ARTICLE

Procedures in the 1st Year of Life for Children With Trisomy 13 and Trisomy 18, a 25-Year, Single-Center Review

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Care of the child born with trisomy 13 or 18 has evolved over the past few decades, leading to increased healthcare utilization. We hypothesized that there has been an increase in procedures across all intensity types, including major, invasive procedures. We performed a retrospective-cohort study of children with trisomy 13 or 18 from 1990 to 2014 in a quaternary, free-standing children's hospital. Children were identified using ICD-9 billing diagnoses. Procedures were identified during these encounters and categorized by intensity (major, intermediate, or minor). One hundred thirty-two children with trisomy 13 or 18 were identified. In children with trisomy 13, major procedures increased from period 1 (1990–1997) to period 3 (2006–2013) from 0.11 to 0.78 procedures per patient. For trisomy 18, the increase between the time periods was from 0.14 to 1.33 procedures per patient. By the end of the study period, nearly all trisomy 13 patients had a major procedure and the majority of those with trisomy 18 had undergone a major procedure. Estimated 1-year survival for those with a major procedure was 30% and 22% for trisomies 13 and 18, respectively. In conclusion, there was an increasing rate of procedures per patient of all intensity levels over the 25-year study period. Given differences in characteristics in those with trisomies 13 and 18, and effects of intervention on survival, an individualized approach to care of these patients should be employed by parents and healthcare providers, using factors such as trisomy type, infant gender, co-morbidities, and parental preference.

KEY WORDS: trisomy 13; trisomy 18

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INTRODUCTION

The three most common autosomal trisomies that survive to birth are trisomy 21 (Down syndrome), trisomy 18 (Edwards syndrome), and trisomy 13 (Patau syndrome) [Rasmussen et al., 2003]. While trisomy 21 is considered to generally have a good prognosis, trisomies 13 and 18 have previously been considered incompatible with life, with median survival time for trisomy 13 reported as 8.5–10 days, and 6–14 days for trisomy 18 [Brewer et al., 2002; Wu et al., 2013]. This early mortality is largely due to the incidence of central apnea, and complications from the multiple congenital anomalies associated with these trisomies, particularly congenital heart disease [Brewer et al., 2002]. Historically, an estimated 5–10% of children survive for greater than 1 year [Rasmussen et al., 2003; Lakovschek et al., 2011], but more recent studies report survival as high as 11–19% [Meyer et al., 2016; Nelson et al., 2016], suggesting that the term "lethal abnormality" is both inaccurate and inappropriate [Carey, 2012].

There has been a trend in recent years toward providing life-prolonging

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medical interventions in this population. The fourth edition of *Smith's Recognizable Patterns of Human Malformations* (1988) recommended "limitation of all medical means for prolongation of life" [Smith and Jones, 1988], but subsequent editions' recommendations have changed to "limitation of extraordinary medical means for prolongation of life should be seriously considered. However, the personal feelings of the parents and the individual circumstances of each infant must be taken into consideration" [Jones et al., 2013].

This trend has been reflected in the publication of several case series looking at the incidence of invasive, life-prolonging interventions in patients with trisomies 13 and 18, including cardiac surgery. These reports have shown overall improved survival in patients who underwent cardiac and GI surgical intervention [Kaneko et al., 2009; Kobayashi et al., 2010; Maeda et al., 2011; Muneuchi et al., 2011; Costello et al., 2015]. This corresponds with national administrative datasets from North America and Japan, which demonstrate similar trends in increased hospitalizations, numbers of interventions, and survival after discharge [Nelson et al., 2012; Ishitsuka et al., 2015; Nelson et al., 2016]. However in most of these studies, each hospitalization record was removed of personal identifiers, and those authors were unable to link multiple hospitalizations and procedures to the same patient.

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To better understand patient care trends over time for children with trisomy 13 or 18, we sought to determine the frequency and intensity of procedures, while accounting for multiple hospitalizations and outpatient visits for the same patient. We hypothesized that the number of procedures per patient increased over time across all levels of procedure intensity.

To better understand patient care trends over time for children with trisomy 13 or 18, we sought to determine the frequency and intensity of procedures, while accounting for multiple hospitalizations and outpatient visits for the same patient.

MATERIALS AND METHODS

This is a 25-year, retrospective cohort study of children with trisomies 13 or 18 admitted to a free-standing children's hospital in St. Louis, Missouri from January 1, 1990 to December 31, 2014. The hospital serves as a quaternary pediatric referral center with full subspecialty surgical services including cardiothoracic surgery and an attached ambulatory care center. The study was approved by the Saint Louis University Institutional Review Board.

Discharge billing records were queried for *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) diagnosis codes of 758.1 (Trisomy 13) or 758.2 (Trisomy 18) for all encounter types. For each encounter, all corresponding ICD-9 procedure codes were extracted from the hospital discharge billing record. The dataset included up to 15 diagnoses and procedures per encounter, and also included demographic data such as date of birth, dates of admission and discharge, gender, and insurance. We excluded emergency department encounters unless they were admitted to the inpatient ward as part of the same encounter, since the billing records were likely to be limited to acute discharge diagnoses and therefore incomplete [Gorelick et al., 2007]. We limited analyses to procedures occurring within the 1st year of age to mitigate the impact of data from a few patients who had multiple procedures after 1 year. The participants were then grouped into three study periods, based on date of birth; period 1 was from January 1, 1990 to December 31, 1997; period 2 was from January 1, 1998 to December 31, 2005; and period 3 was from January 1, 2006 to December 31, 2013 and the procedures were evaluated for an additional year, through 2014.

Procedure intensity for each ICD-9 code was determined using the principles of pain, risk, and time. Pain intensity was evaluated by expected level of pain and the need for general anesthesia. Level of risk was determined by the site of the procedure and invasiveness of the intervention. Time was determined by the expected duration of the intervention and expected recovery time. Using a combination of these factors, procedure intensity was then categorized by the authors as minor, intermediate, or major (Supplementary Appendix A). Examples of minor procedures included umbilical vein catheterization (38.92) and intubation with mechanical ventilation <96 hr (96.71). Intermediate procedures included diagnostic heart catheterization (37.23), thoracentesis (34.91), and intubation with mechanical ventilation for ≥ 96 consecutive hours (96.72). Major procedures included total repair of tetralogy of Fallot (35.81) and trachea fistula repair (31.73). If multiple related procedures were coded for a single procedure episode, they were counted as one procedure. For example, if a participant had procedure codes for an exploratory laparotomy (54.11) and lysis of peritoneal adhesions (54.59) in the same encounter, it was considered as only one major procedure.

Inpatient encounters included inpatient admissions or overnight observations. Outpatient encounters included clinic visits and ambulatory surgical visits without an overnight stay.

After tabulating the number of procedures for each of the three time periods, we limited analysis to patients who received care within 365 days after birth. We calculated the procedures per patient during each time period and assessed the difference in mean procedure count, stratified by trisomy group between time periods. This approach allowed us to examine changes in procedure intensity over time. Results were reported as rate ratios with period 1 as the denominator, permitting us to express change as the relative increase or decrease between periods. An alpha of 0.05 was selected for determining statistical significance.

Using a second approach to evaluate procedure intensity, we calculated the percentage of children receiving at least one procedure in the 1st year of life for 5-year rolling windows of time by procedure intensity and trisomy type. For example, we determined the percentage of trisomy 13 patients who received a major procedure during the 1st year of life between 2000 and 2004, 2001 and 2005, 2002 and 2006, 2003 and 2007, and so on. This rolling-window method minimizes distortion attributable to variation in annual number of cases.

Survival outcomes of patients who underwent interventions were then estimated. We used a Kaplan–Meier analysis to determine the association between receiving a major procedure and 1-year survival. Our available data contains only billing discharge dispositions (e.g., home or died), therefore a proxy for survival was created based on the date of last encounter. As children with complex medical conditions have intense hospital utilization in the last month of life [Feudtner et al., 2003], and patients with trisomy 13 or 18 are likely to receive continuing medical care within the same health system, we used the following method to determine survival analysis: when hospital disposition was not death, it was assumed death occurred one day after the discharge date of the last encounter. This results in a conservative estimate of survival. Like other analyses described in this study, it was limited to those children whose initial presentation occurred in the 1st year after birth. An alpha of 0.05 was selected for determining statistical significance for the Kaplan–Meier analysis log-rank comparison.

RESULTS

Over the 25-year period, 132 unique children met the inclusion criteria (Table I). Fifty-seven patients (43%) were identified with trisomy 13 and 75 patients (57%) had trisomy 18. The majority had their initial clinical presentation within the 1st week after birth (58%), and 78% presented within the 1st year. There was a slight preponderance of female patients, especially in those with trisomy 18.

The 132 patients identified had 234 total inpatient and outpatient encounters (Table I). Fifty-six percent of inpatient admissions in this cohort were in children with trisomy 18. Among the entire population there were 312 procedures performed. Fewer major procedures were performed on children with trisomy 13 than on children with trisomy 18. Only four cardiac procedures were performed on children with trisomy 13. In children with trisomy 18, there were 37 cardiac procedures. Those 37 cardiac ICD-9 procedure codes were categorized using the Agency for Healthcare Research and Quality's Clinically Classification Software [AHRQ, 2015]. The most common were "Other OR heart procedures" (18 procedures), "Other OR procedures on vessels of the head and neck" (8 procedures), and "Diagnostic heart catheterizations" (5 procedures). These data are not shown.

We then limited analysis to procedures performed within the 1st year after birth (Table II). There were 103 patients who presented within 365 days after birth. In both trisomies 13 and 18, there was an increase in the total number of procedures and the average number of procedures performed per child across each time period. In infants with trisomy 13, the number of major procedures from period 1 (1990–1997) to period 3 (2006–2013) rose from 0.11 to 0.78 procedures per patient. Similarly, major procedures in children with trisomy 18 increased from 0.14 to 1.33 procedures per patient. Overall, the number of children presenting to the medical center with trisomy 13 fell from 18 to 9 patients over the time periods. The number of children with trisomy 18 was relatively stable across each time period. Within the 1st year of life, there were more females than males with trisomy 18 admitted, while there were no gender differences with those with trisomy 13.

Rate ratios between the three time periods are shown in Table III. Children with trisomy 13 who had a major procedure had a rate ratio 7 times higher during period 3 when compared to period 1, reaching statistical significance ($P = 0.04$). Similarly, children with trisomy 18 had a rate ratio 9.8 times higher in period 3 for major procedures when compared to period 1, which was also significant ($P = 0.001$).

The 5-year running averages of those children with trisomy 13 or 18 who had at least one procedure is demonstrated in Figure 1, along with procedure intensities. A fairly consistent rise was noted in the number of children with trisomy 13 receiving a procedure with 100% of patients receiving at least one minor and one major procedure by the study end. A similar trend in increasing procedures of all intensities was also noted in children with trisomy 18. The percentage of patients with a minor procedure gradually increased to 67% in 2004–2008 and subsequently remained steady for the remainder of the study period. Major procedures also showed a similar increase; however, a drop in the number of admissions for trisomy 18 from 2008 to 2009 resulted in fewer procedures during that time frame. By study end, 53% of children with trisomy 18 had at least one major procedure.

Known survival to 1 year is shown in Figure 2, where mortality is defined

TABLE I. Characteristics of Individual Children With Trisomy 13 or 18 and Lifetime Patient Encounters

	Trisomy 13	Trisomy 18	Total
Unique patients (n)	57	75	132
Age at first hospital-based encounter (n (%))			
≤7 Days	32 (56)	45 (60)	77 (58)
8–30 Days	4 (7)	3 (4)	7 (5)
31–365 Days	5 (9)	14 (19)	19 (14)
>365 Days	16 (28)	13 (17)	29 (22)
Gender (% female)	56%	71%	64%
Race (n (%))			
African American/Black	15 (26)	17 (23)	32(24)
White	38 (67)	53 (71)	91 (65)
Other	4 (7)	2 (3)	6 (5)
Unknown	0 (0)	3 (4)	3 (2)
Payor at first hospital-based encounter (n (%))			
Commercial	16 (28)	34 (45)	50 (38)
Medicaid	37 (65)	40 (53)	77 (58)
Other or Self pay	4 (7)	1 (1)	5 (4)
Unique hospital-based encounters (n)	109	125	234
Types of encounters (n (%))			
Inpatient	83 (76)	106 (85)	189 (81)
Outpatient	26 (24)	19 (15)	45 (19)
Procedures (n (%))	134	178	312
Minor	78 (58)	101 (57)	179 (57)
Intermediate	28 (21)	20 (11)	48 (15)
Major	28 (21)	57 (32)	85 (27)

as the age in days on the discharge date of the last encounter. For children with trisomy 13 who underwent at least one major procedure, known survival was 30% at 365 days. For those who did not undergo a major procedure, 3% were known to be alive at 365 days. For children with trisomy 18 who had at least one major procedure, 22% were alive at 365 days. For those who did not have a major procedure, 7% were known to have survived to 365 days. There was a statistically significant increase in known survival to 365 days in both the trisomy 13 and 18 cohorts undergoing at least one major procedure ($P = 0.008$ and $P = 0.001$, respectively).

DISCUSSION

Procedures in children with trisomy 13 or 18 have increased over time in both quantity and intensity. By the end of the 25-year study period, the vast majority of patients with either trisomy 13 or trisomy 18 had at least one minor procedure and most also had at least one major procedure. The types of procedures were not limited to any specific body system and included major cardiac surgeries, GI procedures, and mechanical ventilation (Supplementary Appendix B).

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Over the study period, there was a decrease in patients presenting with trisomy 13. This trend was not observed in those with trisomy 18, except between 2008 and 2009, which corresponds to a brief period when the hospital did not have a board-certified geneticist. The decline in trisomy 13 admissions may be due to improved sensitivity of pre-natal screening and ultrasound, reflecting a change in pre- and post-natal medical decision making. As a free-standing, quaternary children's hospital with a level IV NICU, our admissions are outborn and transferred in for subspecialty evaluation and care. Parents who elect for comfort care may opt for less aggressive obstetrical care and may choose to keep their newborn with them at the outlying hospital [Case et al., 2012]. Those pursuing medical intervention might be more likely to request transfer to a children's hospital for evaluation and treatment.

The 25-year study period allows for the analysis of trends over time. An increase in procedures per patient was noted in all patient types in all procedure intensities. This corresponds to data published by Nelson et al. [2012] which analyzed administrative data from Kids' Inpatient Database (KID), maintained by the Agency for Healthcare Research and Quality. This study of hospital discharge records in the U.S. showed a statistically significant increase in the number of admissions for children with trisomy 18 from 1997 to 2009, but no difference in admissions for children with trisomy 13. It also showed a statistically significant increase in the number of procedures per hospitalization in children with trisomy 13, and an increase in procedures per hospitalization in children

TABLE II. Procedures in the 1st Year of Life by Time Period

	All children (n = 41)			Females (n = 23)			Males (n = 18)		
	Period 1	Period 2	Period 3	Period 1	Period 2	Period 3	Period 1	Period 2	Period 3
Trisomy 13	1990–1997	1998–2005	2006–2013	1990–1997	1998–2005	2006–2013	1990–1997	1998–2005	2006–2013
Total children	18	14	9	11	9	3	4	9	5
Total procedures									
Minor	11	17	28	9	11	17	2	6	11
Intermediate	7	5	5	5	4	2	2	1	3
Major	2	7	7	2	6	3	0	1	4
Procedures per child									
Minor	0.61	1.21	3.11	0.82	1.22	5.67	0.29	1.20	1.83
Intermediate	0.39	0.36	0.56	0.45	0.44	0.67	0.29	0.20	0.50
Major	0.11	0.50	0.78	0.18	0.67	1.00	0.00	0.20	0.67
	All children (n = 62)			Females (n = 44)			Males (n = 18)		
	Period 1	Period 2	Period 3	Period 1	Period 2	Period 3	Period 1	Period 2	Period 3
Trisomy 18	1990–1997	1998–2005	2006–2013	1990–1997	1998–2005	2006–2013	1990–1997	1998–2005	2006–2013
Total children	22	19	21	18	10	16	4	9	5
Total procedures									
Minor	11	46	25	9	37	21	2	9	4
Intermediate	1	6	9	1	5	9		1	0
Major	3	17	28	2	16	28	1	1	0
Procedures per child									
Minor	0.50	2.42	1.19	0.50	3.70	1.31	0.50	1.00	0.80
Intermediate	0.05	0.32	0.43	0.06	0.50	0.56	0.00	0.22	0.00
Major	0.14	0.89	1.33	0.11	1.60	1.75	0.25	0.11	0.00

with trisomy 18, although that was not statistically significant. A limitation of the KID database is that each hospital record consists of a single, de-identified hospital-based encounter. It does not contain outpatient clinic records, and multiple hospitalizations by the same patient cannot be linked. Therefore, the number of procedures per patient over a patient's lifetime cannot be tabulated using KID.

TABLE III. Procedure Rate Ratios Across Time Period Among Children With Trisomies 13 and 18

	Period 2 vs. period 1	*P*	Period 3 vs. period 1	*P*
Trisomy 13				
Minor	1.5	0.07	5.1	<0.001
Intermediate	0.7	0.9	1.4	0.54
Major	3.5	0.04	7	0.005
Trisomy 18				
Minor	4.8	<0.001	2.4	0.01
Intermediate	6.9	0.4	9.4	0.009
Major	6.6	0.0005	9.8	<0.001

Period 1 (1990–1997), period 2 (1998–2005), period 3 (2006–2013).

The 25-year study period allows for the analysis of trends over time. An increase in procedures per patient was noted in all patient types in all procedure intensities. This corresponds to data published by Nelson et al. which analyzed administrative data from Kids' Inpatient Database (KID), maintained by the Agency for Healthcare Research and Quality.

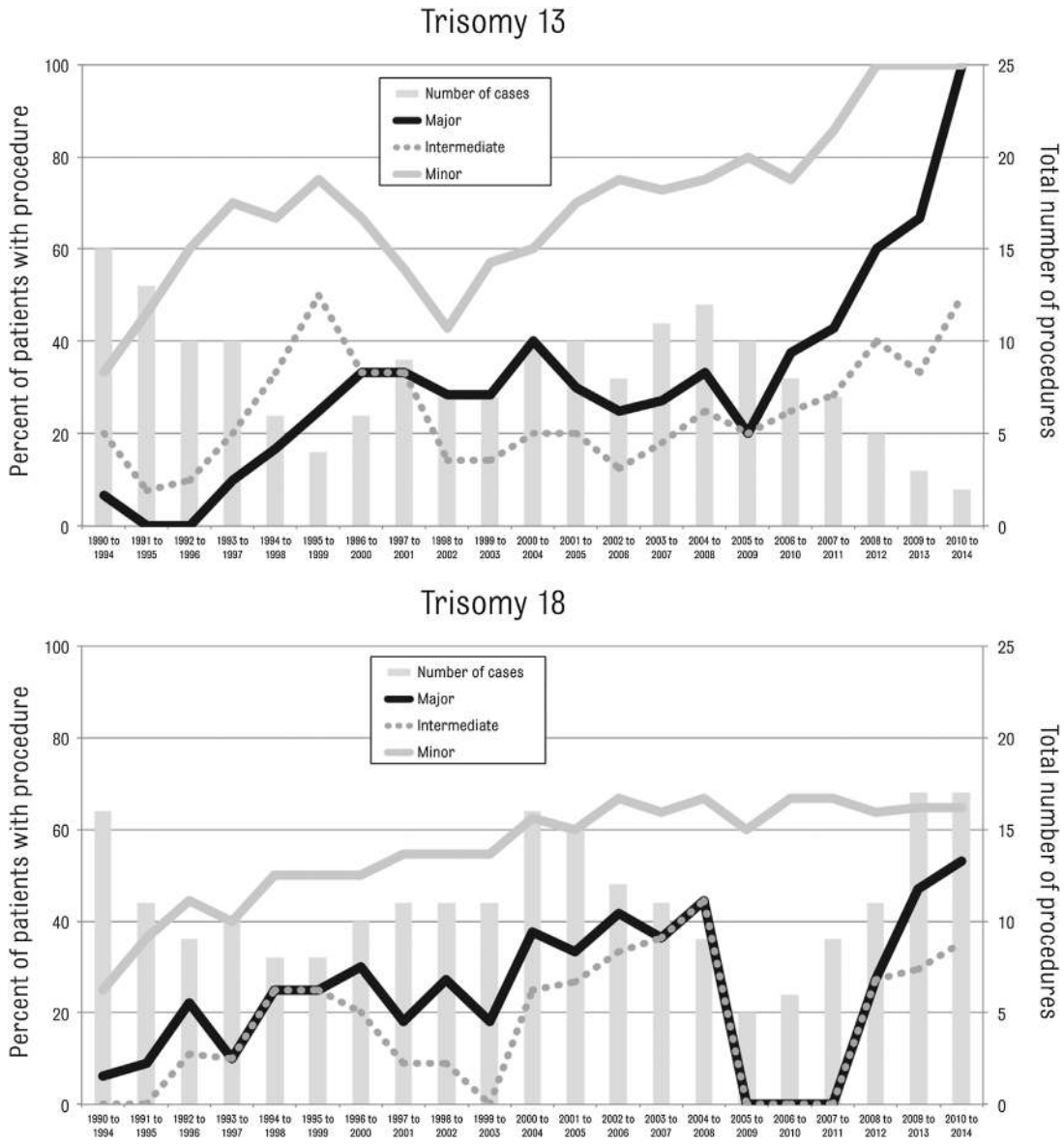

Figure 1. Procedures per person by intensity using a running 5-year average.

Increased intervention in children with trisomy 13 or 18 has also been reflected in several recent studies from Japan, including survival analyses in infants with congenital heart disease. Ishitsuka et al. [2015] utilized a nationwide administrative database to identify over 500 patients with trisomy 13 or 18. Of all patients who underwent any form of surgery, 68.6% were alive at hospital discharge, including 70.8% of patients who received cardiac surgery [Ishitsuka et al., 2015]. Other small studies have also reported a 50–80% short-term survival rate after cardiac surgery [Kaneko et al., 2009; Kobayashi et al., 2010; Maeda et al., 2011; Muneuchi et al., 2011]. In the United States, 34 cardiac surgery interventions have been described in one study using parent-reported data with apparent improved survival in those surveyed [Bruns and Martinez, 2016].

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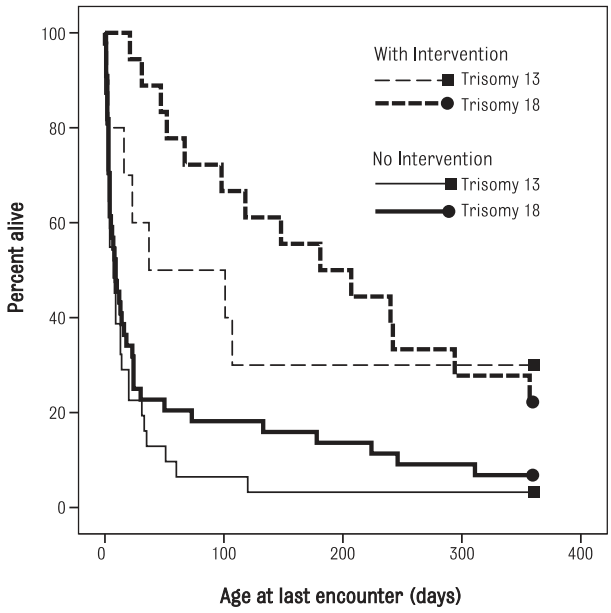

Figure 2. Kaplan–Meier survival curves for children with trisomy 13 or trisomy 18 for those undergoing at least one major procedure versus those who did not receive a major procedure.

Though survival to hospital discharge is a commonly used metric, several small studies have utilized another important metric, survival to 1 year of age. Reported 1-year survival in infants with trisomy 18 undergoing tracheoesophageal fistula repair or cardiac surgery was noted to be 25–27% in two small Japanese case series [Muneuchi et al., 2011; Nishi et al., 2014]. Another Japanese study of infants with trisomy 18 showed a 1-year survival of 11.4% in those infants receiving aggressive care (including invasive interventions) in a neonatal intensive care unit [Ishitsuka et al., 2015]. Survival data from developed countries beyond Japan are limited. A United States study by Subramaniam et al. [2016] in a single center demonstrated an increase in obstetrical or neonatal interventions over time over a 10-year period, but did not find a significant difference in survival time in neonates who received aggressive or non-aggressive intervention (24 days vs. 30 days, $P = 0.9$). In contrast, data from Canadian administrative sources including birth, hospital, and death records suggests improved survival beyond 1 year in those receiving procedural interventions, although survival in children undergoing the most invasive, "major" procedures was not well described [Nelson et al., 2016].

Our data show a similar 1-year survival to the Japanese reports, with a 1-year known survival of at least 22% for infants with trisomy 18 who received major interventions. The method we used to assess survival likely underestimates true survival duration, since we were only aware of the status at the time of the last medical encounter at our facility. Though our true survival rate may be higher, our proxy-defined, 1-year survival for those undergoing procedures still surpasses the previously reported 1-year survival rate of 9–13% for infants with trisomy 18 [Rasmussen et al., 2003; Meyer et al., 2016].

Although clinical features of trisomies 13 and 18 are distinctly different, outcomes of these infants are commonly combined. Additionally, outcomes are commonly reported together for both male and female infants. In our cohort, 71% of the infants with trisomy 18 were female, and since 1998, females have had more procedures per patient than males. In the Nelson et al. [2012] study, females with trisomy 18 comprised 65% of all hospitalizations. There were no gender differences in either study for those with trisomy 13. These data are consistent with published data showing increased mean survival time in females with trisomy 18 [Wu et al., 2013; Nelson et al., 2016]. Given the discrete differences in the genetic diagnoses, and gender survival differences for trisomies 13 and 18, future studies regarding outcomes should clearly separate these distinct syndromes.

The major strength of this study was the ability to identify patient-level information, allowing us to account for procedures over multiple encounters for the same patient. In addition, the 25-year duration of the data collected allowed analysis of changing trends over a significant period of time. Utilizing the same institution helped to reduce inter-hospital and geographical variability. Billing records are not subject to recall bias, selecting all patients with either diagnosis of trisomy 13 or 18, regardless of the department or clinical service to which they presented.

The major strength of this study was the ability to identify patient-level information, allowing us to account for procedures over multiple encounters for the same patient. In addition, the 25-year duration of the data collected allowed analysis of changing trends over a significant period of time.

Limitations of this study include the fact that this is a retrospective cohort. The participants were determined from billing records, and as in all studies of administrative data, coding errors are possible for both diagnosis and procedure codes [Berthelsen, 2000]. The ICD-9 diagnosis codes for trisomy 13 or 18 are unable to discriminate between full or mosaic trisomy diagnoses, but since the incidence of mosaic trisomy is $<5\%$, it is unlikely to affect the results [Carey, 2005]. The timing

of the genetic diagnosis (pre- or post-natal) and the intent to aggressively treat cannot be ascertained. However, given that the hospital is an independent, free-standing children's hospital, it might be inferred that those transferred expected to receive diagnostic evaluation and treatment, rather than palliative care. Our analysis of survival is only a proxy estimate, and likely underestimates survival duration since we do not know the exact date of any death that did not occur in our hospital.

Our study is unique in that it reports individual patient-level data across multiple hospital encounters for infants with trisomy 13 or 18 over a 25-year period. There was a statistically significant increasing rate of procedures per patient on all intensity levels over the 25-year study period, and this correlates with longer survival duration in both trisomies 13 and 18. There were differences in procedure frequency and type among children with trisomies 13 and 18, and differences in procedure frequency by gender. Given this, an individualized approach to these patients should be employed, using factors such as trisomy type, infant gender, comorbidities, and parental preferences to guide mutual decision making with parents and the medical care team.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of this article.