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To operate or not to operate? Assessing NSQIP surgical outcomes in trisomy 18 patients☆

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ABSTRACT

Background: Trisomy 18 is associated with a wide range of potentially fatal congenital conditions. Historically, clinical attitudes on treatment have been ambiguous, with palliative care as the standard of care. The aim of our study was to provide a descriptive analysis of surgical outcomes in patients with trisomy 18.
Study design: We identified patients with trisomy 18 aged 0–18 years using the NSQIP-Pediatric database from 2012 to 2017 and analyzed demographics, surgery types, and perioperative characteristics of patients with trisomy 18 patients undergoing surgical intervention. Additionally, a case-match analysis was performed to assess surgical outcome differences.
Results: A total of 310 patients with trisomy 18 were identified. Thirty-one percent were >5 years of age and 73% were female. The most common surgical types were general surgery procedures (57.4%), followed by orthopedics (18.1%) and ENT (10.3%). Operations performed increased from 8% (2012) to 26% (2017), and only 23% of patients had previous cardiac surgery. Majority of patients had no prior history of malignancy (95%) and 5% had a tracheostomy placed.
Discharge to home was achieved in 74% of patients, with a median total hospital length of stay of 5 days (IQR 17). Furthermore, 90% survived over 30 days from the operation. Thirty-two patients had readmissions and the most common reasons were dehydration, gastrostomy infection or malfunction. Surgical site infections occurred in <3% of patients. No differences in complications, length of stay, reoperations, and readmissions were identified by case-match analysis.
Conclusion: In this data set, patients with trisomy 18 undergoing noncardiac surgical procedures experience excellent surgical outcomes with minimal morbidity and low mortality. Most patients more than a year of age will experience similar outcomes to patients without trisomy 18.
Type of study: Treatment study (retrospective comparative study)
Level of evidence: Level III

1. Introduction

Trisomy 18 is an aneuploidy associated with a multitude of congenital malformations. These commonly range from cardiac, genitourinary, gastrointestinal, neurological, and craniofacial malformations. Physical trademark features include an abnormally shaped head, clenched fists with overlapping fingers, and micrognathia. Trisomy 18 has a live-born prevalence of 1/6000–1/8000 with limited neurodevelopment. The classic phenotype can result from full, mosaic, or partial trisomy; however, this can be extremely variable, especially in patients with partial or mosaic types [5].

Edwards syndrome has been traditionally considered a poor prognosis condition with 80%–90% of cases not surviving past the first year of life [1,2]. However, more recent data show that with appropriate medical/surgical intervention survival is as high as 23% at 5 years of age and 13% at 10 years, and a small number of adults are living into their twenties and thirties [3–5]. Clinical attitudes towards patients with Trisomy 18 have changed over time, where ethics consults and palliative approaches are often recommended [3,6,7]. A survey analysis of multispecialty providers demonstrated that clinicians felt the discussion of cardiac surgery was appropriate; however, most were hesitant owing

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to ethical concerns and insufficient outcome data [7]. Trisomy 18 is now considered a disease compatible with life, and the discussion has shifted towards definitive care [3,6,7,9]. Based on this paradigm change, we decided to perform a descriptive analysis of trisomy 18 patients' outcomes identified using the American College of Surgeons National Surgical Quality Improvement Program-Pediatric (ACS NSQIP-P) Database from 2012 to 2017.

2. Methods

The American College of Surgeons Pediatric National Surgical Quality Improvement Program-Pediatric (ACS NSQIP-P) Database was analyzed from 2012 to 2017. We included all patients with a diagnosis of trisomy 18 using ICD 9 758.2. The NSQIP-P is a prospective clinical database that includes data from 143 participating hospitals in North America, which are abstracted by trained surgical clinical reviewers. Patients less than the age of 18 years who underwent selected general, neurosurgical, urological, otolaryngologic, plastic, and orthopedic procedures are eligible for selection by systematic sampling on an 8-day cycle. Demographic variables were captured, and procedures were examined based on CPT codes and classified by field. Cardiac surgery procedure outcomes are not tracked in this database and hence were excluded. However, previous history of cardiac surgery and type of procedures are part of the database. Moreover, perioperative characteristics such as weight, height, and premature birth comorbidities were assessed. Surgical complications measured included surgical site infection (SSI), dehiscence, unplanned intubation, pulmonary embolism (PE), progressive renal insufficiency, acute renal failure, urinary tract infection (UTI), cardiac arrest requiring cardiopulmonary resuscitation (CPR), bleeding occurrences and sepsis. Regarding surgical outcomes we tracked the number of patients discharged that survived, mortality <30 days, discharge destination, overall mortality, hospital length of stay (LOS), readmissions, and reasons for readmissions. We then conducted a case–control match study to assess for differences in morbidity, mortality, and length of stay when compared to patients without trisomy 18 within the database. Not all cases could be matched given the conditions required for matching and the small sample from the NSQIP database. Cases were matched by age, sex, race, weight, principal procedure type, prematurity, and degree of cardiac risk factors (none, minor, major, severe). Paired T-tests were used for continuous variables and Fisher's test was used for categorical variables.

3. Results

3.1. Demographics and age distribution

A total of 310 patients with trisomy 18 were identified. The majority were female (73%), and most were identified as white patients (71.9%). Seventeen percent were black, 1.3% were Asian, 0.6% were American Indian or Alaska Native and 9% percent were classified as unknown. Regarding patient ethnicity, 13.2% were found to be Hispanic, while 80.3% were reported as non-Hispanic. The age distribution of patients range from 0 to 18 years of age, where only 16% of patients were <30 days of age. The majority were less than 5 years of age, 17.5% were between 6 and 10 years of age, 10% were 11 and 15 years of age and 3.9% were greater than 15 years of age (Table 1).

3.2. Congenital malformations and comorbidities

Twenty-three percent of patients were premature, ranging from 27 to 36 weeks. The overall mean gestational age was 37.3 weeks (SD = 2.571), with a mean birth weight of 1.7 kg (SD = 0.50), and a median weight at the time of surgery of 17 kg (IQR 29). Interestingly, only 3% were DNR at the time of admission. The most common comorbidities reported included cardiac disease (81%), respiratory disease (63%), and neurodevelopmental problems (84%), and 14% had a hematologic disorder (Table 2). The majority of patients had no history of malignancy.

Table 1
Age distribution of patients

Age frequencies	
<30 days, *n* (%)	51 (16.5)
• Median (IQR)	6 (12)
Age distribution, *n* (%)	
• 0–5 years	213 (69)
• 6–10 years	54 (17)
• 11–15 years	31 (10)
• >15 years	12 (4)

n: number, IQR: interquartile range.

3.3. Surgical interventions

The number of surgical interventions on patients with trisomy 18 increased from 26 per year in 2012 to 81 per year in 2017. However, mortality remained unchanged over the years (Fig. 1). Most of these were elective (80.3%) and the majority were classified as an inpatient (85.5%). The most common surgical interventions were General Surgery procedures (57.4%), followed by Orthopedics (18.1%), ENT (10.3%), Neurosurgery (6.1%), Urology (4.2%), and Plastic Surgery (3.9%). See Table 3 for a breakdown of General Surgery procedures. Interestingly, only 4.8% of patients have had a tracheostomy placed ($n = 15$) and 23% of the patients had previous cardiac surgery.

3.4. Surgical complications and outcomes

The most common surgical complications were bleeding (15.8%), unplanned intubation (6.8%), urinary tract infection (2.3%), cardiac arrest requiring cardiopulmonary resuscitation (CPR) (1.6%), pneumonia (1.3%), and sepsis (1.3%). Of the 5 patients that required CPR owing to cardiac arrest, 4 had major cardiac risk factors and 1 had minor risk factors. Only 4 patients (1.3%) had a superficial SSI, while 5 patients (1.6%) had an organ space SSI. Median number of days from operation to discharge was 5 days (IQR 9) and median number of days from operating to death was 18 (IQR 26). Twenty patients were on mechanical ventilation >30 days (expired or transferred to rehab facility) and the total

Table 2
Frequency of comorbidities.

Comorbidities	
Cardiac disease, *n* (%)	
• Severe cardiac risk factors	8 (2.6)
• Major cardiac risk factors	128 (41)
• Minor cardiac risk factors	114 (37)
• No cardiac risk factors	60 (19)
Respiratory disease, *n* (%)	195 (70)
• Mechanical ventilation, asthma, congenital lung disease, oxygen supplementation, tracheostomy, and structural pulmonary abnormality	
Neurodevelopmental problems	261 (84)
• Impaired cognition, seizures, cerebral palsy, structural CNS abnormality, and intraventricular hemorrhage	
Malignancy	
• Current cancer or active treatment of cancer	9 (3)
• Past Hx of cancer	5 (2)
• No current or prior history of cancer	296 (95)
Hematologic disorders	44 (14)
Gastrointestinal malformations	45 (15)
ENT and thoracic	51 (16)
Plastic	36 (12)
Genitourinary malformations	48 (15)
Bone and joint malformations	32 (10)
Other	29 (9)

n: number, CNS: central nervous system, ENT: ear, nose, and throat.

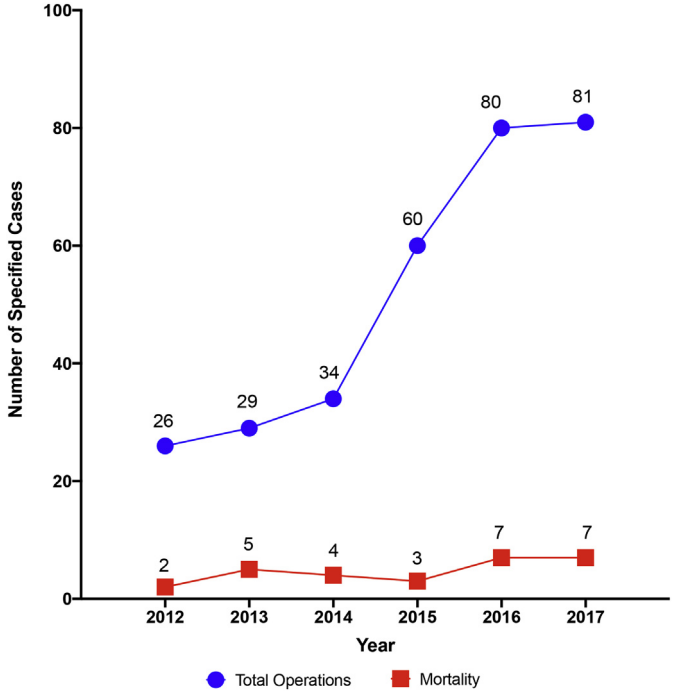

Fig. 1. Surgical outcomes based on operations and mortality per year. Numbers of patients undergoing operations (blue) and those that expired (red) were tracked from 2012 to 2017.

median hospital LOS for this cohort was 5 days (IQR 9). Survival after surgery was 91%, with most patients discharged home (74%). All mortalities in this cohort had cardiac risk factors (minor, major and severe) and most were less than 1 year of age (Table 4). The total number of readmissions was 32 (10.3%), all were unplanned and 10 were reported to be related to the initial operation. The main reasons for readmission reported included cardiac arrest requiring CPR, pneumonia, dehydration, gastrostomy site infections or malfunction. Eighteen patients had an unplanned reoperation (5.8%), of which 7 were reported to be related to the original intervention.

Table 3
Surgical interventions.

General surgery procedures	
Gastrointestinal, *n* (%)	137 (44)
• Laparoscopic/open gastrostomy	68 (22)
• Laparoscopy (Nissen, Toupet)	30 (10)
• Colectomy/colostomy	8 (3)
• Ileostomy	2 (0.6)
• Other[a]	29 (9)
Hernias, *n* (%)	18 (6)
• Omphalocele/gastroschisis	6 (2)
• Paraesophageal/hiatal	7 (2)
• CDH	5 (2)
Thoracic, *n* (%)	14 (5)
• Esophagoplasty (TEF)	12 (4)
• Tracheostomy	2 (0.6)
Hepatic, *n* (%)	8 (3)
• Cholecystectomy	4 (1)
• Hepatectomy	4 (1)
• Kasai	1 (0.3)
Renal/GU, *n* (%)	
• Nephrectomy	1 (0.3)

n: number, CDH: congenital diaphragmatic hernia, TEF: tracheoesophageal fistula.
[a] Small bowel resection or stoma, diagnostic laparoscopy or laparotomy, reduction of volvulus/interception/internal hernia by laparotomy/Ladd procedure, pyloromyotomy, imperforate anus.

Table 4
Mortality of patients by age and cardiac risk factors.

	Mortality (%)
Trisomy 18, *n* = 310	28 (9)
• <30 days of age, *n* = 51	14 (27)
• <1 year of age, *n* = 151	24 (16)
Cardiac risk factors, *n* = 250	28 (11)
• Minor, *n* = 114	4 (3)
• Major, *n* = 128	22 (17)
• Severe, *n* = 8	2 (25)

3.5. Case-matched control study

We compared 154 patients with trisomy 18 to the same number of patients without trisomy 18 from the NSQIP database. There were no differences in hospital total LOS, procedure to discharge, mortality, readmissions, reoperations and complications between the control and trisomy 18 cohorts (Table 5).

4. Discussion

Trisomy 18 is a rare genetic disorder with associated physical features and organ anomalies, often encompassing many systems and major neurologic impairments [8]. Approximately 50% of infants with trisomy 18 will die during the first weeks of life and about 10% will survive past 1 year of life [1]. With the improvement in care and understanding of associated defects, survival in this patient population is now possible into teenage years and early adulthood [1–4,9]. However, it is possible that this subgroup may have a milder phenotype with less comorbidities which can explain their survival. The ethical considerations of these patients have long been debated, but clearly more and more data show that carefully selected patients have a chance of survival and good quality of life [7,10,11].

Our study shows that pediatric patients with trisomy 18 are undergoing multiple surgical interventions with excellent surgical outcomes. These findings could possibly be related to patients with partial or mosaic trisomy which tends to have variable phenotypes. In our cohort, the majority of patients were less than 5 years of age, about 30% of the patients were >5 years of age, and half of these were in their teenage years. Furthermore, about a quarter of patients were premature with a mean birth weight of 1.7 kg. However, the median age at surgery was 1 year, with median weight at surgery of 17 kg. These findings suggest that most interventions occur in older and stronger patients, who potentially have lower rates of mortality. Another interesting finding was the fact that only 3% of the patients were declared DNR at the time of admission. Although this could be because of data entry limitation, we believe it is an accurate estimation that both caregivers and providers now see this as a survivable condition. Similar to the standard knowledge

Table 5
Case-matched control analysis.

Discharge destination	Trisomy 18 *n* = 154	Control patients *n* = 154	P-value
Total hospital length of stay, days (SD)	17.5 (25)	14.70 (35)	0.576
Time from procedure to discharge, days (SD)	11.5 (18)	8.2 (14)	0.071
Mortality, *n*	12	8	0.49
Readmissions, *n*	14	8	0.2694
Reoperations, *n*	8	7	>0.999
Complications, *n*			
• Bleeding/transfusion	18	12	0.337
• Superficial SSI	2	1	>0.999
• Deep SSI	4	3	>0.999
• Organ SSI	4	7	0.541
• Reintubation	5	8	0.573

about these patients' congenital defects and comorbidities, our analysis demonstrated that a significant number of patients have multiple cardiac risk factors, respiratory disorders, and neurodevelopmental impairment, yet, in this dataset only 5% required tracheostomies and 5% were reported to have a malignancy.

The number of surgical interventions increased over the study period from 2012 to 2017. With the caveat of improvements in the database over the years, this could represent a paradigm change by caregivers and providers who are willing to take care of these complex patients. The ACS NSQIP-P database demonstrated that most of these procedures were elective, and up to 14.5% of them were in the outpatient setting. Even though the most common surgeries were related to General Surgery procedures (gastrostomies, fundoplications), an important number of patients underwent complex interventions such as nephrectomies (Wilms), hepatectomies (hepatoblastoma), colectomies, CDH and TEF repairs. These findings highlight the importance of surgical interventions in improving the survival of these patients and provide further insight into the outcomes of this rare condition.

The most common postsurgical complications reported were bleeding, unplanned intubation, UTI, cardiac arrest requiring CPR, pneumonia, and sepsis. However, the rate of superficial SSI was <2% and that of organ space SSI was <2%. Survival >30 days after surgery for patients with trisomy 18 was reported to be greater than 90%, with the majority of these discharged home. The total median hospital LOS was 5 days for all patients, likely related to the need for a procedure required prior to discharge, e.g. gastrostomies. Ten percent of patients were readmitted, with only half of those related to the initial operation. The main reasons reported included cardiac arrest requiring CPR, pneumonia, dehydration, gastrostomy site infections or malfunction. Interestingly, unplanned reoperations were rare and not necessarily related. Moreover, using a case–control analysis, we found no differences in readmission, reoperations, mortality, total hospital LOS, and complications between groups, indicating that patients with trisomy 18 have similar surgical outcomes when compared to the general population.

There are several limitations to our study. First, this is a retrospective review of a clinical database that only captures a portion of specific procedures included in the pediatric ACS-NSQIP. This creates a major bias since this cohort likely represents patients that have already demonstrated increased survival over 1 year of age more likely to undergo an operation. Second, this database continuously expands over the years, and new variables are added throughout the years; however, most of these are related to predictor variables, which do not preclude analysis of outcomes and complications. Third, partial translocation and mosaicism represent the minority of cases with trisomy 18. This subset of patients has a wide range of phenotypes (complete trisomy 18 to apparently normal adults), which may account for differences in outcomes and survival; unfortunately, these data are not available in this database. Fourth, data on prenatal diagnosis, terminations, and miscarriages are unavailable in this database, which limit the evaluation of survival in this patient population. However, we were only interested in the surgical outcomes of patients with trisomy 18 in our study. Fifth, this study cannot determine if interventions caused longer survival or improved quality of life. However, because of the rarity of these diagnoses and variability in their presentation, it is challenging to generate definitive evidence about intervention efficacy. Sixth, not all cases could be matched given the conditions required for matching and we only used a small sample from the NSQIP database. We hope that this study helps further the conversation regarding the definitive treatment of patients with trisomy 18 since these patients can experience long term survival, excellent surgical outcomes and low complications.

The main purpose of our study was to provide a descriptive analysis of surgical outcomes of patients with this rare condition. Given the nature of the data we are not able advocate or recommend any interventions. However, we believe this study can generate further questions that can help understand the different outcomes within this patient population. In the future we plan to perform a multicenter study to evaluate outcomes and survival of patients with trisomy 18 based on their type of genetics (full versus partial versus mosaicism).

5. Conclusion

In this data set, patients with trisomy 18 undergoing noncardiac surgical procedures experience excellent surgical outcomes with minimal morbidity and low mortality. Most patients more than a year of age will experience similar outcomes to patients without trisomy 18.

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