioperative chest tube.

* Fisher's exact test

Table 7

Outcomes in survivors with truncus arteriosus with known 22q11del status[1]

	No deletion (N=26)	22q11 deletion (N=18)	*p*
Hospital length of stay (days) (n=44)	15 (7-53)	16 (10-103)	0.19
Hospital length of stay if discharged home (days)[2] (n=33)	12.5 (8-53)	16 (10-68)	0.23
Hospital length of stay if discharged to another facility (days)[3] (n=11)	24 (7-27)	16 (13-103)	1.00
Duration of mechanical ventilation (hours)	76 (27-375)	115 (22-968)	0.43
Duration of intensive care (days)[4]	4.5 (3-44)	6 (3-78)	0.30
Number of cardiac events	1 (0-6)	2 (0-15)	0.04
Number of non-cardiac events	1 (0-8)	2 (0-19)	0.24
Number of consults	2 (0-5)	5 (2-12)	<0.0001
Number of discharge medications	2 (0-10)	4 (0-8)	0.003
Feeding status at discharge			
Nothing by mouth	0% (0)	6% (1)	
Nasogastric tube feedings	38% (10)	50% (9)	0.35*
Oral feedings	38% (16)	44% (8)	

[1] In-hospital mortality was 10% (n=3) in subjects without 22q11del and 5% (n=1) in subjects with 22q11del (Fisher's exact $p = 0.48$)

[2] Of those discharged home, 20 were 22q11del negative, 13 were 22q11del positive, and 3 had unknown 22q11del status.

[3] Of those discharged to another facility, 6 were 22q11del negative, 5 were 22q11del positive, and 1 had unknown 22q11del status.

[4] The duration of intensive care was defined as the number of days a patient received any treatment that included mechanical ventilation, infusion of a vasoactive medication, temporary pacing, or retained the original perioperative chest tube.

* Fisher's exact test