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

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Objective: The effect of genotype on the outcomes of infant cardiac operations has not been well established. The purpose of the present study was to investigate the effect 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 had undergone operative correction of TA or IAA at the Children's Hospital of Philadelphia from 1995 to 2007, comparing the perioperative outcomes (hospital length of stay, intensive care, mechanical ventilation, risk of cardiac and noncardiac 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 whom 40 (38%) were 22q11del positive. The 22q11del status was unknown in 9 (7 with TA and 2 with IAA). In patients with known deletion status, those with 22q11del had a longer hospital and intensive care length of stay. Subjects with 22q11del also required more frequent operative reintervention and more consultations and were prescribed more medications at discharge. No significant difference was found in method of feeding between those with and without 22q11del at discharge.

Conclusions: In this study, 22q11del is associated with perioperative outcomes in infants undergoing operative correction of TA and IAA, with longer hospital stays and greater resource utilization in the perioperative period. These findings should inform counseling and risk stratification and warrant additional study to identify genotype-specific management strategies to improve outcomes. (*J Thorac Cardiovasc Surg* 2014;148:1597-605)

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This study was supported by the National Institutes of Health (grant P50 HL74731) and the National Center for Research Resources (grant UL1RR024134). Dr O'Byrne was supported by the National Institutes of Health (grant 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 our report.

Disclosures: Dr Tanel has previously served for St Jude Medical, Inc, on a speaker's bureau. Dr O'Byrne reports grant support from Entelligence. All other authors have nothing to disclose with regard to commercial support.

Received for publication Oct 25, 2013; revisions received Jan 13, 2014; accepted for publication Feb 3, 2014; available ahead of print March 12, 2014.

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0022-5223/\$36.00

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<http://dx.doi.org/10.1016/j.jtcvs.2014.02.011>

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

Abbreviations and Acronyms

22q11del	= 22q11.2 deletion
CI	= confidence interval
DHCA	= deep hypothermic circulatory arrest
GI	= gastrointestinal
IAA	= interrupted aortic arch
LOS	= hospital length of stay
TA	= truncus arteriosus communis

METHODS**Study Population**

The institutional review board of the Children's Hospital of Philadelphia approved the protocol for the present study. The subjects were identified by a query of an institutional cardiothoracic surgical database. The inclusion criteria included patients undergoing primary complete operative correction of TA or IAA at the Children's Hospital of Philadelphia from January 1, 1995 to February 28, 2007. Patients with recognized genetic syndromes other than 22q11del were excluded. The diagnosis was confirmed by a review of the preoperative transthoracic echocardiographic reports. Anatomic classification of IAA^{17,18} and TA¹⁹ were performed according to previously published definitions.

Data Collection

A retrospective cohort design was chosen. The data were collected through a review of the hospital medical records. Demographic and relevant clinical information from the index hospitalization were abstracted. The reports from preoperative transthoracic echocardiograms were reviewed to confirm the diagnosis, anatomic classification, and preoperative anatomy. The cohort was divided according to 22q11del status, which was extracted from the clinical and research study records and had been determined using fluorescence in situ hybridization in accordance with standard protocols.²⁰ The outcomes of interest included in-hospital mortality and, in those who survived to discharge, hospital length of stay (LOS), intensive care duration, mechanical ventilation duration, postoperative complications, use of consulting services, feeding methods, and prescribed medications at discharge or transfer to an outside facility.

Each outcome was defined before data collection. Mortality was defined as death before hospital discharge, regardless of hospitalization LOS. Other outcomes were restricted to those who survived to discharge to eliminate disproportionate skew introduced by the subjects who had died before discharge. The LOS was determined for all subjects surviving to discharge. Because a subset of subjects was transferred to outside facilities and their outcomes after transfer were not available, leading to possible missing data, the LOS for all subjects and that for those subjects discharged to home were considered separately. The duration of intensive care was defined as the interval from between postoperative admission to the cardiac intensive care unit to (1) discontinuation of mechanical ventilation, (2) removal of chest tubes and intracardiac catheters, (3) removal of temporary pacing wires, and (4) discontinuation of any and all intravenous inotropic medications. For the purposes of analysis, the rates of these events were compared for both all cardiac events and each individual event. Cardiac events were defined as any of the following: delayed sternal closure, arrhythmias requiring medical therapy, pericardial effusions or hemopericardium drained by way of pericardiocentesis, cardiac catheterizations in the postoperative period, operative mediastinal exploration, extracorporeal membrane oxygenation, reoperation, and cardiac arrest requiring resuscitation, all before hospital discharge. Noncardiac events, including seizures confirmed by electroencephalography, infections prompting antimicrobial treatment, long-term airway management such as tracheostomy, pleural

effusions requiring mechanical drainage, number of consultations requested, and so forth were considered in 3 levels of analysis. First, all noncardiac events were pooled and considered together. Second, the noncardiac events were divided into the following categories: neurologic, gastrointestinal (GI), hematologic, infectious, airway and respiratory, pulmonary, renal, and other. Finally, post hoc, additional analyses of specific events in the noncardiac systems was performed to determine whether the rates differed between the 22q11del-positive and -negative subjects. Feeding status at discharge was classified into 1 of the following categories: parenteral nutrition, oral feeding, or feeding that involved some portion 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

The study population demographics and clinical characteristics are reported using standard summary statistics. Continuous variables are presented as the mean $\pm$ standard deviation or median and range, as appropriate. For categorical variables, the frequencies and percentages are reported. The cohort was divided by 22q11del status. The subjects with TA and IAA were first considered as a single cohort, because the 2 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, LOS, and reintervention.^{13,21} To support this analysis, subgroup analyses of TA and IAA were performed separately. For those whose 22q11del status was unknown, the baseline characteristics were summarized and sensitivity analyses performed, first positing that all subjects with unknown deletion status were 22q11del positive and then that they all were 22q11del negative.

Differences in outcomes between the 22q11del-positive and -negative groups were analyzed using the chi-square test or Fisher's exact test (with Fisher's exact test noted) for categorical variables and the Wilcoxon rank sum test for continuous variables, as applicable. $P < .05$ was considered statistically significant. All analyses were performed using StataSE, version 12.1 (StataCorp, College Station, Tex).

We had full access to, and take full responsibility for, the integrity of the data. All of us have read the report and agree to it as written.

RESULTS**Study Population**

A total of 104 subjects met the inclusion criteria (57 with TA and 47 with IAA), of whom 40 (38%) were 22q11del positive. Nine subjects (2 with IAA and 7 with TA) did not have the 22q11del status assessed. Of those with known deletion status, the proportion of subjects with 22q11del was not significantly different between those with TA and those with IAA (35% vs 45%, $P = .31$). The subjects with IAA underwent surgery at a younger age than those with TA (2 days; range, 0-8; vs 5 days; range, 1-124; $P < .0001$). Otherwise, no differences were found in the demographic and preoperative characteristics between those with IAA (Table 1) and TA (Table 2). In terms of the operative characteristics, the cardiopulmonary bypass time was longer in the patients with IAA (96 minutes; range, 65-230) than in those with TA (81 minutes; range, 57-354; $P = .02$). Also, deep hypothermic circulatory arrest (DHCA) was used in a greater proportion of subjects with IAA (98%) than with TA (85%, $P = .04$), and the DHCA

TABLE 1. Characteristics of subjects with interrupted aortic arch

Characteristic	No deletion (n = 26)	22q11del (n = 21)	Unknown deletion status (n = 2)	P value
Sex				.24
Female	42 (11)	62 (13)	0 (0)	
Male	58 (15)	38 (8)	100 (2)	
Age at operation (d)	2 (0-7)	2.5 (1-8)	2 (2-2)	.73
Race				.10
White	77 (20)	48 (10)	100 (2)	
Black	12 (3)	33 (7)	0 (0)	
Other	12 (3)	19 (4)	0 (0)	
Gestational age				1.00
Full term	85 (22)	86 (18)	100 (2)	
Premature	15 (4)	14 (3)	0 (0)	
Age at diagnosis				1.00
Prenatal	35 (9)	38 (8)	50 (1)	
Postnatal	65 (17)	62 (13)	50 (1)	
Admission weight (kg)	3.1 ± 0.8	2.7 ± 0.5	2.7 ± 0.5	.03
Feeding status at admission				.62
Nothing by mouth	89 (23)	95 (20)	100 (2)	
Oral feeding	12 (3)	5 (1)	0 (0)	
Intubated on admission	31 (8)	38 (8)	100 (2)	.76
Anatomic subtype				<.01
IAA type A	35 (9)	0 (0)	50 (1)	
IAA type B	65 (17)	100 (21)	50 (1)	
Aberrant subclavian artery	31 (8)	52 (11)	50 (1)	.13
CPB time (min)	93 (65-227)	98 (75-230)	76.5 (74-79)	.21
DHCA	96 (25)	100 (21)	100 (2)	1.00
DHCA time (min)	41 (28-100)	52 (35-88)	34.5 (28-45)	.03

Data presented as % (n), mean ± standard deviation, or median (range). 22q11del, 22q11 Deletion; IAA, interrupted aortic arch; CPB, cardiopulmonary bypass; DHCA, deep hypothermic circulatory arrest.

time, when required, was greater in the subjects with IAA (46 minutes; range, 28-100) than in those with TA (37 minutes; range, 3-68; $P = .008$). In those with IAA, the DHCA time was not independently associated with 22q11del status ($P = .8$) or the presence of coronary artery anomalies ($P = .1$). In those with TA, neither arch anomaly ($P = .6$) nor 22q11del status ($P = .3$) was independently associated with the DHCA time.

Effect of 22q11del on Perioperative Outcomes

For each of the 89 subjects with a known deletion status, the effect of 22q11del on the postoperative course was assessed (Table 3). No significant difference was found in the time spent in the hospital before surgery between those with (3 days; range, 0-124) and without (3 days; range, 1-58) 22q11del ($P = .83$). In-hospital mortality was not different between those 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, $P = .5$). Of the total cohort, 22 of 89 (25%) subjects were transferred to another facility

TABLE 2. Characteristics of subjects with truncus arteriosus communis

Characteristic	No deletion (n = 29)	22q11del (n = 19)	Unknown deletion status (n = 7)	P value
Sex				.77
Female	52 (15)	58 (11)	57 (4)	
Male	48 (14)	42 (8)	43 (3)	
Age at operation (d)	4.5 (1-124)	4.5 (2-58)	20.5 (4-43)	.78
Race				.52
White	69 (20)	84 (16)	29 (2)	
Black	24 (7)	11 (2)	57 (4)	
Other	7 (2)	5 (1)	14 (1)	
Gestational age				.74
Full term	72 (21)	79 (15)	71 (5)	
Premature	28 (8)	21 (4)	29 (2)	
Timing of diagnosis				.56
Prenatal	45 (13)	58 (11)	43 (3)	
Postnatal	55 (16)	42 (8)	57 (4)	
Admission weight (kg)	3.0 ± 0.8	2.8 ± 0.6	3.0 ± 0.6	.26
Feeding status at admission				.47
Nothing by mouth	69 (20)	90 (17)	57 (4)	
Tube feeding	1 (3)	0 (0)	0 (0)	
Tube and oral feeding	1 (3)	0 (0)	0 (0)	
Oral feeding	24 (7)	11 (2)	43 (3)	
Intubated on admission	10 (3)	21 (4)	43 (3)	.41
Anatomic subtype				.33
TA type 1	52 (15)	63 (12)	57 (4)	
TA type 2	28 (8)	26 (5)	43 (3)	
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
IAA	21 (6)	5 (1)	0 (0)	.22
Coronary anomaly (n = 28)	41 (7/17)	38 (3/8)	33 (1/3)	.6
CPB time (min)	78 (60-168)	77 (57-354)	89 (75-134)	.82
DHCA	83 (24)	84 (16)	100 (7)	1.0
DHCA time (min)	37 (26-62)	35 (3-68)	44 (31-57)	.40

Data presented as % (n), median (range), or mean ± standard deviation. 22q11del, 22q11 Deletion; TA, truncus arteriosus communis; IAA, interrupted aortic arch; CPB, cardiopulmonary bypass; DHCA, deep hypothermic circulatory arrest.

*Truncal valve abnormality defined as moderate or greater truncal valve stenosis or regurgitation on preoperative transthoracic echocardiogram.

before discharge at a median of 7 days postoperatively (range, 7-103 days). Additional information regarding 18 of these 22 subjects (88%) was available, with 17 surviving to discharge and 1 dying >120 days after transfer. No clinical records were available for 4 subjects, representing 12% of those transferred before discharge and 4.5% of the total cohort. To determine the maximum possible effect on the mortality rates, a sensitivity analysis was performed positing that the 4 subjects lost to follow-up had all died before discharge. No significant difference was found in mortality between those with and without 22q11del (data not shown). This was true for the entire cohort and in the

TABLE 3. Outcomes in truncus arteriosus and interrupted aortic arch survivors of perioperative period with known deletion status*

Variable	No deletion (n = 51)	22q11del (n = 38)	P value
Hospital LOS (d) (n = 89)	14 (7-58)	18 (9-103)	.004
Hospital LOS if discharged home† (d) (n = 67)	14 (8-58)	18 (9-68)	.009
Hospital LOS if discharged to another facility‡ (d) (n = 22)	17 (7-27)	17.5 (10-103)	.3
Duration of mechanical ventilation (h)	74 (26-1038)	123 (22-968)	.01
Intensive care duration (d)§	4 (2-56)	7 (3-78)	.02
Cardiac events (n)	1 (0-7)	2 (0-15)	.02
Noncardiac events (n)	1 (0-9)	2 (0-19)	.12
Consultations (n)	1 (0-5)	4.5 (2-12)	<.0001
Discharge medications (n)	2 (0-10)	4 (0-8)	.0003
Feeding status at discharge			.37
Nothing by mouth	2 (1)	3 (1)	
Nasogastric tube feeding	43 (22)	58 (22)	
Oral feeding	55 (28)	40 (15)	

Data presented as median (range) or % (n). 22q11del, 22q1 Deletion; LOS, length of stay. *In-hospital mortality was 7% (n = 4) in subjects without 22q11del and 5% (n = 2) in subjects with 22q11del (Fisher's exact test, $P = .5$). †Of those discharged home, 39 were 22q11del negative, 28 were 22q11del positive, and 4 had unknown 22q11del status. ‡Of those discharged to another facility, 12 were 22q11del negative, 10 were 22q11del positive, and 1 had unknown 22q11del status. §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.

separate subgroup analyses of the subjects with IAA and TA.

The LOS in the survivors was greater in the 22q11del-positive subjects than in the 22q11del-negative subjects (18 days; range, 2-103; vs 14 days; range, 17-96; $P = .02$; Table 3). Subgroup analyses of the subjects who were discharged home also demonstrated a longer LOS in 22q11del-positive subjects ($P = .009$). However, for those transferred to another institution (rather than discharged directly home), the LOS at our institution was not

TABLE 4. Perioperative cardiac events in survivors of the perioperative period

Event	No deletion (n = 51)	22q11del (n = 38)	P value
Cardiac arrest	4 (2)	13 (5)	.11
Cardiac reoperation*	14 (7)	37 (14)	.01†
Delayed sternal closure	11 (6)	12 (5)	.84
Extracorporeal membrane oxygenation	2 (1)	3 (1)	.83
Pericardiocentesis	6 (3)	13 (5)	.24
Postoperative cardiac catheterization	6 (3)	18 (7)	.08
Postoperative heart block	8 (4)	13 (5)	.66
Tachyarrhythmia requiring medical treatment	16 (8)	16 (6)	.99

Data presented as % (n). 22q11del, 22q1 Deletion. *Reoperations included thoracic duct ligation in 2, ventricular septal defect closure in 3, pacemaker placement in 2, conduit replacement in 1, and truncal root replacement in 1; the remainder were mediastinal exploration with or without washout. †Statistically significant.

significantly different ($P = .32$). 22q11del was associated with a longer mechanical ventilation duration (123 hours; range, 22-968; vs 74 hours; range, 26-1038, $P = .01$) and longer intensive care duration (7 days; range, 3-48; vs 4 days; range, 2-56; $P = .02$).

In addition, the 22q11del-positive subjects experienced more cardiac adverse events than did their 22q11del-negative counterparts ($P = .02$; Table 3) and were at greater risk of cardiac reoperation (relative risk, 2.7; 95% CI, 1.2-6.0; $P = .01$; Table 4). The total number of noncardiac events was not increased in subjects with 22q11del ($P = .12$; Table 5). When the noncardiac events were divided by system, only GI events were more common in the 22q11del-positive than in the 22q11del-negative subjects ($P < .04$). The post hoc analysis of specific GI events (necrotizing enterocolitis, GI bleeding, gastroesophageal reflux, and radiologic studies) did not demonstrate any specific differences between 22q11del-positive and -negative subjects. The number of infection-related events was not significantly different between the 22q11del-positive and -negative subjects ($P = .17$).

TABLE 5. Noncardiac events in survivors of the perioperative period

Event	No deletion (n = 51)	22q11del (n = 38)	P value
Gastrointestinal*			.04
0	88 (45)	71 (27)	
≥1	12 (6)	29 (11)	
Hematologic			.9
0	94 (48)	95 (36)	
≥1	6 (3)	5 (2)	
Infectious			.17
0	76 (39)	63 (25)	
≥1	24 (12)	37 (15)	
Neurologic			.36
0	86 (44)	79 (30)	
≥1	14 (7)	21 (8)	
Pulmonary			.86
0	88 (45)	89 (34)	
≥1	12 (6)	11 (4)	
Renal			.08
0	92 (47)	100 (38)	
≥1	8 (4)	0 (0)	
Respiratory/airway			.21
0	73 (37)	55 (21)	
1	14 (7)	26 (10)	
≥2	14 (7)	18 (7)	
Other			.64
0	80 (41)	76 (29)	
≥1	20 (10)	24 (9)	

Data presented as % (n). 22q11del, 22q1 Deletion. *Gastrointestinal events included necrotizing enterocolitis in 20, barium swallow in 15, barium enema in 3, esophageal perforation or tear in 2, gastrointestinal bleeding in 2, and nuclear medicine milk scan in 2, and ascites, esophagram, gastroenteritis, intestinal stricture, liver infarction, omphalocele, pH probe, and rectal biopsy in 1 each. No difference was seen in the rate of individual gastrointestinal events by 22q11 deletion status (data not shown).

TABLE 6. Outcomes in survivors with interrupted aortic arch and known 22q11 deletion status*

Variable	No deletion (n = 25)	22q11del (n = 20)	P value
Hospital LOS (d) (n = 45)	14 (8-58)	22 (9-59)	.004
Hospital LOS if discharged home (d)† (n = 34)	14 (8-58)	25 (9-59)	.01
Hospital LOS if discharged to another facility (d)‡ (n = 11)	13.5 (9-19)	19 (10-49)	.19
Mechanical ventilation duration (h)	70 (26-1038)	135 (46-635)	.007
Intensive care duration (d)§	4 (2-56)	7 (3-48)	.02
Cardiac events (n)	1 (0-7)	2 (0-9)	.27
Noncardiac events (n)	1 (0-9)	2 (0-13)	.28
Consultations (n)	2 (1-5)	4 (2-9)	.0001
Discharge medications (n)	2 (0-4)	3 (0-8)	.04
Feeding status at discharge			.45
Nothing by mouth	4 (1)	0 (0)	
Nasogastric tube feeding	48 (12)	65 (13)	
Oral feeding	48 (12)	35 (7)	

Data presented as median (range) or % (n). 22q11del, 22q1 Deletion; LOS, length of stay. *In-hospital mortality was 4% (n = 1) in subjects without 22q11 deletion and 5% (n = 1) in subjects with 22q11 deletion (Fisher’s exact test, $P = .7$). †Of those discharged home, 19 were 22q11del negative, 15 were 22q11del positive, and 1 had unknown 22q11del status. ‡Of those discharged to another facility, 6 were 22q11del negative, 5 were 22q11del positive, and none had unknown 22q11del status. §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.

The number of consultations performed by other specialties was greater in the 22q11del-positive subjects than in those without ($P < .0001$), with greater rates of consultation from genetics (95% vs 61%, $P < .001$), immunology (82% vs 2%, $P < .001$), endocrinology (37% vs 7%, $P = .001$), and ophthalmology (24% vs 4%, $P = .009$) in 22q11del-positive versus -negative subjects. The rates of consultation for neurology (24% vs 13%, $P = .2$), plastic surgery (13% vs 7%, $P = .3$), urology (13% vs 4%, $P = .1$), feeding team (55% vs 37%, $P = .09$), general surgery (21% vs 9%, $P = .1$), and neonatology (18% vs 11%, $P = .3$) were greater in the 22q11del-positive subjects but the differences were not statistically significant.

The number of discharge medications was greater in the 22q11del-positive patients compared with the 22q11del-negative subjects ($P = .0005$). An analysis of medications prescribed in >10% of subjects demonstrated that calcium supplements (42% of 22q11del-positive subjects vs 10% of 22q11del-negative subjects, $P < .001$) and metoclopramide (32% of 22q11del-positive subjects vs 12% of 22q11del-negative subjects) were prescribed to a greater proportion of 22q11del-positive than 22q11del-negative subjects. Ranitidine (39% of 22q11del-positive subjects and 25% of 22q11del-negative subjects, $P = .2$) had a greater rate of prescription in 22q11del-positive subjects but the difference was not significant. Digoxin ($P = 1.0$) and

TABLE 7. Outcomes in survivors with truncus arteriosus with known 22q11del status*

Variable	No deletion (n = 26)	22q11del (n = 18)	P value
Hospital LOS (d) (n = 44)	15 (7-53)	16 (10-103)	.19
Hospital LOS if discharged home (d)† (n = 33)	12.5 (8-53)	16 (10-68)	.23
Hospital LOS if discharged to another facility (d)‡ (n = 11)	24 (7-27)	16 (13-103)	1.00
Mechanical ventilation duration (h)	76 (27-375)	115 (22-968)	.43
Intensive care duration (d)§	4.5 (3-44)	6 (3-78)	.30
Cardiac events (n)	1 (0-6)	2 (0-15)	.04
Noncardiac events (n)	1 (0-8)	2 (0-19)	.24
Consultations (n)	2 (0-5)	5 (2-12)	<.0001
Discharge medications (n)	2 (0-10)	4 (0-8)	.003
Feeding status at discharge			.35
Nothing by mouth	0 (0)	6 (1)	
Nasogastric tube feeding	38 (10)	50 (9)	
Oral feeding	62 (16)	44 (8)	

Data presented as median (range) or % (n). 22q11del, 22q1 Deletion; LOS, length of stay. *In-hospital mortality was 10% (n = 3) in subjects without 22q11del and 5% (n = 1) in subjects with 22q11del (Fisher’s exact test, $P = .48$). †Of those discharged home, 20 were 22q11del negative, 13 were 22q11del positive, and 3 had unknown 22q11del status. ‡Of those discharged to another facility, 6 were 22q11del negative, 5 were 22q11del positive, and 1 had unknown 22q11del status. §The intensive care duration 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.

furosemide ($P = .3$) were not prescribed at different rates between the 2 groups. Captopril was prescribed less frequently in the 22q11del-positive than in the 22q11del-negative subjects, although the difference was not statistically significant (8% of 22q11del-positive subjects and 24% of 22q11del-negative subjects, $P = .05$). The proportion of the study population receiving oral versus tube feedings was not significantly different at discharge between those with 22q11del and those without (Fisher’s exact test, $P = .4$).

Effect of 22q11del on Outcomes in IAA Subgroup

The study population included 47 subjects with IAA and known 22q11del status, of whom 44% were 22q11del positive. The admission weight was lower in the 22q11del-positive subjects ($P = .03$) and type B interruption was more prevalent relative to the 22q11del-negative subjects (100% vs 65%; $P < .01$). No other preoperative characteristics differed between the 22q11del-positive and -negative subjects (Table 1). The cardiopulmonary bypass time was not significantly different between those with and without 22q11del ($P = .21$). The proportion of patients for whom DHCA was used was not significantly different ($P = .82$); however, among those who underwent DHCA, the DHCA time was greater in 22q11del-positive subjects ($P = .03$). Otherwise, no differences were found in the characteristics of the operations performed.

No difference in mortality was measured between the 22q11del-positive and -negative subjects (Fisher's exact test, $P = .70$). Just as was seen in the larger cohort, the LOS ($P = .004$), LOS if discharged home ($P = .01$), duration of mechanical ventilation ($P = .007$), and intensive care duration ($P = .02$) were all greater for the 22q11del-positive subjects than in their 22q11del-negative counterparts (Table 6). The number of cardiac events and noncardiac events was not significantly different between the 22q11del-positive and -negative subjects. In subjects with 22q11del, the number of consultations ($P = .0002$) and number of medications prescribed at discharge ($P = .04$) were greater. To assess for confounding by the subtype of IAA, a subgroup analysis of those 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. No difference was found in the proportion of subjects with moderate or greater truncal valve stenosis or regurgitation ($P = .74$) or an IAA ($P = .14$) between the deleted and nondelivered subjects. No differences were found in the operative characteristics between the groups. Specifically, no differences in cardiopulmonary bypass time, proportion undergoing DHCA, and, among those undergoing DHCA, DHCA times were found (Table 2). A subgroup analysis was performed to assess whether the DHCA times were associated with anatomic abnormalities independent of 22q11del status. For subjects with IAA, neither the anatomic anomalies of arch branching ($P = .1$) nor 22q11del status ($P = .8$) was associated with increased DHCA time. In subjects with TA, neither anomalous coronary branching patterns ($P = .6$) nor 22q11del status ($P = .3$) was associated with an increased DHCA time.

In-hospital mortality in subjects with and without 22q11del was not significantly different ($P = .48$). Although the differences in the LOS ($P = .19$), intensive care duration ($P = .30$), and mechanical ventilation duration ($P = .43$) between the 22q11del-positive and -negative subjects were not statistically significant in the TA subgroup, the point estimates for each were larger in those with 22q11del than in those without (Table 7). A greater number of cardiac adverse events occurred in 22q11del-positive subjects relative to 22q11del-negative subjects ($P = .04$). The number of consultations ordered and number of discharge medications prescribed were greater in those with 22q11del than in those without 22q11del ($P < .0001$ and $P = .004$, respectively).

Sensitivity Analyses for Unknown 22q11del Status

For the 9 subjects with an unknown 22q11del status, sensitivity analyses were performed, first positing that all

subjects with unknown deletion status were 22q11del positive and then that they all were 22q11del negative. Sensitivity analyses assuming that the subjects with unknown status were 22q11del positive biased the analyses toward the null but did not change the numeric trends reported in the complete analyses. Also, the analyses assuming that subjects with unknown deletion status were 22q11del negative biased the results away from the null, with increased statistical significance, but again without any changes in the associations reported (data not shown).

DISCUSSION

The present study has identified clinically relevant differences in perioperative outcomes between the 22q11del-positive and -negative infants undergoing operative correction of IAA and TA. The 22q11del-positive subjects required a longer total LOS, longer mechanical ventilation duration, and longer intensive care duration. They also underwent more repeat cardiac operations. Moreover, in the subjects with 22q11del, the use of noncardiac medical resources was greater, because they underwent more consultations and were discharged with more medications. No differences were found in the in-hospital mortality, nor were significant differences found in the number of infections or feeding practices on discharge. The subgroup analysis of subjects with IAA who were 22q11del positive demonstrated a similarly prolonged mechanical ventilation duration, intensive care duration, and LOS, relative to the 22q11del-negative subjects. The differences in LOS, mechanical ventilation, and intensive care were not significant in the subjects with TA; however, the point estimates remained consistent with those observed in the IAA subgroup and the whole study cohort. The 22q11del-positive subjects with either anatomic lesion experienced more postoperative cardiac events, underwent more consultations, and were discharged with a larger number of medications. We have concluded that, in subjects undergoing neonatal cardiac surgery, 22q11del was associated with a longer and more complex postoperative course that was not explained by the number of infections or differences in feeding practices at discharge.

Previous studies have identified associations between the anatomic features of IAA and TA and the risk of perioperative mortality and morbidity; however, they did not identify how these are related to 22q11del. In IAA, type B anatomy has been identified as a risk factor for mortality.²² In TA, a dysplastic and regurgitant truncal valve,^{9,23} associated arch interruption,^{9,23} and coronary anomalies²⁴ have been associated with greater short-term mortality. None of these studies assessed the association of 22q11del status and mortality. The association between 22q11del and type B interruption has been well documented.^{20,25} Although a small case series raised the

question of whether 22q11del was associated with an 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 Likewise, the study found no association between 22q11del and interruption of the aortic arch in patients with TA.²⁷ To our knowledge, no studies have demonstrated 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 yet been performed.

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 cohort²⁸⁻³⁰; however, in doing so, the variability in cardiac phenotype and operative strategy introduced could have masked differences in the outcome. Also, dividing these cohorts for subgroup analyses by a single genetic or cardiac diagnosis has been limited by the small sample sizes and the resultant potential for a type II error. One study of children with tetralogy of Fallot with pulmonary atresia (pulmonary atresia with ventricular septal defect) demonstrated increased 5-year mortality, with most deaths occurring during hospitalizations in association with one in a sequence of operations.³¹ More recently, a study focusing on children who had undergone complete operative correction for tetralogy of Fallot (with or without preceding aortopulmonary shunt) found that 22q11del was associated with longer intensive care stays without a significant difference in perioperative mortality.¹⁶ These studies have illustrated that sufficiently powered studies of single anatomic lesions can demonstrate that 22q11del is associated with perioperative outcomes. To our knowledge, no study has assessed the role of 22q11del on perioperative outcomes after operations in infancy, nor has any study assessed the outcomes specifically in subjects with TA or IAA.

In the present 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 5-year mortality independent of pulmonary atresia anatomy and presence of major aortopulmonary collaterals.³¹ In our study, the subjects with 22q11del required a prolonged intensive care duration, mechanical ventilation duration, and LOS than the subjects without 22q11del. The increased number of cardiac reoperations suggested an increased burden of residual anatomic lesions and/or cardiovascular dysfunction that could explain the longer duration of each stage of care. However, other factors could also contribute to these observations, and, because these periods were

nested, they might be, in part, related to one another. Because the present study was retrospective, it was limited in its ability to explain the underlying cause or causes of the observed differences. However, for each interval (eg, mechanical ventilation, intensive care, and total hospital stay), several potential factors can be examined.

The intensive care and mechanical ventilation duration are the product of multiple factors. The observed differences in our study were not the result of infectious adverse events, for which no differences were found between the 22q11del-positive and -negative subjects. This is in contrast to earlier studies that identified immunodeficiency and associated infections as a source of tremendous morbidity and mortality¹⁵ and consistent with more recent studies that have not observed a difference in infectious complications.^{16,31} Likewise, no difference was found in the incidence of noncardiac events overall between the 22q11del-positive and -negative subjects. Specifically, no significant difference was found in the rate of infectious events. In our cohort, the greater rate of DHCA use and longer DHCA times and greater rate of cardiac reoperation and cardiac adverse events were consistent with possible primary cardiac issues that prolonged the intensive care stay and mechanical ventilation. In our analysis, neither 22q11del status nor anatomic abnormalities was an independent risk factor for DHCA time; however, we acknowledge that could have resulted from a type II error. These factors deserve additional study.

The total LOS was influenced, not only by the duration of intensive care, but also by the events that occurred after the intensive care stay. Despite our intuition, feeding issues were not different between those with and without 22q11del and presumably did not influence the LOS. A significant difference was found in the incidence of GI events in survivors; however, the post hoc analysis did not demonstrate differences in the specific events within this category. This category included 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 test. Thus, it is unclear what the effect of the difference in the GI event rate had on the hospital LOS. The incidence of the other noncardiac adverse events was not different between the 22q11del-positive and -negative subjects. The 22q11del positive subjects did undergo a greater number of subspecialty consultations and were prescribed more medications at discharge than the 22q11del-negative subjects. This is consistent with children undergoing operative correction of tetralogy of Fallot¹⁶ and might indirectly implicate noncardiac causes for the prolonged LOS. These issues deserve additional investigation.

A subgroup analysis of subjects with IAA and TA was performed to determine whether the association of

22q11del with perioperative outcomes was different for the 2 cardiac lesions. The association between 22q11del status and LOS, mechanical ventilation duration, intensive care duration, and cardiac events remained statistically significant in the IAA subgroup. In subjects with TA, the point estimates of each variable pointed to a difference between the 22q11del-positive and -negative subjects; however, these differences were not statistically significant. We would argue that because the differences in the point estimates in the TA subgroup were similar to those in the whole cohort, the lack of statistical significance seen in the TA subgroup was likely the result of a type II error owing to the small sample size. Confirmation in other studies would be helpful; however, we acknowledge that this would be difficult with rare conditions such as TA.

The present study had several additional limitations. First, our retrospective study spanned a period of 13 years (1995 to 2007) with results that reflect those eras. The operations were distributed evenly across the study period (as assessed by visual inspection of histograms) whether the 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 had a differential effect on the comparisons between the subjects with and without 22q11del. Second, the 22q11del status was not known in all cases (8.6%), which was not atypical of the era. Sensitivity analyses demonstrated that the uncertainty was increased by the introduction of missing exposure data but would not change the direction of the associations observed. Third, the rates of mortality were expressed as rates before discharge or transfer instead of mortality before 30 days postoperatively and before discharge. A sensitivity analysis using the latter definition did not demonstrate a significant difference in mortality between those with and without 22q11del. A sensitivity analysis assessing the effect of loss to follow-up for the 5 subjects transferred to other institutions also showed no effect on the conclusion that no difference was present in mortality by 22q11del status. In addition, although the primary outcomes chosen for the present study (mechanical ventilation duration, intensive care duration, LOS, and number of consultations and discharge medications) are commonly used outcomes, they were dependent on clinician choice. The outcomes were clearly defined in our study design; however, the intensive care practice varied, with no clinical protocols guiding the timing of extubation and discontinuation of vasoactive support and central catheters. Whether the clinicians were aware of 22q11del status and what effect that potentially had on their decision-making was not ascertainable in our study. Finally, many events (eg, in-hospital mortality and individual cardiac and noncardiac adverse events) were rare, and ours was likely underpowered to detect differences in these outcomes.

CONCLUSIONS

In this study, 22q11del was associated with prolonged care in the 22q11del-positive subjects compared with the 22q11del-negative subjects, suggesting an increased burden of residual cardiovascular disease and other comorbid disease and increased resource usage. Also, 22q112 deletion syndrome was not associated with increased perioperative mortality in infants undergoing neonatal repair of TA or IAA. These findings suggest that the genotype should be taken into account as a part of the preoperative risk assessment and counseling. Future studies should attempt to identify modifiable risk factors to reduce these differences.

The authors acknowledge Sharon Edman, who acted as a database manager for this project.

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;34:1687-94.
2. Brown JW, Ruzmetov M, Okada Y, Vijay P, Turrentine MW. Truncus arteriosus repair: outcomes, risk factors, reoperation and management. *Eur J Cardiothorac Surg*. 2001;20:2210-7.
3. Henaine R, Azarnoush K, Belli E, Capderou A, Roussin R, Planché C, et al. Fate of the truncal valve in truncus arteriosus. *Ann Thorac Surg*. 2008;85:172-8.
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;200:451-6.
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. *J Thorac Cardiovasc Surg*. 2009;138:911-6.
6. Urban AE, Sinzobahamvya N, Brecher AM, Wetter J, Malorny S. Truncus arteriosus: ten-year experience with homograft repair in neonates and infants. *Ann Thorac Surg*. 1998;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. *J Thorac Cardiovasc Surg*. 1996;111:849-56.
8. Thompson LD, McElhinney DB, Reddy M, Petrossian E, Silverman NH, Hanley FL. Neonatal repair of truncus arteriosus: continuing improvement in outcomes. *Ann Thorac Surg*. 2001;72:391-5.
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. *J Thorac Cardiovasc Surg*. 1997;113:869-78; discussion 878-9.
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. *Ann Thorac Surg*. 2011;92:2184-91; discussion 2191-2.
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. *Congenit Heart Dis*. 2010;5:262-70.
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. *Ann Thorac Surg*. 2012;93:164-9; discussion 169.
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. *J Thorac Cardiovasc Surg*. 2013;145:1046-57.e1.
14. Kobrynski LJ, Sullivan KE. Velocardiofacial syndrome, DiGeorge syndrome: the chromosome 22q11.2 deletion syndromes. *Lancet*. 2007;370:1443-52.
15. Marmon LM, Balsara RK, Chen R, Dunn JM. Congenital cardiac anomalies associated with the DiGeorge syndrome: a neonatal experience. *Ann Thorac Surg*. 1984;38:146-50.

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. *J Thorac Cardiovasc Surg.* 2013;146:868-73.
17. Celoria GC, Patton RB. Congenital absence of the aortic arch. *Am Heart J.* 1959; 58:407-13.
18. Van Praagh R, Bernhard WF, Rosenthal A, Parisi LF, Fyler DC. Interrupted aortic arch: surgical treatment. *Am J Cardiol.* 1971;27:200-11.
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. *Am J Cardiol.* 1965;16:406-25.
20. Goldmuntz E, Clark BJ, Mitchell LE, Jawad AF, Cuneo BF, Reed L, et al. Frequency of 22q11 deletions in patients with conotruncal defects. *J Am Cardiol.* 1998;32:492-8.
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. *J Thorac Cardiovasc Surg.* 2009;138:1139-53.
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. *J Thorac Cardiovasc Surg.* 2005;129:343-50.
23. Hanley FL, Heinemann MK, Jonas RA, Mayer JE, Cook NR, Wessel DL, et al. Repair of truncus arteriosus in the neonate. *J Thorac Cardiovasc Surg.* 1993; 105:1047-56.
24. de la Cruz MV, Cayre R, Angelini P, Noriega-Ramos N, Sadowinski S. Coronary arteries in truncus arteriosus. *Am J Cardiol.* 1990;66:1482-6.
25. Marino B, Digilio MC, Persiani M, Di Donato R, Toscano A, Giannotti A, et al. Deletion 22q11 in patients with interrupted aortic arch. *Am J Cardiol.* 1999;84: 360-1. A9.
26. Marino B, Digilio MC, Dallapiccola B. Severe truncal valve dysplasia: association with DiGeorge syndrome? *Ann Thorac Surg.* 1998;66:980.
27. McElhinney DB, Driscoll DA, Emanuel BS, Goldmuntz E. Chromosome 22q11 deletion in patients with truncus arteriosus. *Pediatr Cardiol.* 2003;24: 569-73.
28. Anaclerio S, Di Commo V, Michielon G, Digilio MC, Formigari R, Picchio FM, et al. Conotruncal heart defects: impact of genetic syndromes on immediate operative mortality. *Italian Heart J.* 2004;5:624-8.
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.* 2013;34:341-7.
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. *J Thorac Cardiovasc Surg.* 2009;138: 565-70.e2.
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. *Ann Thorac Surg.* 2003;76:567-71.