Congenital Heart Surgery on In-Hospital Mortality in Trisomy 13 and 18

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abstract

BACKGROUND AND OBJECTIVES: Congenital heart disease (CHD) is common in trisomy 13 (T13) and trisomy 18 (T18), but surgical repair has not been offered in most centers. Data on outcomes of congenital heart surgery (CHS) for T13 and T18 are lacking. We sought to determine the impact of CHS on in-hospital mortality in T13 and T18.

METHODS: Data from the 2004 to 2015 Pediatric Health Information System database were used to identify inpatients with T13 or T18 and CHD. Data were restricted to newborns with T13 or T18 admitted at ≤14 days of age. Hospital readmissions were examined to analyze longer-term in-hospital mortality. In-hospital mortality and length of stay were compared between infants with and without CHD and with and without CHS.

RESULTS: The study cohort included 1020 infants with T18 and 648 infants with T13. CHD was present in 91% of infants with T18 and 86% of infants with T13. CHS was performed in 7% of each group. In-hospital mortality was decreased in those who underwent CHS (64% lower in T18 [P <.001]; 45% lower in T13 [P = .003]) and remained decreased throughout the 24 months of follow-up. In-hospital mortality was decreased in infants with higher weight, female sex, and older age at admission.

CONCLUSIONS: CHS is associated with decreased in-hospital mortality in T18 and T13. These results suggest CHS may be beneficial in select cases.

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WHAT'S KNOWN ON THIS SUBJECT: Congenital heart disease is exceedingly prevalent in trisomy 13 (T13) and trisomy 18 (T18). Smaller studies evaluating surgical versus medical management in T13 and T18 have shown lower mortality and higher postoperative survival beyond 1 year in surgical groups.

WHAT THIS STUDY ADDS: At a time when many centers elect not to perform congenital heart surgery in T13 and T18, the current study reveals that congenital heart surgery decreases in-hospital mortality by over 50%, and the effect remains consistent out to 24 months.

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Trisomy 18 (T18) and trisomy 13 (T13) are the second and third most common aneuploidies in humans, respectively, after trisomy 21 (T21).[1] Both carry a grave prognosis and are generally considered lethal syndromes. The median survival duration is 5 to 13 days for T13 and, similarly, 6 to 15 days for T18.[2–4] Multiple congenital anomalies are the rule in both T18 and T13, with cardiac lesions being highly prevalent.

Congenital heart disease (CHD) occurs in up to 90% of patients with T18[5] and in up to 80% of patients with T13.[6] Septal defects, whether atrial or ventricular, and patent ductus arteriosus make up the majority of CHD cases in these groups.[3] More complex CHD cases, such as double outlet right ventricle, complete atrioventricular canal defect, hypoplastic left heart syndrome, transposition of the great arteries, and coarctation of the aorta, are not uncommon.[6,7] At present, because of the markedly short life expectancy associated with the condition, the management of CHD is typically limited to medical strategies in these patients. Palliative congenital heart surgery (CHS) in patients with T18 and T13 has been reported, with some centers having described complete repair.[8–10] However, data on outcomes after CHS in these patients are lacking. We sought to determine if CHS impacts in-hospital mortality in patients with either T18 or T13.

METHODS

Study Population

With the approval of the institutional review board of the University of Arkansas for Medical Sciences, data were obtained from the Pediatric Health Information System (PHIS), a large, inpatient administrative database of 44 participating children's hospitals in the Child Health Corporation of America, a children's hospital consortium. The PHIS data include detailed, deidentified information on each inpatient's demographics, diagnoses, procedures, medications, and outcomes. Data quality assurance is ongoing and data from individual hospitals are accepted when classified errors for a given quarter occur less frequently than a criterion threshold of 2%. The study design was a multicentered, retrospective cohort investigation of all patients cared for in children's hospitals participating in the PHIS. Inclusion criteria were patients who were ≤14 days of age at the time of admission and an *International Classification of Diseases, Ninth Revision* (ICD-9) code for CHD and either T13 (ICD-9: 758.1) or T18 (ICD-9: 758.2). The admission age of ≤14 days was used because reported median survival duration in both groups is <14 days. Data were limited to the time period from January 1, 2004, to September 31, 2015. Patients were excluded if they had a diagnosis of both T13 and T18, an additional diagnosis of T21, or a second admission within 14 days of life.

Data queried from the PHIS included demographic variables, principal and secondary diagnosis codes, admission to the ICU, mechanical ventilation, procedures performed, duration of hospital length of stay (LOS), and survival to hospital discharge. Principal diagnoses were grouped into categories on the basis of organ systems. Those patients who did not undergo any procedure of any type were defined as patients who received comfort care. Hospital-specific patient identifiers were used to examine longer-term in-hospital mortality in subsequent hospital admissions.

Statistical Analysis

Descriptive statistics were summarized as the mean ± the SD or as the median with interquartile ranges (IQRs) for continuous variables and count (percentage) for categorical variables when appropriate. Mann–Whitney *U* tests were used to compare continuous variables between groups. Pearson tests were used to compare categorical variables between groups. Multivariable logistic regression was used to predict the odds of mortality in the CHS and no CHS groups, while adjusting for age at admission (days), sex, birth weight (kg), and hospital volume. Kaplan-Meier analysis was used to determine freedom from in-hospital mortality. A statistical significance is indicated when *P* values are <.05. For paired analysis, the *P* values were adjusted for multiple comparisons by using Bonferroni correction. All analyses were completed by using statistical software R version 3.2.5 (R Foundation, Vienna, Austria).

RESULTS

We identified 3553 patients with T18 and T13, of whom 1668 were ≤14 days of age at the time of admission and composed the study groups. There were 1020 infants in the T18 group and 648 infants in the T13 group (Fig 1). For both groups, the median age at admission was <1 day (IQR: 0–1). Of the 1020 infants with T18, 925 had CHD (91%). Of the 648 infants with T13, 555 had CHD (86%). Septal defects (atrial and ventricular) and patent ductus arteriosus represented the vast majority of CHD cases. In both T18 and T13, CHS was performed in 7% of patients with CHD. The distributions of CHD and CHS are demonstrated in Fig 2.

In those patients with CHD, mortality was highest during the first hospital admission (63%). Overall, 51% of the total sample population (*N* = 1480) either died in the hospital or were discharged and transferred to hospice. In those patients undergoing CHS, the median LOS before CHS (in cases of multiple heart surgeries,

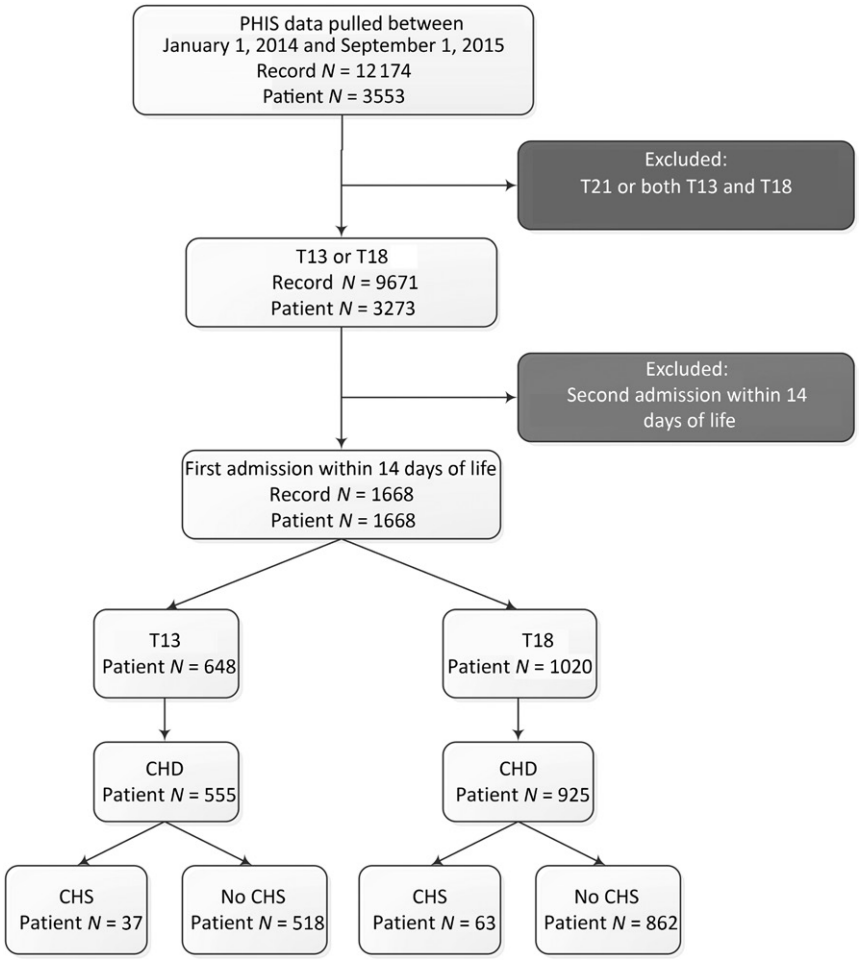

FIGURE 1

T13 and T18 analytical sample. Steps used to derive the analytical sample are shown. Subjects were excluded if they had a diagnosis of T21, a diagnosis of both T13 and T18, or if they were readmitted to the hospital within 14 days of life.

the date of the last surgery was used) was 5 days (IQR: 2–10) in T13 and 7 days (IQR: 3–34) in T18 (Supplemental Table 4). For those patients who did not undergo CHS, the median age at last follow-up was 10 days (IQR: 5–34) for T13 and 15 days (IQR: 5–82) for T18. Among patients who underwent CHS, the median age at last follow-up was 141 days (IQR: 46–571) for T13 and 278 days (IQR: 63–1029) for T18.

In-hospital mortality was significantly lower in those patients who underwent CHS (Tables 1 and 2). Multivariate analysis revealed decreased mortality in both the T18 CHS group ($P < .027$) and the T13 CHS group ($P < .041$). CHS was associated with a marked increase in freedom from in-hospital mortality ($P < .0001$) for both T13 and T18 (Fig 3). There was no impact of era on the improved in-hospital mortality in the CHS groups (Supplemental Fig 4).

Infants were mechanically ventilated before surgery for a median duration of 2 days (IQR: 1–5) in the T13 group and 3 days (IQR: 1–8) in the T18 group (Supplemental Table 4). After CHS, infants were mechanically ventilated for a median duration of 2 days (IQR: 1–13) in the T13 group and 8 days (IQR 2–17) in the T18 group. Zero tracheostomies were performed during the first admission for the T13 group undergoing CHS (Supplemental Table 5). Three (5%) patients with T18 undergoing CHS had a tracheostomy during their first admission, as compared with 3 patients (0.4%) with T18 who did not have CHS ($P = .005$).

Gastrostomy tube placement was more common among patients who underwent CHS. In patients with T13, 8 patients (22%) who underwent CHS also had a gastrostomy tube placed during their first admission, as compared with 40 (8%) with T13 who did not have CHS ($P = .01$) (Supplemental Table 5). Similarly, in patients with T18, 16 patients (25%) who underwent CHS also had a gastrostomy tube placed during their first admission, as compared with 137 (16%) with T18 who did not have CHS ($P = .005$).

In patients who underwent CHS, there were a total of 21 in-hospital deaths during the study period, 10 in the T18 group and 11 in the T13 group. The most common CHS performed in those who died was a systemic-to-pulmonary artery shunt (7 patients). Among the survivors, postoperative LOS after a systemic-to-pulmonary artery shunt was 15 days (IQR: 11–32) for T13 and 39 days (IQR: 36–45) for T18 (Supplemental Table 4). Additional deaths after CHS occurred after patent ductus arteriosus ligation, repair of tetralogy of Fallot, repair of coarctation of the aorta, concomitant closure of an atrial septal defect and ventricular septal defect, and tricuspid valvuloplasty. Of note, the 2 patients who underwent Norwood operations did not experience in-hospital death.

There was no significant in-hospital mortality difference between infants with T18 and T13 without a diagnosis of CHD and those with CHD who did not undergo CHS (Table 3). Conversely, LOS was higher in those with CHD who did not undergo CHS compared with those without CHD. Patients with CHD who received comfort care had a shorter LOS without a difference in mortality

TABLE 1 Comparison Between Patients With CHS and No CHS in T13 and T18

Characteristics	T13 (*N* = 555)			T18 (*N* = 925)		
	CHS (*n* = 37)	No CHS (*n* = 518)	*P*	CHS (*n* = 64)	No CHS (*n* = 861)	*P*
Age at admission, d	0 (0–1)	0 (0–1)	.7	0.5 (0–2)	0 (0–1)	.006
Gestational age, wk	38 (37–39)	37 (35–38)	.034	37 (35.5–38.5)	37 (35–39)	.64
Birth weight, g	2800 (2328–3228)	2430 (1930–2910)	.001	2410 (2130–2931)	1930 (1520–2311)	<.001
Infection	16 (43%)	128 (25%)	.013	31 (48%)	255 (30%)	.002
Mechanical ventilation	36 (97.3%)	330 (63.7%)	<.001	63 (98.4%)	555 (64.5%)	<.001
LOS, d	30 (19–59)	8 (4–18)	<.001	43 (22–84)	10 (4–25)	<.001
In-hospital mortality	11 (30%)	284 (55%)	.003	10 (16%)	383 (44%)	<.001

Data are presented as counts with percentiles or as medians with the first and third quartiles, as appropriate.

compared with those with CHD who received standard care without CHS.

DISCUSSION

The current study in a large, multicentered cohort reveals a significant in-hospital mortality reduction in patients with T18 and T13 who underwent CHS. The authors of previous smaller studies have evaluated surgical versus medical management in T18 and T13. Costello et al[8] examined mortality after CHS versus expectant management in 18 patients with T18 and CHD and found a 50% mortality rate in the expectant management group and a 29% mortality rate in the surgical group; however, the survival difference was not statistically significant. Similarly, Graham et al[9] reported a 91% survival rate to discharge among 35 infants with T13 and T18 undergoing CHS. Recently, Nelson et al[3] reported on survival after surgical interventions in a

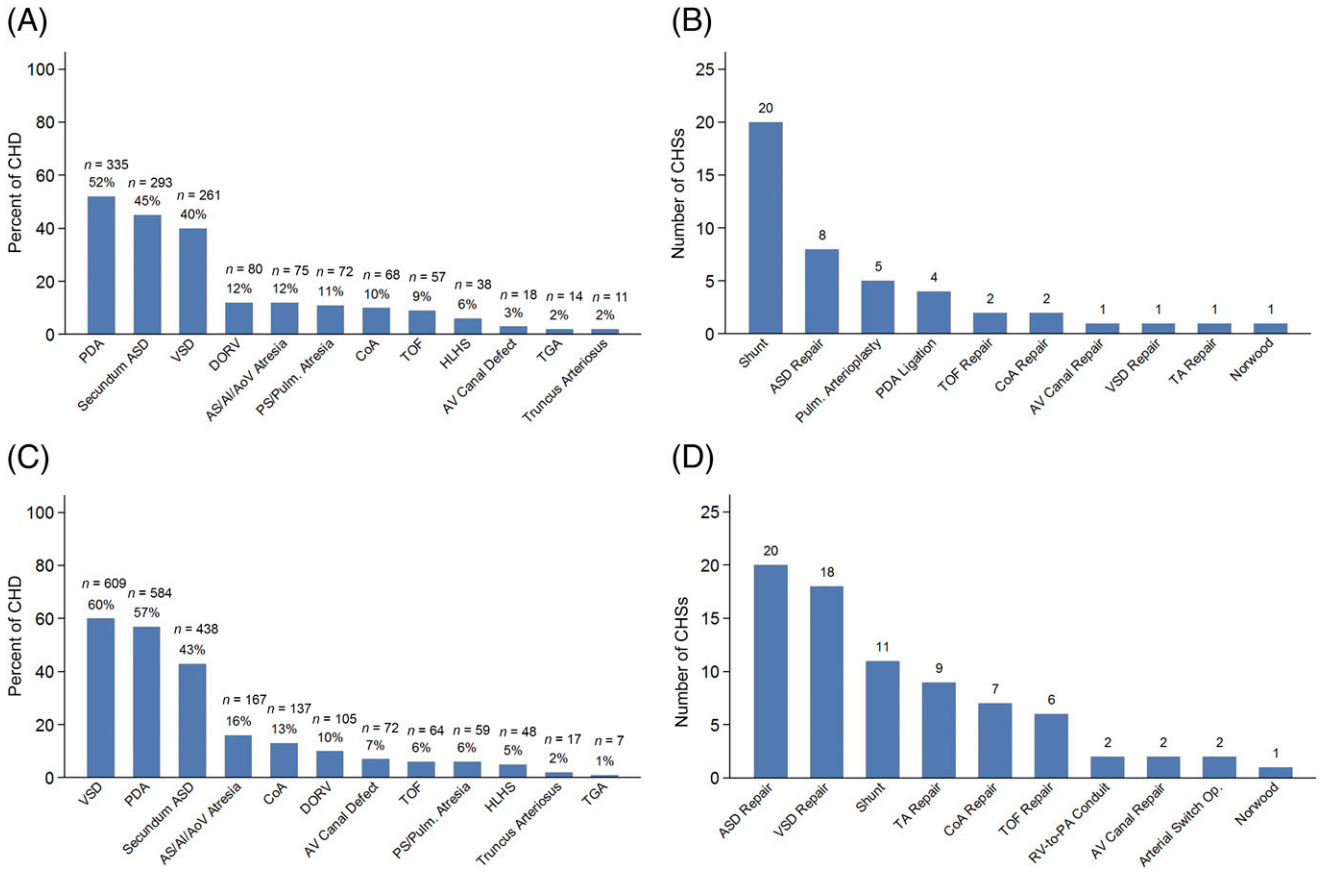

FIGURE 2

Incidence of CHD and distributions of CHS in T13 and T18. A, Frequencies of CHD in T13. B, Counts of CHSs in T13. C, Frequencies of CHD in T18. D, Counts of CHSs in T18. AI, aortic insufficiency; AoV, aortic valve; AS, aortic stenosis; ASD, atrial septal defect; AV, atrioventricular; CoA, coarctation of the aorta; DORV, double outlet right ventricle; HLHS, hypoplastic left heart syndrome; PDA, patent ductus arteriosus; PS, pulmonary stenosis; Pulm, pulmonary; RV-to-PA conduit, right ventricle to pulmonary artery conduit; Shunt, systemic to pulmonary artery shunt; TA, truncus arteriosus; TGA, D-transposition of the great arteries; TOF, tetralogy of Fallot; VSD, ventricular septal defect.

TABLE 2 Multiple Logistic Regression Showing the Effect of Multiple Risk Factors on Mortality T13 and T18

Risk Factors	Contrast	T13 ($N = 519$)[a]		T18 ($N = 872$)[b]	
		Odds Ratio (95% CI)	*P*	Odds Ratio (95% CI)	*P*
CHS	Yes versus no	0.45 (0.21–0.97)	.041	0.43 (0.20–0.91)	.027
Age at admission, d	1 d increase	0.86 (0.78–0.94)	.001	0.86 (0.80–0.93)	<.001
Birth weight, kg	1 kg increase	0.52 (0.40–0.69)	<.001	0.27 (0.20–0.35)	<.001
Sex	Male versus female	1.50 (1.04–2.17)	.028	1.51 (1.11–2.06)	.009
Center volume	Increase of 5 cases	1.01 (0.88–1.15)	.91	0.98 (0.93–1.04)	.59

CI, confidence interval.

[a] For T13, 519 observations were used to fit the logistic model. Of 519, $N = 278$ (54%) died. The C-statistic for the model was 0.68. The net sample reflected missing variable counts: $N = 1$ for sex and $N = 36$ for birth weight.

[b] For T18, 872 observations were used to fit the logistic model. Of 872, $N = 372$ (43%) died. The C-statistic for the model was 0.746. The net sample reflected missing variable counts: $N = 1$ for sex, $N = 208$ for gestational age, and $N = 52$ for birth weight.

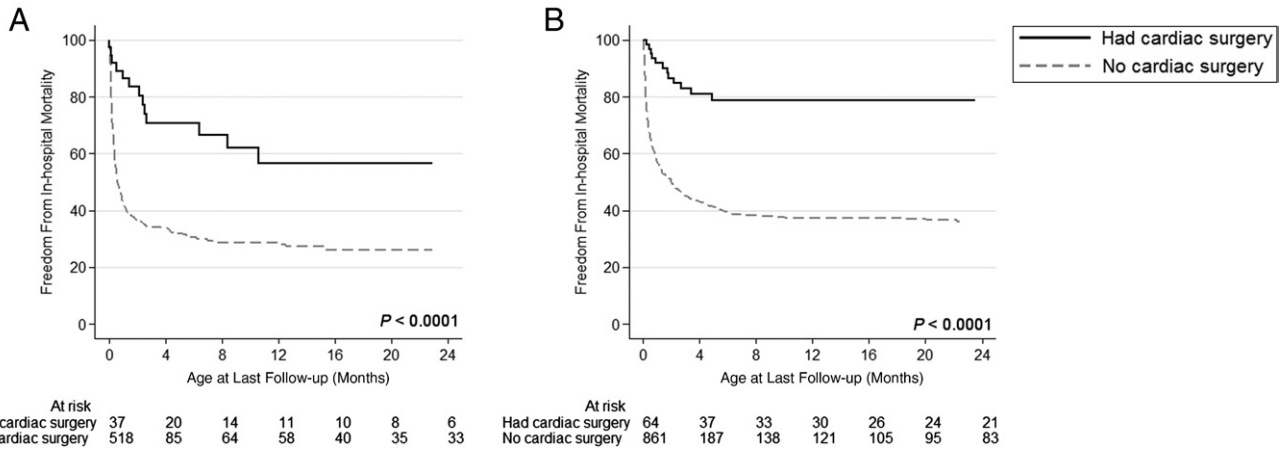

FIGURE 3
Two-year freedom from in-hospital mortality in T13 and T18. A–B, Significantly decreased in-hospital mortality in patients with T13 and T18 who underwent CHS.

TABLE 3 Comparison Between Patients With CHD and No CHD in T13 and T18

Characteristics	T13						T18					
	CHD, No CHS ($N = 518$)			*P*[a]			CHD, No CHS ($N = 861$)			*P*[a]		
	Group 1: No CHD	Group 2: Comfort Care	Group 3: Standard Care	1 vs 2	1 vs 3	2 vs 3	Group 1: No CHD	Group 2: Comfort Care	Group 3: Standard Care	1 vs 2	1 vs 3	2 vs 3
	($N = 93$)	($n = 63$)	($n = 455$)				($N = 95$)	($n = 100$)	($n = 761$)			
LOS, d	3 (1–13)	4 (1–7.5)	9 (4–20.5)	.99	<.001	<.001	4 (1–14)	3 (1–10)	11 (5–27)	.47	<.001	<.001
In-hospital mortality	52 (56%)	26 (41%)	258 (57%)	.22	.99	.063	36 (38%)	35 (35%)	348 (46%)	.99	.44	.13

Data are presented as counts with percentiles or as medians with the first and third quartiles, as appropriate.

[a] Bonferroni adjusted *P* values for multiple comparisons.

heretofore relatively large cohort of patients with T18 and T13 (254 with T18 and 174 with T13). In that study, CHD was reported in only 32% of those with T13 and 37% of those with T18. These low rates of CHD reported by Nelson et al[3] raise the question of ascertainment bias in their sample when viewed in the light of our work and that of others.[5,6] Additionally, only 12 of the patients in that study underwent CHS. Notably, in the 6 patients with T13 who underwent CHS, the median postoperative survival was 8.3 years (IQR: 0–11.3), although it was 9.7 years (IQR: 0–11.3) when limiting to only the first CHS. Conversely, the median postoperative survival in those with T18 was 7.4 years (IQR: 0.1–15) and was markedly lower (0.3 years, (IQR: 0–15]) when limiting to only the first CHS. Maeda et al[11] showed a 56% postoperative survival rate after CHS in T18 and CHD, with postoperative follow-up from 2 to 216 months. Though the mortality after CHS in the current study was markedly decreased, it remains significantly higher than

overall mortality from CHS in the general population,[12] which must be considered when CHS is being contemplated. Nevertheless, the present findings suggest that CHS may not be futile, at least not in the short-term, in patients with T13 and T18. Additionally, these results suggest that CHS may allow families to be able to take their children home and avoid dying in the hospital.[13,14] The authors of previous studies have reported that 52% of parents of children with T13 and T18 voiced the goal of bringing their child home.[13] In addition, 61% of parents in that study reported a fear of life in the hospital. Notably, that study included parental self-reported data from a total of 146 children with CHD, of whom 25 underwent CHS, most commonly ventricular septal defect closure.

This study is not only the largest study of T18 and T13 ever reported, but it is also the first in which it has been shown that greater weight, older age at admission, and female sex are associated with improved survival in T18 and T13 infants undergoing CHS. Older age and greater weight have been previously associated with improved survival after CHS in large, nonspecific patient cohorts.[15,16] Meyer et al[2] showed that prematurity, particularly between 32 and 36 weeks, was linked to diminished survival in T13 and T18. Boghossian et al[17] found higher mortality in infants with T13 and T18 who had low birth weight. Studies investigating sex differences in survival after CHS in pediatric patients are limited. Klitzner et al[18] previously showed that female sex is associated with increased mortality after CHS in a nonspecific cohort of patients. Our data in infants with T18 and T13 reveal an opposite effect of sex on survival after CHS. In keeping with our results, the authors of a few smaller studies have demonstrated increased survival in girls with T13 and T18, though these authors did not specifically investigate the impact of CHS.[4,7,19,20] The etiology of this difference in survival between sexes is uncertain and represents an opportunity for further investigation. However, our findings provide the groundwork for risk stratification of patients with T13 and T18, which, when used to inform CHS decision-making, could potentially result in further improved survival rates after CHS in those with increased weight, older age, and female sex.

The current management of CHD in patients with T13 and T18 is reminiscent of the historic management approach to patients with T21 and a complete atrioventricular canal defect. In the 1960s and 1970s, repair of complete atrioventricular canal defects was performed sparingly and variably[21] in patients with T21 because of a perceived elevated mortality risk, ostensibly caused by high pulmonary vascular resistance or associated comorbidities.[22] Some patients underwent pulmonary artery banding as a palliative approach to congestive heart failure and pulmonary vascular disease. However, in recent years, the belief in an elevated mortality risk for patients with T21 undergoing CHS has been discredited, and CHS in T21 is now standard.[23–26] In the current study, 7% of patients with CHD and T13 or T18 underwent CHS. Unfortunately, with the relatively small numbers of CHS per year over the nearly 12-year study period, our data set was not powered to determine if the rates of CHS in patients with T18 and T13 have changed over time. We suspect that they have, but a larger data set would be required to make this determination.

Irrespective of CHS, CHD was not associated with increased in-hospital mortality in either T13 or T18. This finding suggests an interaction between other significant congenital anomalies often present in T13 and T18 and the hemodynamic impact of CHD. Variable phenotypic presentation and genotype (mosaicism, partial or unbalanced translocation, or complete trisomy) may impact clinical outcomes and impact the ability to predict mortality risk more precisely.[3] The authors of previous studies have suggested that the types of CHD present in T13 and T18 are unlikely to be lethal in infancy, thereby making CHS unjustifiable.[6] In the most prevalent forms of CHD represented in T13 and T18, CHS may not be warranted in the neonatal period; however, the symptomatic burden of CHD often precipitates surgical intervention. Additionally, respiratory dysfunction and pulmonary abnormalities, which have been reported to be the cause of death in T18 for those <1 month of age,[27] are exacerbated by the presence of CHD. It is likely that removing the influence of even relatively simple forms of CHD on respiratory issues played a role in the improved survival-to-hospital-discharge rate seen in our study. This study revealed relatively low median ventilator days both pre- and postoperatively in both T13 and T18. Though the percentage of patients with tracheostomy during first admission was higher in the T18 group undergoing CHS, the overall incidence of tracheostomy was low in both groups.

As might be anticipated, those patients in the current study with CHD who were categorized as "comfort care" had the shortest LOS. Additionally, infants with CHD receiving care involving standard medical procedures excluding CHS had increased LOS when compared with both those without CHD and those with CHD receiving comfort care; however, there was no associated increase in survival rate. Given the high costs of care coupled with the decreased survival rate in patients with T13 and T18, this important finding must be considered when counseling families.

Additionally, these data may help to frame discussions and future studies on appropriate resource allocation for patients with T13 and T18.

The current study is limited by the retrospective nature. The classifications of medical and anatomic diagnoses by ICD-9 codes in the PHIS database are dependent on those recorded by the billing physicians during the hospitalization and on the hospital billing coders. Given the stringent procedures used for quality assurance of the data within the PHIS database and the fact that T13, T18, and the anatomic diagnoses in the study are specific, the likelihood of classification errors and miscoding making a significant impact on the findings of the study is limited. The PHIS database lacks information on the surgical decision-making process and the outpatient clinical course. At present, information related to the outpatient experience is limited to qualitative surveys. Mosaicism cannot be identified in the data set and was not accounted for in the patient groups, which may influence the overall survival of T13 and T18 patients. However, it has been shown that mosaicism does not significantly impact mortality and morbidity in some studies.[5,28–32] Extracardiac diagnoses that may influence the clinical course and survival of these patients were beyond the scope of this study and were not evaluated. Our study was not powered to stratify mortality on the basis of the complexity of CHD cases; however, the most common CHS performed in T13 was systemic-pulmonary artery shunt, suggesting complex CHD.

CONCLUSIONS

In-hospital mortality occurs in half of neonates with T13 and T18 within the first few days of life. CHD in these patients does not confer increased in-hospital mortality, and CHS is associated with significantly decreased in-hospital mortality. Those patients with CHD who undergo comfort care have the shortest LOS.

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ABBREVIATIONS

CHD: congenital heart disease
CHS: congenital heart surgery
ICD-9: *International Classification of Diseases, Ninth Revision*
IQR: interquartile range
LOS: length of stay
PHIS: Pediatric Health Information System
T13: trisomy 13
T18: trisomy 18
T21: trisomy 21

COMPANION PAPER: A companion to this article can be found online at www.pediatrics.org/cgi/doi/10.1542/peds.2017-2809.

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