Relationship Between Hospital Surgical Volumes and Length of Stay for Index Conditions in Pediatric Surgery: A Canadian Population-Based Study

by

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Table of Contents Page

LIST OF TABLES....v
LIST OF FIGURES....vii
ABSTRACT....ix
LIST OF ABBREVIATIONS USED....x
GLOSSARY....xii
ACKNOWLEDGEMENTS....xi
CHAPTER 1: INTRODUCTION....1
CHAPTER 2: LITERATURE REVIEW....3
2.1 THEORETICAL FRAMEWORK FOR THE VOLUME-OUTCOME RELATIONSHIP....3
2.2 ADULT LITERATURE ON THE VOLUME OUTCOME RELATIONSHIP....3
2.3 THE IMPACT OF ADULT VOLUME-OUTCOME RESEARCH....5
2.4 PEDIATRIC SURGERY....6
2.4.1 Pediatric Surgery Training in Canada....6
2.4.2 Complexity of Pediatric Surgery and Case Volumes....7
2.4.3 Delivery of Pediatric Surgery in Canada....8
2.4.4 Centralization and Subspecialization in Pediatric Surgery....9
2.4.5 Limitation of Centralization of Care In Pediatric Surgery....10
2.5 EVIDENCE OF THE VOLUME-OUTCOME RELATIONSHIP IN PEDIATRIC SURGERY....12
2.5.1 Volume-Outcome Research Design....13
2.6 SUMMARY OF KNOWLEDGE GAP....18
2.7 RATIONALE FOR CURRENT STUDY....19
2.7.1 Hirschsprung's Disease....20
2.7.2 Esophageal Atresia with Tracheoesophageal Fistula....21
2.7.3 Bladder Exstrophy....23
2.7.4 Intended Contribution....26

CHAPTER 3: RESEARCH OBJECTIVES....27
3.1 RESEARCH OBJECTIVES....27
3.2 RESEARCH QUESTIONS....27
3.3 STUDY HYPOTHESES....27
CHAPTER 4: METHODOLOGY....28
4.1 STUDY DESIGN....28
4.2 DATA SOURCES....28
4.3 STUDY POPULATION....28
4.4 MEASURES....29
4.4.1 Definition of Hospital Volume....29
4.4.2 Primary and Secondary Outcomes....29
4.4.3 Patient Characteristics....30
4.5 STATISTICAL ANALYSIS....31
4.5.1 Software....31
4.5.2 Analysis....31
4.5.3 Descriptive Statistics....31
4.5.4 Regression Analysis: Length of Stay....32
4.5.5 Sensitivity Analysis for Length Of Stay....32
4.5.5 Exploratory Analysis of Secondary Outcomes....33
4.6 ETHICS APPROVAL....35
CHAPTER 5: RESULTS....36
5.1 RESULTS FOR HIRSCHSPRUNG'S DISEASE....36
5.2 RESULTS FOR ESOPHAGEAL ATRESIA WITH TRACHEOESOPHAGEAL FISTULA....45
5.3 RESULTS FOR BLADDER EXSTROPHY....57
CHAPTER 6: DISCUSSION....63
6.1 DISCUSSION OF MAIN FINDINGS....63
6.2 STUDY LIMITATIONS....70
6.3 STUDY STRENGTHS....73

CHAPTER 7: CONCLUSION.....75

BIBLIOGRAPHY.....76

APPENDIX A: International Classification of Diseases Codes, 10th Edition and Canadian Classification of Intervention Codes used to identify patients for inclusion in this study.....85

APPENDIX B: Additional Figures for Hirschsprung's Disease.....88

APPENDIX C: Additional Figures for Esophageal Atresia with Tracheoesophageal Fistula.....91

APPENDIX D: Additional Figures for Bladder Exstrophy.....93

List of Tables

Table 1. Characteristics of neonatal Hirschsprung's disease patients who underwent an anorectal pull-through surgery (n=563).....38

Table 2. Postoperative complications for neonatal Hirschsprung's disease patients who underwent an anorectal pull-through surgery (n=563).....39

Table 3. Incidence rate ratios for the association between length of stay and hospital volume calculated using various regression models, for patients with Hirschsprung's disease.....42

Table 4. Comparison of pediatric patients with Hirschsprung's disease treated at high-volume and low-volume hospitals in the study period.....44

Table 5. Comparison of outcomes in pediatric patients with Hirschsprung's disease treated at high-volume and low-volume hospitals in the study period.....45

Table 6. Characteristics of neonatal patients with esophageal atresia and tracheoesophageal fistula who underwent reconstructive surgery (n=278).....47

Table 7. Postoperative complications for patients with esophageal atresia and tracheoesophageal fistula patients who underwent surgical repair (n=278).....49

Table 8. Incidence rate ratios for the association between length of stay and hospital volume calculated for patients with esophageal atresia and tracheoesophageal fistula, using various regression models.....51

Table 9. Comparison of pediatric patients with esophageal atresia with tracheoesophageal fistula treated at high-, medium-, and low-volume hospitals in the study period.....54

Table 10. Comparison of outcomes in pediatric patients with esophageal atresia with tracheoesophageal fistula treated at high-, middle- and low-volume hospitals in the study period, with cut-offs based on restricted cubic spline analysis.....55

Table 11. Comparison of outcomes in pediatric patients with esophageal atresia with tracheoesophageal fistula treated at high-, middle- and low-volume hospitals in the study period, with cut-offs based on tertiles.....56

Table 12. Comparison of outcomes in pediatric patients with esophageal atresia with tracheoesophageal fistula treated at HVHs and LVHs, in the study period, using highest quartile as the volume cut-off.....56

Table 13. Characteristics of neonatal patients with bladder exstrophy who underwent reconstructive surgery (n=37) 59

Table 14. Postoperative complications for neonatal bladder exstrophy patients who underwent reconstructive surgery (n=37).....60

Table 15. Incidence rate ratios for the association between length of stay and hospital volume calculated for patients with bladder exstrophy, using various regression models.....62

List of Figures

Figure 1. Drawings showing (A) diseased segment of rectum and colon characteristic of Hirschsprung's Disease and resection with anastomosis, resulting from pull-through procedure, and (B) colostomy on infant, which is sometimes performed prior to pull-through surgery.....21

Figure 2. Drawings depicting the variants of esophageal atresia with and without tracheoesophageal fistula, along with the Gross classification, prevalence, and description.....22

Figure 3. Drawing demonstrating the exposed bladder and open urethra (see "penis"), characteristic of bladder exstrophy. A diagram of how the bladder and penis are repaired is provided.....25

Figure 4. Cohort selection flow chart for patients with Hirschsprung's disease.....36

Figure 5. Incidence rate ratios and their 95% confidence intervals for the association between length of stay and hospital volume, for patients treated for Hirschsprung's disease.....41

Figure 6. Restricted cubic spline models (three knots) showing the estimated probability of A) blood transfusion at the time of index surgery, B) 1-year readmission for any cause, C) 30-day readmission for any cause, D) 1-year readmission for Hirschsprung's associated enterocolitis, E) 30-day any reoperation, and F) 1-year any reoperation in relation to hospital volume, for patients with Hirschsprung's disease. The solid dark blue line indicates the estimated probability for the spline model and the light blue area represents the 95% confidence intervals.....43

Figure 7. Cohort selection flow chart for patients with esophageal atresia and tracheoesophageal fistula.....46

Figure 8. Incidence rate ratios and their 95% confidence intervals for the association between length of stay and hospital volume, for patients with esophageal atresia and tracheoesophageal fistula.....50

Figure 9. Restricted cubic models (three knots) showing the estimated probability of A) blood transfusion at the time of index surgery, B) 1-year readmission for any cause, C) 30-day readmission for any cause, D) esophageal dilatation within 1 year of index admission, E) 30-day any reoperation, and F) 1-year any reoperation in relation to hospital volume, for patients with esophageal atresia with tracheoesophageal fistula. The solid dark blue line indicates the estimated probability for the spline model and the light blue area represents the 95% confidence intervals. 53

Figure 10. Cohort selection flow chart for patients with bladder exstrophy.....57

Figure 11. Percentage of patients treated for A) Hirschsprung's disease, B) esophageal Atresia with tracheoesophageal fistula, and C) bladder exstrophy, by Canadian province.....58

Figure 12. Incidence rate ratios and their 95% confidence intervals for the association between length of stay and hospital volume for patients with bladder exstrophy.....62

Abstract

Background: Hospital volume is commonly defined as the average number of procedures performed annually, for a given condition, at a single hospital. This measure has been associated with adult patient outcomes for many surgical conditions. The volume-outcome literature has shown that adult patients have improved survival, decreased length of stay (LOS), and readmission rates, when they are treated at a high-volume hospital (HVH). This has guided care delivery through centralization of expertise and minimum operative targets. At present, the literature to on the volume-outcome relationship in pediatric surgery is inconclusive. There is a need for robust context-specific research to determine whether hospital volume is associated with pediatric patient outcomes after surgery, to inform whether it should be used as a metric to guide pediatric surgical delivery.

Study Objective: To measure the association between hospital volume and length of stay (LOS), and to characterize the association between hospital volume and in-hospital mortality, readmission, reoperation, and blood transfusion, for infants treated for Hirschsprung's disease (HD), esophageal atresia (EA) with tracheoesophageal fistula (TEF), or bladder exstrophy (BE).

Methods: This is a retrospective cohort study of patients treated for HD, EA/TEF, and BE that analyzed data from the Canadian Institute for Health Information (CIHI), covering a period from April 2010 to March 2023. Negative binomial modeling was used to characterize the association between hospital volume and LOS, when adjusting for patient characteristics. Restricted cubic splines were used to model the nonlinear association between hospital volume and binary outcomes. Splines were visually assessed to identify any point of inflection that would permit dichotomization of hospital volume in a clinically meaningful way.

Results: Up to 18 Canadian hospitals were found to provide pediatric surgery. No significant association was detected between hospital volume and LOS for patients treated for HD (n=563) or BE (n=37). In the analysis of 278 patients who underwent repair of EA/TEF, the relationship between hospital volume and LOS was significant, though the magnitude of effect was not clinically important [IRR 1.04 (95% CI 1.01, 1.08), p-value = 0.013]. Mortality was a rare outcome; no in-hospital deaths occurred in patients treated for HD or BE, and the mortality rate in patients with EA was 2.5%. A threshold of 6 cases per year was identified in the spline models for HD, above which the probability of blood transfusion decreased and the probability of 1-year readmission increased. The spline models for patients with EA/TEF, demonstrated the relationship between hospital volume and the selected outcomes were non-linear, though no clear points of inflection were identified.

Conclusion: To our knowledge, this project represents the largest volume-outcome study on Canadian children born with HD, EA/TEF, and BE. The results are congruent with previous literature suggesting the strong volume-outcome relationships in adult surgery are not generalizable to complex pediatric surgery.

List of Abbreviations Used

AB	Alberta
BC	British Columbia
BE	Bladder exstrophy
CAPSNet	The Canadian Pediatric Surgery Network
CBAR	Canadian Biliary Atresia Registry
CDH	Congenital diaphragmatic hernia
CCI	Canadian Classification of Health Interventions
CCO	Cancer Care Ontario
CHARGE	Syndrome consisting of coloboma, heart defects, atresia choanae, growth retardation, genital abnormalities, and ear abnormalities
CI	Confidence Interval
CIHI	Canadian Institute for Health Information
CS	Craniosynostosis
DAD	Discharge Abstract Database
DAG	Directed acyclic graph
EA	Esophageal atresia
ECMO	Extracoporeal membrane oxygenation
FY	Fiscal Year
GA	Gestational age
GEE	Generalized estimating equation
G-tube	Gastrostomy tube
HAEC	Hirschsprung associated enterocolitis
HD	Hirschsprung disease
HVH	High-volume hospital
ICC	Intraclass correlation
ICD-10	International Classification of Diseases 10th Revision
IQR	Interquartile range
KID	Kid's Inpatient Database
LRT	Likelihood ratio test
LVH	Low-volume hospital

MB	Manitoba
MIBEC	Multi-Institutional Bladder Exstrophy Consortium
MVH	Middle volume hospital
NACRS	National ambulatory care reporting system
NFL	Newfoundland
NG	Nasogastric
NICU	Neonatal Intensive Care Unit
NS	Nova Scotia
OHIP	Ontario Health Insurance Plan
ON	Ontario
OR	Operating Room
OR	Odds ratio
PEI	Prince Edward Island
PHIS	Pediatric Health Information System
PUMA	Pediatric Urology Midwest Alliance
QC	Quebec
RPDB	Registered Persons Database
SES	Socioeconomic status
SK	Saskatchewan
TEF	Tracheoesophageal fistula
TKA	Total knee arthroplasty
TPN	Total parenteral nutrition
U.K.	United Kingdom
U.S.	United States
VACTERL	Vertebral defects, anal atresia, cardiac defects, TEF, renal anomalies, and limb abnormalities
VIF	Variance inflation factor
WHO	World Health Organization

Glossary

Biliary Atresia	A condition in which the bile ducts outside and inside the liver are scarred and blocked. Bile is unable to flow into the intestine and damages the liver, due to its accumulation.
Bladder Exstrophy	A complex, rare disorder in which the bladder and abdominal wall do not fully form, leaving the pubic bones separated and the bladder exposed to the atmostphere.
Centralization	A process of concentration of resources, which includes infrastructure, staff, material, knowledge, and research.
Charlson Comorbidity Index	A frequently used mortality predictor, based on a scoring system for the number and type of patient comorbidities.
Cloacal anomalies	A congenital condition in which the rectum, vagina and urologic structures are joined into one common channel. These conditions require specialized surgical treatment.
Esophageal Atresia	A congenital disorder in which the esophagus does not form properly or completely.
Hirschsprung's Disease	A birth defect in which nerve cells are missing from a portion of the rectum and colon.
Hospital Volume	The number of specific surgeries performed at an institution over a given period of time.
Subspecialization in surgery	When a surgeon develops an expertise in one area or discontinues the broad practice of their specialty to concentrate on one area of surgery.
Tertiary centers	Facilities that provide medical care that requires highly specialized skills, technology, and support services.
Tracheoesophageal Fistula	A condition in which there is an abnormal connection between the esophagus and trachea.

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Chapter 1: Introduction

The provision of quality pediatric care in Canada is a social expectation. As outlined by the World Health Organization (WHO) in their 2018 publication *Delivering quality health services: a global imperative for universal health coverage*, this requires health services to be timely, equitable, integrated and efficient.[1] In the field of pediatric surgery, there is an increasing focus on initiatives that may increase the quality of surgical care by improving patient outcomes and minimizing resource utilization.[2] In particular, there has been increasing interest in the volume-outcome relationship.

In the adult literature, numerous studies have shown that higher hospital volume is associated with lower postoperative mortality and morbidity rates for numerous procedures.[3] This has been coined "the volume-outcome relationship". Though many studies on this topic have methodological limitations, the results have been widely accepted by the surgical community owing to the sizeable populations that have been examined, the magnitude of effects, and clinical plausibility of the findings.[4] Volume thresholds for various complex procedures have subsequently been suggested, to optimize patient outcomes and limit the number of hospitals with low levels of activity.[5] Consequently, centers of excellence have emerged.

It may seem intuitive that the volume-outcome relationship would apply to pediatric surgery, however, the limited research on this topic has been varied. Underlying differences between adult and pediatric surgery may explain why studies have been inconsistent in their findings. Complex surgery in children is rare, infrequently associated with mortality, and, in many countries including Canada, already centralized through children's hospitals, with specialized surgeons. Nevertheless, in an era where patient outcomes and safety are being scrutinized, there is concern amongst the surgical community with regards to maintaining competency in wide variety

of procedures.[6] Discussions on whether pediatric surgery should be further subspecialized or centralized are common, though limited information is available to guide these initiatives. As such, there is a need for volume-outcome research specific to the Canadian context to better inform whether volume is a helpful metric for guiding care delivery.

This work aimed to fill the gap on the volume-outcome relationship in pediatric surgery, by identifying whether a relationship exists between annual hospital volume and patient length of stay (LOS), following surgical treatment of three important congenital conditions: Hirschsprung's disease (HD), esophageal atresia (EA) with tracheoesophageal fistula (TEF), and bladder exstrophy (BE). Exploratory analysis was also performed to determine whether annual hospital volume is associated with other patient outcomes, including mortality, readmissions, and reoperation.

Chapter 2: Literature Review

2.1 Theoretical Framework for the Volume-Outcome Relationship

The underlying premise of the volume-outcome relationship is that morbidity, mortality, and expenditures, are reduced when surgeries are executed by surgeons and hospitals that perform a larger number of a given procedure. Hospital volume, i.e., the number of surgeries performed at an institution over a given period, is typically understood to be a proxy for provider experience and resources.[7] In 1979, Luft and colleagues published a landmark study describing this relationship: decreased mortality was reported for certain surgeries, when procedures were performed at high volume hospitals (HVHs).[8] This association gained significant interest in the literature, as it was thought to help guide delivery of care. Specifically, whether certain surgeries should be centralized to HVHs.

Two pathways have been proposed to explain how volume is related to patient outcomes: The "practice-makes-perfect" hypothesis, by which physicians and hospitals with a greater number of patients develop better skills, and the "selective referral" hypothesis, which is based on the notion that physicians and hospitals that have better outcomes attract more patients.[9] Regardless of conflicting theories, it is widely accepted that volume is a proxy measure for other factors that affect care, such as the surgeon's training and experience, cohesiveness of the surgical team, availability of adjunct therapies, staffing of nurses, intensivists, anaesthesiologists, and other specialists that may serve in the treatment of patients with complex diseases.

2.2 Adult Literature on the Volume Outcome Relationship

Following the publication by Luft *et al.*, several other researchers set out to characterize the surgical volume-outcome relationship.[8,10] In a 2002 landmark study by Birkmeyer *et al.*, published in *The New England Journal of Medicine*, Medicare data from the 1990s was used to

assess the relationship between hospital volume and mortality for eight types of major cancer resections.[11] Hospitals were classified into quintiles, based on the average number of procedures performed annually. After adjusting for age, sex, race, year of procedure, Social Security income, urgency of admission, and Charlson Comorbidity Index score, the authors found that HVHs had lower 30-day mortality rates for colectomy, gastrectomy, esophagectomy, pancreatic resection, nephrectomy, cystectomy, and pneumonectomy.[11] Importantly, the difference in mortality between HVHs and low volume hospitals (LVHs) for most procedures was too great to be attributed to chance or unmeasured confounding.[11] For example, in the case of esophageal cancer, the odds of postoperative mortality following esophagectomy at very HVHs was 64% lower (OR 0.36 [95% CI 0.26-0.50]) than for those who had surgery at a very LVHs.[11]

To date, thousands of studies have explored the association between surgical volume and adult patient outcomes for numerous procedures, across several disciplines, and the results are consistent. A review by Dudley *et al*. in 2000, demonstrated that 123 out of 128 studies showed that higher surgical volume was associated with lower mortality for 40 different procedures.[12] Meta-analyses have been performed, such as that by Hendricks *et al*., which found reduced in-hospital mortality at HVHs (OR 0.69; 95% CI 0.61-0.77) for complex intraabdominal surgeries.[13] Of note, in this meta-analysis, the difference in mortality for complex procedures between HVHs and LVHs was significant and increased almost linearly with a rising number of patients.[13] Interestingly, the same relationship did not hold true for more routine (i.e., non-complex) surgeries, such as hernia repairs.[13] This may be explained by the underlying pathway linking hospital volume to patient outcomes, which has yet to be established.

2.3 The Impact of Adult Volume-Outcome Research

The sheer number of studies demonstrating a favorable association between surgical outcomes and HVHs in adult surgery has made the data reliable. Thus, literature on the volume-outcome relationship has impacted healthcare delivery. Various regulatory bodies have made recommendations for surgical volume thresholds, limiting what should be performed at centers with low activity.[10,14] Volume-based referral strategies have also been suggested as a feasible approach to quality improvement.[15]

In Canada, volume-based quality initiatives have been undertaken, such as the consensus for Thoracic Surgical Oncology Standards established by Cancer Care Ontario (CCO), that outlines annual minimums of 20 esophagectomies and 150 pulmonary resections, as targets for tertiary centers.[16] In 2007, CCO implemented a policy to regionalize lung cancer surgery in Ontario to 14 designated hospitals, with the goal of reducing adverse patient outcomes. A study by Bendzsak *et al*. compared patient outcomes in the preregionalization interval (January 1, 2004 and December 31, 2007) to those in the regionalization interval (January 1, 2008 to December 31, 2012) and found that regionalization was associated with a significant reduction in the mean LOS, without an increase in readmissions.[17]

Similarly, to concentrate expert care, the Canadian Association of Bariatric Physicians and Surgeons guidelines use hospital volume, amongst other criteria, to distinguish level 1, 2, and 3 bariatric centres.[18] Level 1, 2, and 3 centers must perform an annual minimum of 250, 100, and 50 bariatric surgeries, respectively.[18] This designation is meant to increase standardization of bariatric care across Canada while mitigating risk and improving patient outcomes.[18]

2.4 Pediatric Surgery

It was only towards the mid 1990s that research directed at the volume-outcome relationship in pediatric surgery began to emerge. Early studies looked at pediatric mortality following cardiac surgery,[8] though gradually, research broadened to look at the volume-outcome relationship for pediatric appendectomy, brain tumor resection, tracheostomy, and the surgical treatment of intussusception.[9] Quickly, it became apparent that many common pediatric procedures were being performed at hospitals with low volumes (< 5 cases per year).[10] The rarity of disease in children has thus posed a unique challenge to studying the volume-outcome relationship in pediatric surgery and although an increasing number of studies exist on the topic, it remains unclear whether hospital or surgeon caseloads impact pediatric patient outcomes for many specialized surgeries.

The field of pediatric surgery differs from adult care not only in terms of the rarity of diseases requiring complex surgery, but also by how surgeons are trained, and the distribution of treatment centers across Canada. These differences must be considered when studying the volume-outcome relationship, as they may influence study design and the interpretation of results.

2.4.1 Pediatric Surgery Training in Canada

Surgeons who practice pediatric general surgery complete the same training as those who go on to practice in adult care, i.e., they have obtained a Royal College certification in general surgery. Those who are interested in performing complex and rare procedures in adult surgery subsequently complete a fellowship. Pediatric general surgery is one such fellowship, whereby surgeons are responsible for performing a wide variety of procedures involving several body systems. Pediatric general surgeons treat several common conditions, such as inguinal and umbilical hernias, and appendicitis; however, they also treat rare congenital malformations,

including congenital diaphragmatic hernias (CDH), anterior abdominal wall defects (e.g. gastroschisis, omphaloceles, etc.), intestinal malrotations, bronchopulmonary malformations, and genitourinary conditions.

2.4.2 Complexity of Pediatric Surgery and Case Volumes

In Canada, children up to 17 years of age account for approximately 5% of inpatient surgical procedures.[19] Half of these surgeries represent procedures on older, healthy children outside of children's hospitals.[19] For example, a Canadian study found that after excluding children with complex medical conditions, 49.7% of pediatric inguinal hernia repairs were performed by adult general surgeons, in Ontario.[20] Another study by Bos *et al.* demonstrated that 72% of appendectomies performed on patients aged 17 years or younger, in Canada, were done by adult general surgeons.[21] These statistics underscore that pediatric surgery is rare, with only select surgeries being performed by pediatric surgeons. These numbers also suggest that the volume of routine surgeries being done by pediatric surgeons may be relatively low in comparison to their adult counterparts.

While general surgeons may be able to perform routine procedures on children, such as hernia repairs or appendectomies, the benefits of working with a specialized team are important to acknowledge. For many pediatric conditions, surgery depends heavily on the support of other specialties, such as radiology, pathology, intensive care, specialized nursing, and anesthesiologists.[22] There is evidence to suggest that anesthesia is more complex in younger patients; relative to adults, there is a higher incidence of cardiac arrest and death in pediatric patients undergoing general anesthetic.[22] Pediatric subspecialization of anesthesiologists, and other team members, is therefore important for reducing surgical risk.

Pediatric surgeons are trained to treat rare diseases. The incidence of pediatric disease is much lower than adult disease, even when comparing rare complex adult surgeries to pediatric cases. To exemplify this, a comparison can be drawn between two complex hepatobiliary surgeries: The pancreaticoduodenectomy (i.e., the Whipple procedure), which is mainly performed in adults to resect pancreatic cancer, and the Kasai portoenterostomy, which is performed in infants for treatment of biliary atresia. Biliary atresia is a rare congenital disorder in which all, or part of the extra-hepatic bile ducts, are obliterated.[23] Expert surgical management is required for both procedures, and both diseases are fatal if left untreated. In 2015, there were 52 hepatopancreatobiliary surgeons, in Canada, who performed a median of 15.0 ($\pm$ 11.1) Whipple procedures annually.[24] Comparatively, approximately 18-22 children are born with biliary atresia annually, in Canada.[25] As such, the majority of pediatric hospitals perform less than 3 Kasai portoenterostomy procedures per year.[25] The number of cases performed by individual surgeons is even lower.

2.4.3 Delivery of Pediatric Surgery in Canada

In Canada, pediatric surgeons practice exclusively in university-affiliated free-standing children's hospitals or pediatric units within academic medical centers. Thus, pediatric surgery is provided through 15 distinct centers.[19,26] There are no pediatric surgeons in Prince Edward Island (PEI), New Brunswick, nor in the Northwest, Nunavut, and Yukon Territories. In 2019, there were 24, 17, 11, 7, 6, 4, 3, and 2 pediatric surgeons practicing in Ontario (ON), Quebec (QC), Alberta (AB), British Columbia (BC), Manitoba (MB), Nova Scotia (NS), Saskatchewan (SK), and Newfoundland (NFL), respectively.[26]

Pediatric surgical care in Canada is regionalized, and involves specialized teams.[24] This distribution of care may allow for health resources and program planning to reflect the needs and

preferences of the local population. Given the rarity of many congenital conditions requiring surgical intervention, however, there has been much discussion around further centralization of pediatric surgery and further subspecialization of surgeons.

2.4.4 Centralization and Subspecialization in Pediatric Surgery

Across all fields of medicine, there is a growing emphasis on quality of care, cost-efficient health care delivery, and improved outcomes.[27] The concentration of medical and surgical expertise into a multidisciplinary team with a consistent approach and who is experienced with the long-term consequences of congenital diseases, is thought to be a quality improvement initiative.[27] This has been coined "centralization of care", whereas subspecialization refers to when a physician, e.g., pediatric general surgeon, discontinues the broad practice of their specialty to concentrate on a particular area or disease.[28]

Centralization has been successfully adopted for the delivery of certain pediatric surgeries, such as biliary atresia, in some countries. For example, in 1999, treatment of patients with biliary atresia in the United Kingdom (UK) was centralized to 3 centres.[29] Finland also centralized the care of patients with biliary atresia, in 2005, from 5 hospitals to a single center with 3 subspecialized surgeons and a multidisciplinary team. In both cases, studies found that patient outcomes improved post-centralization.[29,30] Subspecialization has also been embraced in several regions, and evidence suggests that it may be underway, in Canada.

A 2015 survey study by Langer *et al*., found that American and Canadian pediatric surgeons reported a wide range of subspecialization for 44 different procedures.[31] Surgeries for which there was the highest degree of subspecialization (meaning not all surgeons could perform the surgery) were renal and liver transplant, fetal surgery, and bariatric surgery.[31] Surgical groups with higher case numbers were more likely to subspecialize and it appeared that subspecialization

was also associated with referral patterns, rather than a formal policy within a group.[31] It remains unclear whether these patterns exist due to an underlying belief in the volume-outcome relationship, or whether they result from personal relationships.[31]

Interestingly, in another Canadian survey study examining practice patterns in the treatment of BE and cloacal anomalies, the vast majority (94.8%) of surgeon participants agreed that surgical volumes affect outcomes.[32] Correspondingly, 83.8% felt that referring these complex patients to a consortium, comprised of a few centers with interest/expertise, would be favorable, though at the time of the survey, only 10% and 29% reported always or sometimes referring these patients outside of their hospital for treatment, respectively.[32] This study shows that, although there is expressed interest in centralization of care, this is not reflected in current practice.

2.4.5 Limitations of Centralization of Care in Pediatric Surgery

Apprehensions exist towards initiatives for optimization of pediatric surgical care.[31] Notably, there is concern that these measures will impact the viability of training programs, that centralization and subspecialization may decrease the number of jobs available for the increasing number of pediatric surgeons graduating from training programs, or lead to decreased reimbursement, skill levels and/or job satisfaction for surgeons who may experience a decrease in the number of index and complex cases performed.[31]

For patients, centralization may require some families having to travel longer distances, dislocating them from support networks.[29] It may also be associated with an additional economic burden, delays in care due to the logistics of transferring patients, as well as the loss of skills and training opportunities in referring centers.[29]

Subspecialization may impact surgeons' level of comfort and/or ability to manage more complex problems while on call and has implications for succession planning for the surgical team,

in the event that a subspecialized surgeon leaves the practice suddenly.[31] As such, there is a need for robust research to assist with policy-making around centralization of care. More specifically, there is a need for high-quality volume-outcome research on specific surgeries and territories of interest.

The need for context or region-specific volume-outcome research, to guide care delivery, is best understood through comparison. For example, the geographic differences between the UK, a territory with a total area of 243,610 km^2,[38] and Canada, which has a total area of 9.985 million km^2,[39] lead to different challenges for centralization of care. Namely, the differences in population density and distribution/location of hospitals, may impact how easily centralization is carried out. Additionally, underlying differences in populations and healthcare systems between nations may impact the role volume plays in patient outcomes. In the case of biliary atresia, where treatment has been centralized to 3 hospitals in the UK, research has not yet supported adoption of a centralized system in Canada. In a 2010 study by Schreiber *et al*., it was described that biliary atresia is treated at 12 Canadian centers, of which 6 perform less than 1 case annually, 4 perform 1-3 cases annually, and 2 centers see more than 3 cases annually.[25] The authors found no difference in overall survival between the 3 groups and concluded that caseload did not importantly affect outcomes for Canadian patients with biliary atresia.[25] This study had several limitations, namely the arbitrary selection of less than 5 and greater than 5 cases annually for designation of LVHs and HVHs, respectively, for survival analysis. The authors adjusted for age at the time of surgery and only assessed survival as an outcome. Limitations in generalizability of pre-exiting studies and finite research in the Canadian context show that further evidence is required to ensure the benefits of centralization of care outweigh its limitations.

2.5 Evidence on the Volume-Outcome Relationship in Pediatric Surgery

Currently, a limited number of studies on the volume-outcome relationship, for high-risk pediatric surgeries, have been published. Results of these studies have been more heterogeneous than in other disciplines, as highlighted in Levaillant's scoping review, which demonstrated that only 15 of 22 (68.2%) pediatric studies found a significant volume-outcome relationship, in comparison to 75-100% of studies in other surgical specialties.[5]

In a landmark systematic review published in *JAMA Pediatrics* in 2013 by McAteer and colleagues, the authors identified 63 studies evaluating the volume-outcome relationship for 25 distinct pediatric procedures.[7] Studies in pediatric general surgery focused mainly on CDH repair, treatment of biliary atresia, appendectomy, and pyloromyotomy. These studies varied significantly in design and results. Notably, categorization of volume differs from one study to the next, even for the same procedure. Amongst these studies, there was also variability in effect size of the volume-outcome relationship for various outcomes.

In reviews by Morche *et al*., looking at patient outcomes following CDH repair and treatment of gastroschisis, the authors were unable to complete meta-analyses, due to the heterogeneity of the literature.[33,34] They note that crude mortality rates varied widely across the 5 studies on CDH repair and not all studies adjusted for confounders.[33] They concluded that it was uncertain whether hospital volume was associated with outcomes for neonates undergoing surgical treatment of CDH.[33] Results of the 12 studies included in the gastroschisis review varied significantly in terms of the reported magnitude of effect, though were more consistent in suggesting that management of newborns with gastroschisis at HVHs may lead to reduced in-hospital mortality.[34] These reviews support that conclusions drawn from the current body of literature on the volume-outcome relationship for pediatric procedures are insufficient for guiding changes in the delivery of care.

2.5.1 Volume-Outcome Research Design

Reviews on the volume-outcome relationship for pediatric surgery reflect that the literature is afflicted by several methodologic discrepancies. Studies vary in terms of the procedure examined, the selected exposure and outcomes, and adjustments made for confounders and covariates. Study design may be guided by recommendations in the literature.

Selection of the Procedure to be Studied

There is no clear evidence on how or why certain surgeries are selected for evaluation of the volume-outcome relationship. However, given the current body of work that exists, factors taken into consideration include the prevalence of the procedure, the potential for variation in outcomes, and the availability of data. In pediatric general surgery, selection of conditions may be particularly influenced by which databases are available. For example, the Canadian Pediatric Surgery Network (CAPSNet) is a national registry devoted to the study of CDH and gastroschisis, which facilitates research on these conditions.[49] Similarly, the Canadian Biliary Atresia Registry (CBAR) collects information on the treatment of biliary atresia, to optimize standards of care and provide a national collaborative platform for research, education, and knowledge transfer.[49] The availability of this data appears to be reflected in the current literature, with surgical volumes of CDH, gastroschisis, and biliary atresia being more commonly examined than other conditions.

Defining the Exposure Variable

In the volume-outcome literature, caseload has been examined at both the hospital and surgeon level. The definition of high and low volumes at both levels are highly specific to the procedure under review and the region being studied. It is recognized that the same amount of surgeries can be defined either as high or low volume, depending on the condition studied and

geographic location.[35] Notably, this measure may be defined in many ways and rationale for specific cut-off values is infrequently explained in the literature.[35]

In much of the literature, hospital volume refers to the number of procedures performed annually, at a given hospital. This variable is often interpreted as a proxy measure, recognizing that many factors may be behind the volume-outcome relationship, such as compliance with evidence-based processes of care; level of specialization (e.g., specialized units/teams/nursing support), and the availability of resources (diagnostic imaging, neonatal intensive care, etc.).[36]

Though this measure is usually described as the number of cases performed annually, there is variation in how it is measured. Annual hospital volumes may be pooled over a given period to calculate a mean. Others calculate annual caseloads by taking the number of surgeries performed during same calendar year as a patient's hospital admission, or on the hospital's caseload in the 12 months before a patient's hospital admission/surgery.[35] A standard definition of hospital volume has not been established, though findings suggest that conclusions are similar, regardless of how volume is defined.[35]

In analyses, hospital volume may be treated as a continuous or categorical variable. The review by McAteer and colleagues found that volume was rarely (17% of studies) treated as a continuous variable in pediatric studies.[7] As a continuous measurement, volume may provide difficult to interpret results, limiting the ability to guide clinical recommendations. Ideally, volume-outcome studies succeed in defining HVHs and LVHs, or establishing minimum recommended case volumes, over which patient outcomes are acceptable. In much of the literature, this has been achieved by categorizing hospital volume by quantiles. In some cases, ranking is done separately for each year of observation, allowing the rank of a hospital to change from one year to another if volume changed over time.[37] McAteer *et al*. recommend defining volume

categories *a priori* to enhance generalizability and limit bias.[7] Another school of thought exists, however, whereby cut points are identified based on volumes associated with particularly higher or lower surgical complications/adverse outcomes. One approach for achieving this is through restricted cubic splines analysis.[38] Using restricted cubic splines, the non-linear relationship between hospital volume and risk of each outcome is modeled, then examined to identify if any inflection points can be used to dichotomize annual volume, in a clinically meaningful way.[38]

Selecting the Outcome Measure

Numerous metrics of health care may be used to infer quality, though outcome measures have been commonly used because of ease of interpretation. As per a 2023 consensus report by Domenghino *et al*., in *Nature Medicine*, outcomes should be disease, procedure, and context-dependent.[39] Commonly measured outcomes are described below.

Mortality

Mortality is frequently used as an outcome measure because it is binary and unequivocal. Procedural-related morality, intraoperative death, intensive care unit (ICU) mortality, and in-hospital mortality have all been considered in the literature. Death is also often measured at fixed intervals (e.g., 30 days, 6 months, or 1 year), which may eliminate differences related to LOS between hospitals, but introduces the possibility for error by accounting for post-discharge care over which hospitals or surgeons have limited control.

Despite widespread use of mortality as an outcome, in pediatric surgery, death is often too rare an outcome to be used as a measure for operative quality or failure. Currently, survival following surgical treatment of most complex congenital conditions approaches 90%.[40] In a large cross-sectional study of 200,554 pediatric patients undergoing inpatient surgical procedures, the

overall 30-day mortality rate was 0.6%.[41] Thus, researchers and clinicians have expanded their interest and focused on capturing other meaningful outcomes.

Length of Stay

LOS has been used as an important metric for healthcare quality improvement in the literature.[42,43] Prolonged LOS has implications for patient safety, health outcomes, healthcare costs, and the social well-being of families.[44] It has been suggested that if hospital LOS decreases, care is more efficient, effective, and is directly associated with patient mortality and morbidity.[45] This measure broadly captures the care course of patients; LOS may be affected by time to diagnosis, access to therapeutics, surgeon proficiency, and discharge planning.[44] For this reason, LOS is a measure of interest for both healthcare systems and patients.

Readmissions

Readmissions are an outcome measure commonly examined in the volume-outcome literature. Readmission following discharge for a reason related to the first hospitalization is considered to be an indicator of inappropriate discharge, poor discharge planning, or insufficient care coordination.[46] Readmission, like mortality, is often measured at a fixed time interval, such as 30 days. Of note, readmissions measured at a greater time interval, e.g., at 1 year, may provide information on procedural complications that require frequent inpatient management, or planned sequential treatment or reintervention.

Reoperation

Reoperation has been a commonly selected outcome measure for quality assessment, as nonfatal complications are often too procedure specific to be useful across the heterogenous range of general surgery procedures.[47] Also, reoperation is more common than mortality for most

procedures and easily tracked with administrative data.[47] As such, reoperation rates have been used as quality improvement targets.[47]

Blood product transfusion

Transfusions may be required to maintain hemodynamic stability and oxygen delivery perioperatively, in the context of anemia and/or blood loss. However, blood transfusions are not benign, and be associated with febrile or allergic reactions, and increased morbidity.[48] Duration of operation and intraoperative blood loss or need of transfusion, have been measured as outcomes, where relevant.[49,50]

Other Measures of Morbidity and Surgical Complications

There appears to be little consistency as to which surgical complications are selected for analysis in pediatric surgery volume-outcome studies, though surrogate measures reflecting postoperative recovery, such as treatment costs, have been measured alongside specific complications.[5,7,51] Other frequently cited post-operative complications include superficial and deep incisional surgical site infection (SSI), wound dehiscence, urinary tract infection, pneumonia, sepsis, unplanned intubation, and acute renal failure.[7,41,52] For clinical relevance, it is critical that selection of surgical complications be tailored to the procedures and patient population being studied, in volume-outcome studies.

Risk Adjustment and Confounding

To meaningfully compare surgical outcomes across hospitals or surgeons, it is necessary to include risk profiles of all patients in an analysis. Risk adjustment is the process of statistically accounting for differences in patient case mix that influence health outcomes.[46] Without

appropriate risk adjustment, hospitals and providers that care for sicker patients may appear to perform worse, and patients may be misled about the relative quality of care.[46]

Several important pediatric patient characteristics have been associated with worse outcomes in the perioperative period. The most cited factors include prematurity[40,53,54,55], birth weight[40,44,56,53,54], age at the time of surgery[40,43,57,58], and presence of other congenital anomalies[40,43,56,54]. Risk adjustment may be carried out by incorporating these variables into regression models. Even though it is possible to adjust for measured risk factors, the presence of unmeasured patient attributes (e.g. disease severity) means that risk adjustment is imperfect.

Adjustment for clustering is another important consideration, as patients being studied are nested within hospitals, though often not included in volume-outcome study analyses. As reported in the McAteer study[7], only 43% of studies accounted for clustering.

2.6 Summary of Knowledge Gap

There is increasing interest from the medical community in the centralization of complex pediatric surgical care and the subspecialization of pediatric surgeons. However, unlike in adult surgery, where surgical care at HVHs is associated with improved outcomes, there is currently insufficient evidence to support these initiatives. Further research on the volume-outcome relationship in pediatric surgery could help guide policy and care delivery.

To date, much of the literature on the volume-outcome relationship has been conducted in the U.S., where fundamental differences from Canada's healthcare system may impact the volume-outcome relationship. Notably, in the U.S., children may be treated at different types of hospitals (e.g., free-standing children's hospitals, children's hospitals within general hospitals, and neonatal units within community hospitals) and insurance may impact how care is delivered.[56,87]

As previously described, literature on the volume-outcome relationship for pediatric surgery is also limited by its heterogeneity. There is a need for consistent study design to increase interpretability and ensure reliability of results. Often, the definition of HVHs and LVHs is arbitrary; categorization may be performed by quantiles without clear indication of how outcomes relate to hospital volume as a continuous variable. Furthermore, outcome measures vary from one study to the next, and variability in patient characteristics between HVHs and LVHs is infrequently reported.

To better understand the current distribution of pediatric surgical care and patient outcomes in our country, it is imperative that the volume-outcome relationship be studied using Canadian data and that robust methodologies be employed to carry out this research.

2.7 Rationale for Current Study

The current work aims to contribute towards filling the aforementioned knowledge gap, by conducting a volume-outcome study for three congenital conditions using national Canadian health data. The surgical conditions of interest, each described in detail below, are Hirschsprung's disease (HD), esophageal atresia (EA) with tracheoesophageal fistula (TEF), and BE. HD, EA/TEF, and BE were selected as important congenital conditions to study for the following reasons:

(1) A gap exists in the literature on the volume-outcome relationship for the treatment of these diseases.
(2) All three conditions require surgical treatment in infancy, when surgical risk is highest.
(3) Treatment of these conditions is only carried out at tertiary care hospitals by specialty trained surgeons.
(4) The incidence of HD and EA/TEF is similar to that of many other congenital malformations managed by pediatric surgical specialists.

(5) Treatment standards and surgical technique for HD and EA/TEF repair have been relatively stable over the past 10 years.

(6) HD and EA/TEF represent index cases in pediatric general surgery. Their numbers are often collected by training portfolios to reflect that a trainee had adequate breadth of exposure during fellowship—they are truly representative of the identity of the specialty.

(7) BE is much rarer than the two other conditions selected and will help illustrate whether volume-outcome results are generalizable to an even wider scope of conditions.

2.7.1 Hirschsprung's Disease

HD is a congenital anomaly where neural crest cells fail to migrate along the full length of the large intestine, resulting in a functional large bowel obstruction.[59] This means that children born with this disease have difficulty passing stool. Babies may present with abdominal distention, vomiting, and delayed passage of meconium (i.e., a newborn's first bowel movement). Most patients are diagnosed in the 1st year of life with a substantial proportion (80%) presenting in the first month. A full-thickness rectal biopsy is performed to obtain a diagnosis. The incidence of HD has been documented to be 1 to 3 per 10,000 live births.[60] Following diagnosis, infants who are less than 6 months may be candidates for rectal irrigations for bowel decompression, but definitive treatment is a surgical pull-through procedure, where the diseased (i.e., aganglionic segment) is resected (see *Figure1A*).[31,61] At the time of surgery, collaboration with a pathologist is required to identify the transition zone to healthy bowel. Depending on the length of the diseased segment, diversion with an ostomy may be considered (*Figure 1B*). In approximately 3 to 12% of cases, the entire colon is diseased, which is termed total colonic aganglionosis.[61] This condition is associated with higher morbidity and mortality, compared to short-segment HD, and patients may undergo an increased number of surgical interventions, due to complications (e.g. stricturing, obstruction,

or fecal incontinence).[62] In general, recognized perioperative complications following a pull-through procedure include Hirschsprung-associated enterocolitis (HAEC), retrocolic abscess, need for reoperation, and readmission for reasons such as incontinence or constipation.[63,64]

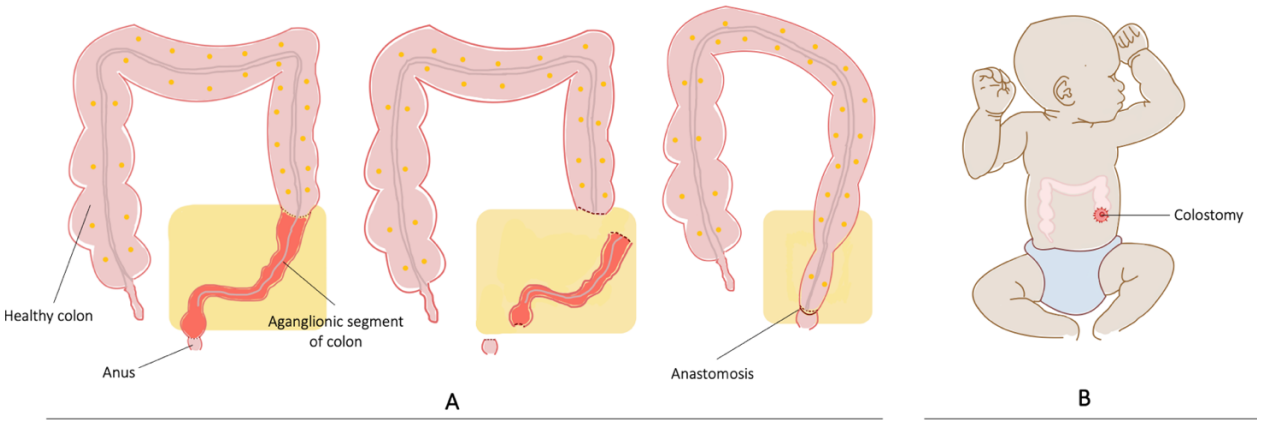
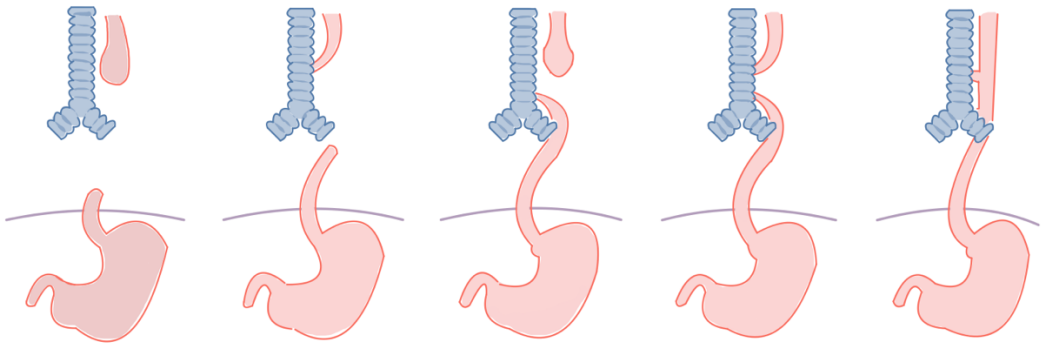


Figure 1. Drawings showing (A) diseased segment of rectum and colon characteristic of Hirschsprung's Disease and resection with anastomosis, resulting from pull-through procedure, and (B) colostomy on infant, which is sometimes performed prior to pull-through surgery.

2.7.2 Esophageal Atresia with Tracheoesophageal Fistula

During normal fetal development, the trachea, which connects the throat to the lungs, and the esophagus, which connects the back of the mouth to the stomach, start out as a single tubular structure.[76] EA with or without TEF is the result of failure of separation or complete development of the esophagus and trachea. EA is when the esophagus is in two segments, thus preventing oral passage to the stomach (*Figure 2*, see Gross Type A). TEF is when a connection (i.e., fistula) exists between the esophagus and trachea (*Figure 2*, see Gross Type E). There are five basic types of EA/TEF.[65] The Gross classification is the most widely recognized. In order of prevalence, they are EA with a distal TEF (86% incidence, Gross Type C), EA without TEF (7%, Gross Type A), TEF without EA (4%, Gross Type E, also referred to as "H-type"), EA with proximal and distal TEF (2%, Gross Type D), and EA with a proximal TEF (1%, Gross Type B).[65]

EA/TEF occurs at an incidence of 1 in 2,500 to 1 in 4,500 live births.[66] Approximately 50% of patients with EA/TEF have associated congenital anomalies, such as VACTERL (vertebral defects, anal atresia, cardiac defects, TEF, renal anomalies, and limb abnormalities) or CHARGE (coloboma, heart defects, atresia choanae, growth retardation, genital abnormalities, and ear abnormalities) syndrome.[76] Babies with EA cannot swallow their saliva, or any liquids. Those with TEF may be able to swallow and feed, however liquids often leak through the fistula and travel into the lungs, causing infection (i.e., pneumonia). Patients with EA/TEF may present with coughing or choking when swallowing, difficulty breathing, and/or vomiting. Diagnosis is achieved by inserting a nasogastric tube (NG). If this does not pass through the nasal canal and down into the stomach (confirmed by X-ray), then EA is likely.[66] Bronchoscopy and/or a barium swallow may be required to diagnose a TEF, if EA is not also present.[66]



Gross Classification	Type A	Type B	Type C	Type D	Type E
Prevalence	7%	1%	86%	2%	4%
Description	Pure EA	Atresia with proximal TEF	Atresia with distal TEF	Proximal and distal TEF	Pure TEF

Figure 2. Drawings depicting the variants of esophageal atresia with and without tracheoesophageal fistula, along with the Gross classification, prevalence, and description.

Patients diagnosed with EA/TEF require timely surgical intervention, usually within the first days of life, and are admitted to the neonatal intensive care unit (NICU) postoperatively to undergo monitoring for complications such as an anastomotic leak, which may require

reoperation.[65] The overall goal of surgery is to reconstruct the esophagus and divide any fistulas, preventing any further communication between the esophagus and trachea. In EA, if the esophageal ends are too far apart, and cannot be joined in an initial surgery, patients may require a gastrostomy tube for feeding. Overall survival following treatment of EA/TEF is estimated at 90%, with a higher risk of mortality with extremely low birth weight (< 1000 g) and/or the presence of associated congenital anomalies.[76,67] Post-operative complications in patients treated for EA/TEF include anastomotic stricture and recurrent TEF.[67] Patients with anastomotic stricture require dilation of the stricture, and for patients who fail to respond to dilations, anastomotic revision may be required.[77] It has been shown that 17% of patients with EA/TEF readmitted within 1-year of their index surgery undergo esophagoscopy and dilation,[54] and these are the common procedures for patients to have received upon readmission to hospital.[54] Patients with EA/TEF are also susceptible to tracheomalacia (a condition whereby the cartilage of the trachea is weak and collapses during breathing), dysphagia (i.e., difficulty swallowing), respiratory tract infections and esophagitis (i.e., inflammation of the esophagus).[67]

2.7.3 Bladder Exstrophy

BE is another rare complex congenital malformation of the pelvis, in which there is abnormal lower abdominal wall development, leaving the bladder splayed open to the atmosphere (*Figure 3*).[68] The bladder in unable to store urine in this disease, and any urine produced by the kidneys drains into the open defect. The pelvic bones are also not properly developed, and patients usually have significant pubic diastasis. BE occurs at an incidence of 1 in 10,000 to 1 in 50,000 live births.[68] Depending on the extent of the defect, patients may have abnormal development of the bladder, epispadias (when the urethra is incompletely formed), widening of the pubic bones, abnormal development of genitalia, inguinal hernias and displacement of the umbilicus.[69]

Diagnosis is often made on prenatal ultrasound, and otherwise at the time of birth.[83] This condition is recognized to be a surgical challenge that is best performed by an experienced pediatric urologist. The goals of surgery are to recreate normal anatomical and physiologic bladder, bladder neck, and urethra for the purposes of maintaining upper urinary tract health, urinary continence, sexual function, and cosmesis.[69,70] This typically involves closure of the bladder and abdominal wall, repair of the epispadias, ureteral reimplantation, and bladder neck reconstruction. Children will often also undergo pelvic osteotomies, to deepen their flattened pelvis, close the pubic diastasis, and allowing for a tension-free closure of the abdominal wall.

It is expected that most children born with classic bladder exstrophy will require multiple surgical procedures through their life span, but a successful primary closure of the bladder in infancy is regarded as the most important factor associated with an acceptable functional outcome in the future[71]. This study is focused on the primary closure of the bladder, which takes place either in the neonatal period or a few months after birth.

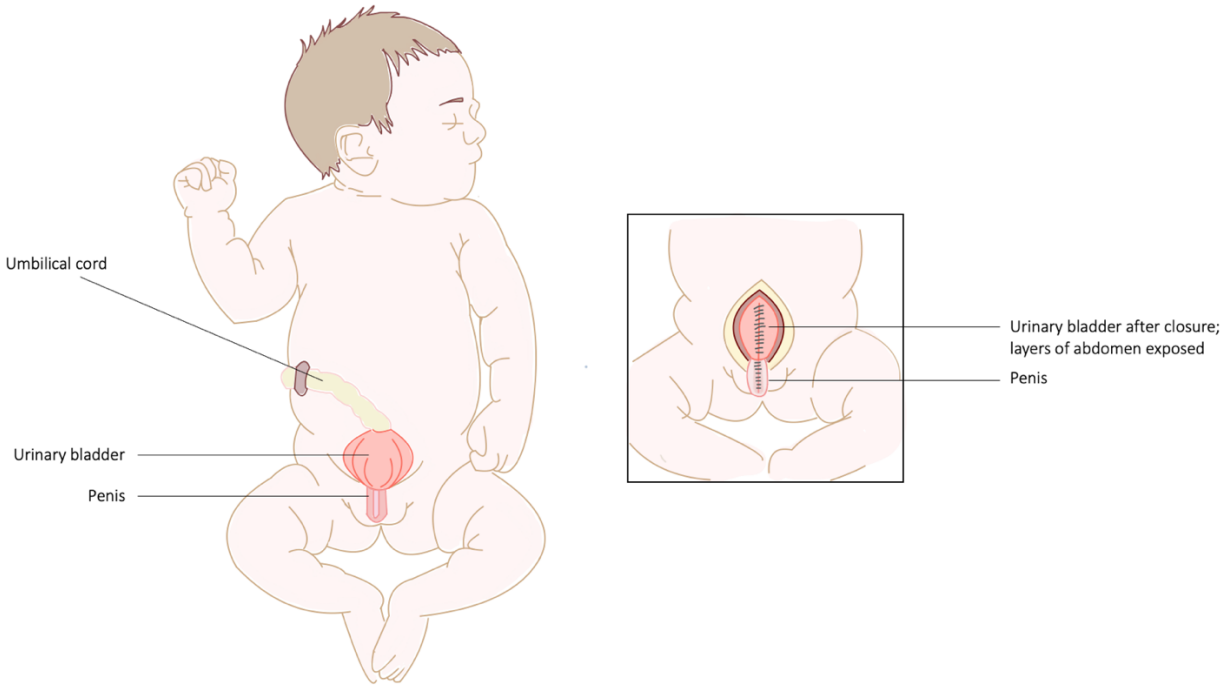


Figure 3. Drawing demonstrating the exposed bladder and open urethra (see "penis"), characteristic of bladder exstrophy. A diagram of how the bladder and penis are repaired is provided.

In the U.K., BE care was centralized to two centers, in 2000, to concentrate expertise, with the goal of improving patient outcomes.[72] Experts have expressed that advancements in the treatment of BE have been propelled forward by increasing volumes at centers of expertise, though data on patient outcomes remains limited.[85] Similarly, in the U.S., consortiums exist to coordinate and provide care to patients with BE. The Multi-Institutional Bladder Exstrophy Consortium (MIBEC) was formed in 2013.[70] MIBEC is a collaborative initiative between expert multidisciplinary teams at three institutions, with the aim of reducing the variability in surgical care and improving outcomes for patients with this rare condition.[70] The Pediatric Urology Midwest Alliance (PUMA) is another group of surgeons from five children's hospitals (located in Chicago, Rochester, Cincinnati, Columbus, and Indianapolis) that strives to provide continuous surgical education, perform collaborative research, and facilitate international missions and

intensive surgical immersion experiences.[86] These surgeons travel between each other's institutions to observe and mentor each other during complex surgeries, such as BE, based on the concept that increased exposure and experience is better.[86] For example, rather than taking part in just one or two bladder exstrophy operations per year, PUMA surgeons may take part in more than a dozen.[86]

2.7.4 Intended Contribution

This work provides important insight into patient demographics and the current distribution of care in Canada, for the selected congenital conditions. Methods have been carefully selected in attempt to overcome some of the shortcomings of the volume-outcome literature. Namely, hospital volume is treated as a continuous variable in the analysis, to best elucidate its relationship with LOS and other outcomes. The results of this work may help guide Canadian policies designed to ensure pediatric patients requiring resource demanding procedures are obtaining care in environments equipped to deliver the best possible outcomes.

Chapter 3: Research Objectives

3.1 Research Objectives

The objective of this study is to understand how hospital volume is related to outcomes for pediatric patients treated for HD, EA/TEF, or BE. Specifically:

1. To determine the association between hospital volume and length of stay (LOS) for infants treated for HD, EA/TEF, or BE.
2. To explore the association between hospital volume and in-hospital mortality, 30-day/1-year readmission, 30-day/1-year reoperation, and blood transfusion, for infants treated for HD, EA/TEF, or BE.

3.2 Research Questions

1. Is there a hospital volume threshold above which patients undergoing surgery for HD, EA/TEF and BE have a significantly shorter LOS in hospital?
2. Is there a hospital volume threshold above which patients undergoing surgery for HD, EA/TEF and BE have significantly lower odds of in-hospital mortality, readmission, reoperation, and blood product transfusion?

3.3 Study Hypotheses

Based on the current body of work that exists on this topic, it is expected that no significant association will be detected between hospital volume and patient LOS, for infants treated for HD, EA/TEF, and BE. Similarly, it is expected that no significant association will be detected between hospital volume the secondary outcomes being studied (in-hospital mortality, reoperation, readmission, blood product transfusion).

Chapter 4: Methodology

4.1 Study Design

This is a multi-institutional retrospective cohort study of pediatric infants diagnosed with HD, EA/TEF, or BE, who underwent operative repair, between April 1st, 2010 and March 31st, 2023. Each of the congenital conditions was assessed separately, to determine whether operative volumes for that specific condition were significantly associated with patient outcomes.

4.2 Data Sources

Data was obtained from the Discharge Abstract Database (DAD), which is maintained by the Canadian Institute for Health Information (CIHI). The DAD captures administrative, clinical, and demographic information on hospital discharges (including deaths and transfers). Patients with HD, EA/TEF or BE were selected using International Statistical Classification of Diseases and Related Health Problems, 10th Revision, Canada (ICD-10-CA) codes. These codes were developed by the WHO and enhanced by CIHI to meet Canadian data needs. Data from CIHI included all patients aged up to 18 months with a diagnosis for at least one of the conditions of interest. Data for a follow-up period of 1 year was included for each patient. To identify which patients underwent an index surgery for their disease, in the study period, Canadian Classification of Health Interventions (CCI) codes were used. The CCI codes classify a broad range of interventions, including therapeutic and diagnostic interventions. For a complete list of the ICD-10-CA and CCI codes used to identify patients in our study, refer to *Appendix A*.

4.3 Study Population

Pediatric patients with an ICD-10-CA diagnosis code for HD, EA/TEF, or BE, aged up to 18 months at the time of index surgery, between April 1st, 2010 and March 31st, 2023, were included in the study. Patients with pure EA (Gross type A), congenital esophageal stenosis, and cloacal

exstrophy were excluded, as the complexity of the surgical treatment for these disease variants differs from that of the remaining study cohort, therefore representing outliers. Patients residing and undergoing surgical treatment in Quebec were also excluded from this work, as data from Quebec is unavailable through CIHI. Patients treated in fiscal years (FY) 2010/11 and 2011/12 were similarly excluded from the analysis because their hospital volume exposure was unknown. These patients, however, were included in the calculations of hospital volumes.

4.4 Measures

4.4.1 Definition of hospital volume

The exposure of interest in this study was hospital volume for each of HD, EA/TEF, and BE. In this study, volume was defined as the average annual number of surgeries, for any single condition, performed by a hospital during the preceding 2 years. The average was taken over 2 years to smooth out year-to-year variation in volume, while minimizing the number of patients excluded due to their hospital's cases not being identifiable in the database during the entire look-back period.

4.4.2 Primary and Secondary Outcomes

The primary outcome of interest in this work was LOS at the time of index admission. LOS is a derived measure, representing the difference, in days, between admission date and discharge date. A patient's index admission was defined as the first hospital stay during which they received a corrective surgical procedure (i.e. index surgery) for their congenital anomaly. The surgical procedures of interest for each congenital condition are listed in *Appendix A*. LOS was treated as a continuous measure for analyses.

Secondary postoperative outcomes of interest were examined and treated as binary measures. These included in-hospital mortality (i.e., any death that occurred in a patient at their

index admission), rates of blood transfusion, 30-day, and 1-year any reoperation (i.e., whether a patient underwent an additional intervention for the same condition within 30 days or 1 year of their index procedure), as well as 30-day and 1-year readmission for any cause. 1-Year readmission for esophageal dilatation was also examined in patients who underwent surgical intervention for EA/TEF. Similarly, 1-year readmission for HAEC in patients treated for HD was examined.

4.4.3 Patient characteristics

Several patient characteristics were selected *a priori* for risk adjustment, based on their prevalence in the literature, and their association with the outcomes being measured. These included gestational age (in completed weeks at delivery), age at index admission (in months), sex, weight at the time of index admission (in grams), and diagnosis of a congenital cardiac anomaly (see ICD-10-CA codes in *Appendix A*). Cardiac anomalies were selected as a surrogate for the presence of other congenital anomalies, as these are amongst the most common anomalies found in patients with HD, EA/TEF, and BE and have been specifically linked to the outcomes of interest.[40,53] Age was provided in months and when a patient was less than one month of age at the time of their admission, this was indicated as "<1" in the CIHI dataset. For patients with HD who were admitted at less than one month of age, uniformly distributed random numbers within the range of 0.33 to 0.97 were used to replace "<1", representing an age range of 10 to 29 days. In the case of EA/TEF and BE, age was simply dichotomized (i.e., <1 month and ≥1 month) because of the large number of patients who were less than 1 month of age at their index admission. To further characterize the three cohorts, additional patient diagnoses were identified using ICD-10-CA codes (see *Appendix A*).

4.5 Statistical Analysis

4.5.1 Software

All analyses were conducted using SAS 9.4M7 software (SAS Institute, Cary, NC), accessed through the CIHI Secure Access Environment (SAE), at the IWK Health Centre.

4.5.2 Analysis

Each CIHI dataset for the selected conditions was closely examined. Admissions were provided in chronological order, and individual patients were identified by meaningless but unique numbers (MBUN). In cases where the MBUN was missing, the data was inspected and a MBUN was assigned to each admission, unless it appeared that the data may represent the same patient, in which case, the same MBUN was assigned. This was the case for only one patient with HD. The dataset was inspected for other missing data and any patterns of missingness (i.e., data missing completely at random, at random, or missing not at random). When less than or equal to 6% of records contained missing values, then a complete case analysis was carried out. Missing data greater than 6% was visually examined. In cases where the missingness was associated with a selected patient covariate (GA, age at admission, or sex), then that variable was excluded from the analysis.

4.5.3 Descriptive Statistics

Separate analyses were carried out for HD, EA/TEF and BE. The number of individuals included in each patient cohort is reported along with patient characteristics. The distribution of all continuous measures was assessed, using frequency plots and histograms. Medians and their associated IQR are presented. For categorical variables, frequencies are displayed as counts and percent represented [n (%)]. For comparison of binary and categorical groups, χ^2 test was used, and continuous variables were compared using the Wilcoxon rank-sum, where appropriate.

4.5.4 Regression Analysis: Length of Stay

LOS in days was treated as a count variable in this work, as has previously been done in the literature. A negative binomial mixed model was selected for analysis, as LOS data was overdispersed and measures were not independent; patients are clustered by hospital, thus patients' LOS within hospitals are possibly correlated. The mixed models aimed to incorporate individual hospitals as a random effect, to control for the nested data structure. Unfortunately, the adjusted mixed models did not converge. As such, the random effects were dropped, and negative binomial regression was used to evaluate the association between LOS and hospital volume. Models were adjusted for patient covariates selected *a priori*. Gestational age and weight were found to be strongly correlated, by Pearson's correlation coefficient (0.8), thus only GA was selected for risk adjustment, to avoid multicollinearity.

The estimated coefficients of the final model are reported and interpreted as the change in the number of days for a 1 case increase in hospital volume, when all other covariates are held constant. Significance of this relationship will be evaluated based on the Wald statistic (value less than 0.05 indicates significance) and the 95% CI will be examined.

4.5.5 Sensitivity Analyses for Length of Stay

Influential outliers were considered. In some instances, patients remained in hospital for a prolonged period and had multiple comorbidities that were likely contributory to their LOS in hospital. It was hypothesized that these patients may represent influential outliers. For each condition, patients with a prolonged LOS were excluded from the regression analysis to evaluate their impact on the measure of association between LOS and hospital volume. These patients represented those who had a LOS in the top 90^{th} to 95^{th} percentile.

There have been various ways of categorizing hospital volume in the literature and it is unknown whether the definition of hospital volume changes the measures of association between volume and outcome. In this work, the adjusted negative binomial regression analysis was repeated using a second definition of hospital volume: the average number of cases performed by a hospital over the study period and, in the case of BE, a hospital's peak annual number of cases. The later was selected for the BE cohort, as this definition has previously been used in the literature, when cases are very rare.

4.5.6 Exploratory Analysis of Secondary Outcomes

To further understand whether there exists a hospital volume threshold above which patient outcomes are improved, exploratory analysis was conducted on the selected secondary binary outcomes. Mortality was determined when a patient's discharge disposition was indicated as "death". Receipt of blood transfusion was provided directly by CIHI as a binary measure, indicating whether the patient had a transfusion during their index admission. Readmissions were derived by identifying admissions after a patient's index admission. A discharge date from each patient's index admission was generated by adding the LOS to the admission date. Any readmissions that fell within 30 or 365 days of that discharge date were used to identify 30-day and 1-year readmissions. Transfers to other institutions were identified when there were zero days between admissions for a given patient and were not counted as readmissions. Reoperations were identified as any readmission during which the patient received a procedure (this included surgery, insertion of lines, ventilation, etc.).

Separate analyses were conducted for patients with HD, EA/TEF, and BE. Restricted cubic splines with three knots were used to model the relationship between hospital volume and the occurrence of each selected outcome, after adjustment for the patient covariates selected *a priori*.

Restricted cubic splines provide a method for exploring non-linear continuous associations. They consist essentially of piecewise cubic polynomials, where the number of "pieces" is established by the number of windows used.[38] The windows are defined by "knots", the number of which is determined by the user, but typically 5 for fewer is sufficient. Three knots were selected for this work, as this number is recommended when the sample size is small; there should be enough observations in between the knots to be able to fit each polynomial.[73] Though more complex, practically, cubic polynomials are fit to each window with further restrictions to ensure the spline is continuous and smooth at each knot. In the volume-outcome literature, restricted cubic splines may be visually assessed to determine whether any volume threshold(s) exist, where the probability of a patient outcome changes.[74–76]

The non-linear relationship between hospital volume and the probability of each outcome was visually assessed. These plots were inspected for any inflection point that could be used to categorize hospital volume in a clinically meaningful way (LVH vs HVH). As previously done in the literature,[74] if an area of inflection was observed, receiver operating characteristic (ROC) curves were generated relating annual hospital volume to the risk of the selected outcome. The ideal cut point to dichotomize hospital volume is described for each outcome, based on the maximum area under the curve (AUC). When more than one inflection point was present on the spline curves, thresholds for defining high-, middle-, and low-volume hospitals were selected based on where the slope of the spline changed. Notably, the size of the BE cohort was too small to allow for restricted cubic spline analysis. As such, descriptive statistics alone are presented for patients with BE.

For outcomes where hospital volume could be meaningfully categorized, patients were classified according to whether their index surgery was performed at a LVH, middle-volume

hospital (MVH) or HVH. Baseline characteristics were calculated with proportions [*n* (%)], means with 95% CI, and medians with IQR, as appropriate. Similarly, patient outcomes were reported by hospital volume. Comparison between patient groups were carried out using Wilcoxon rank sum tests for continuous variables and χ^2 tests for categorical measures.

4.6 Ethics Approval

This project received ethics approval through the IWK Health Center's Research Ethics Board (File number: 1029175) and was conducted in accordance with the Tri-Council Policy Statement (TCPS) on Ethical Conduct for Research Involving Humans guidelines involving secondary datasets.

Chapter 5: Results

5.1 Results for Hirschsprung's Disease

From April 1st, 2010 and March 31st, 2023, there were 606 patients identified as having a diagnosis of HD. Each patient had up to 8 admissions in the study period. A total of 563 patients with HD underwent an anorectal pull-through procedure. See *Figure 4* for a flow-chart of patient inclusion. Patients who did not undergo a pull-through procedure in the study period most commonly underwent bowel resection and/or ostomy creation. The baseline characteristics for the included study cohort are shown in *Table 1*. The male to female ratio of this cohort was 4:1. Forty-four (8%) patients had a congenital cardiac anomaly. It is important to note that there was significant missing data (>70%) for measurements of weight and GA. As such, they were not used in further analysis.

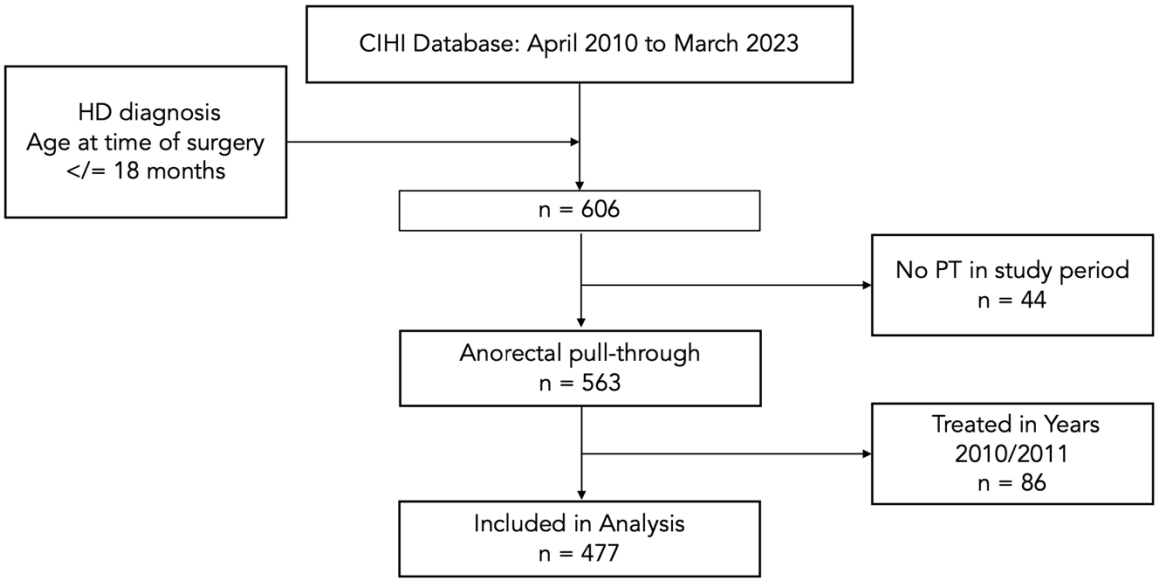


Figure 4. Cohort selection flow chart for patients with Hirschsprung's disease.

The mean number of anorectal pull-through surgeries performed annually in Canada was 43 (SD 6, range 30 to 52), and there did not appear to be any temporal trend. Patients were treated

across 18 hospitals, with two hospitals performing less or equal to 2 pull-though procedures in the study period. Over half [299, (53%)] of all cases were performed in ON, across 6 hospitals. In both NS and NFL, all pull-through procedures were performed at a single hospital. The fewest cases performed by any province, over the study period was five. No hospitals performed fewer than one case over a 2-year period. The median hospital volume was 4 pull-through surgeries per year (IQR 2.5- 8), with a mean hospital volume of 5.3 cases per year (SD 4.1).

The median LOS for index admissions was 5 days (IQR 4-9). The distribution of the LOS was right-skewed, as anticipated (see *Appendix B, Figure A*), with a mean that was much smaller than the variance (11.0 *vs.* 715). Three patients treated at the same hospital in ON were admitted for a single day at the time of their index surgery. One of these patients was treated in 2010, thus excluded from further analysis. None of these patients were transferred to another hospital at the time of discharge. Twenty-nine (5%) patients had a LOS > 30 days and 5 patients (1%) had a LOS greater than 100 days. These patients, with prolonged LOS, were co-morbid. In addition to HD, a diagnosis of chromosomal abnormality, congenital abnormality of intestinal fixation, and congenital malformation of the respiratory system, were common. It is therefore plausible that the LOS for these patients was reflective of conditions other than HD or potential post-operative complications following pull-through procedure.

Table 1. Characteristics of neonatal Hirschsprung's disease patients who underwent an anorectal pull-through surgery (n=563).

Variable	Median (IQR) or n (%)
Age at index surgery (months)	3 (1, 5)
Sex	
Male	451 (80)
Female	112 (20)
Weight at index surgery (grams)†	3528 (3132, 3963)
Low birth weight	45 (8)
Gestational age at birth in total completed weeks‡	39 (38, 40)
Premature	11 (2)
Associated diagnoses before or at the time of pull-through[1]	
Cardiac Anomaly	44 (8)
Down's Syndrome	49 (9)
Other chromosomal abnormality	6 (1)
Enterocolitis at index admission	17 (3)
Sepsis	7 (1)
Associated treatments at the time of surgery[2]	
Mechanical ventilation	50 (9)
Parenteral Nutrition	111 (20)
Admission at which patient underwent index surgery	
1st	517 (92)
2nd	33 (6)
3rd	8 (1)
4th	1 (0.2)
5th	3 (0.5)
7th	1 (0.2)
Province of treatment	
Newfoundland	Suppressed
Nova Scotia	34 (6)
Ontario	299 (53)
Manitoba	30 (5)
Saskatchewan	19 (3)
Alberta	97 (17)
British Columbia	79 (14)
Hospital Volume = Avg. cases performed in prev. 2 years	4 (2.5, 8)
Hospital Volume = Annual Average	3.6 (2.5, 12)

1. Based on ICD-10-CA codes at any admission for patients, except for enterocolitis which was only recorded if documented at index admission.
2. Based on CCI codes recorded at the time of index procedure.
† n= 96; in 86% of the cohort, weight was missing.
‡ n =124; in 78% of the cohort, gestational age was missing.

Only two patients (0.2%) in the study cohort died, and neither of these deaths occurred during the index admission. Sixty-seven (12%) patients received a blood transfusion at their index admission. Two hundred and twenty (39%) patients had a readmission for any cause within 1 year of their pull-through procedure, while 88 (15%) patients had an admission for any cause within 30 days of their index admission. Ten (2%) patients underwent a second anorectal pull-through and 125 (22%) patients underwent reoperation for any cause within 1 year of their index surgery. Forty-five percent (n=56) of reoperations were anal dilations, insertion of lines, and anal Botox injections. Other common procedures included cardiac surgery (e.g. septum repair, pulmonary artery dilation, repair and occlusion), ostomy reversal with anastomosis, creation of colostomy, and bowel resection. See *Table 2* for a comprehensive list of post-operative complications experienced by the study cohort.

Table 2. Postoperative complications for neonatal Hirschsprung's disease patients who underwent an anorectal pull-through surgery (n=563).

Variable	Median (IQR) or n (%)
Length of stay at index admission	5 (4, 9)
Blood product transfusion[1]	67 (12)
Post-operative leak†	6 (1)
Post-operative obstruction†	29 (5)
Post-operative complication†	88 (16)
Post-procedure infection†	49 (9)
1-Year redo anorectal pull-through	10 (2)
1-Year any reoperation	125 (22)
30-Day any reoperation	48 (8)
1-Year readmission for any cause	222 (39)
30- Day readmission for any cause	112 (20)
1-Year readmission for HAEC[2]	45 (8)

1. Blood transfusion indicator was missing for 21 (3.7%) patients.
2. HAEC = Hirschsprung's associated enterocolitis
† Based on ICD-10-CA codes.

Regression Analysis

The relationship between LOS and hospital volume was visually assessed using a scatterplot (see *Appendix B, Figure B*). On inspection, the distribution of datapoints did not appear to follow any trend. An unadjusted negative binomial mixed model was initially used to assess the relationship between LOS and hospital volume and found an incidence rate ratio (IRR) of 1.004 (95% CI 0.871, 1.157). This result is non-significant and suggests that volume played little role in the observed LOS. The adjusted negative binomial mixed model did not converge. When a negative binomial regression was adjusted for patient sex, age, and diagnosis of congenital cardiac anomalies, again, no statistically significant association was detected [IRR 0.985 (95% CI 0.973, 1.017), p-value = 0.184]. The goodness of fit tests show that the deviance residual plots were y-axis unbalanced, likely secondary to the right-skewness of the distribution of LOS (i.e., due to patients with prolonged LOS). When a sensitivity analysis was conducted, excluding patients with a LOS > 30 days, thus excluding possible outliers, the model fit improved. The magnitude of effect of the IRR changed slightly [0.988 (95% CI 0.974, 1.003)], though the association remained non-significant. When an alternate definition of hospital volume was used (i.e., annual average of procedures over the study period), the association between LOS and hospital volume was significant, though the magnitude of effect remained small [IRR 0.978 (95% CI 0.958, 0.999)]. *Figure 5* provides a visual comparison of the IRRs calculated from the various models and the results of all regression analyses are shown in *Table 3*.

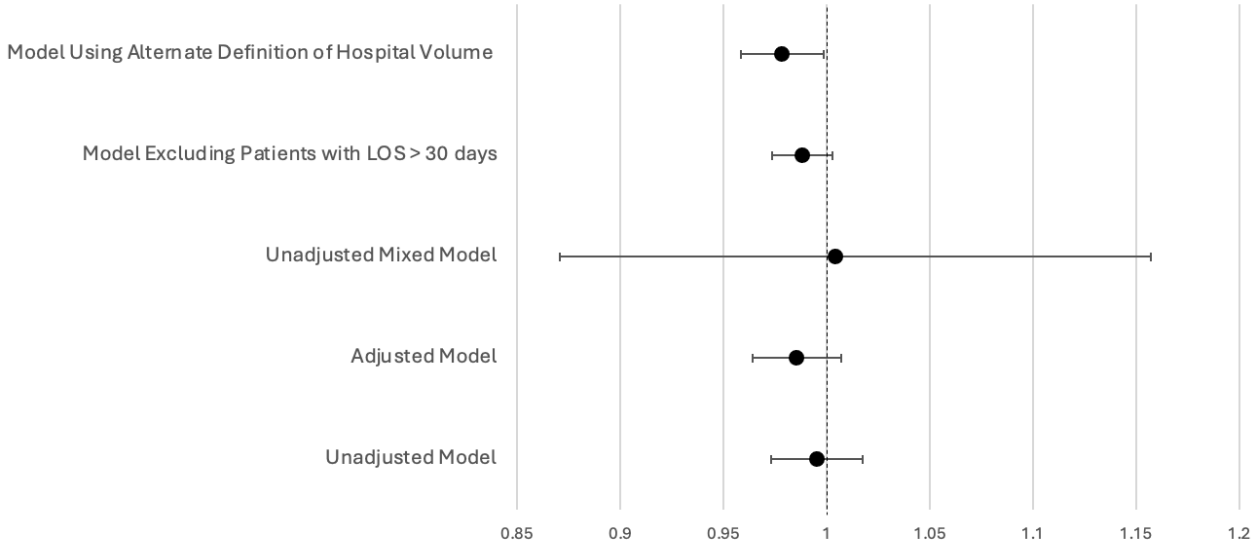


Figure 5. Incidence rate ratios and their 95% confidence intervals for the association between length of stay and hospital volume, for patients treated for Hirschsprung's disease.

Table 3. Incidence rate ratios for the association between length of stay and hospital volume calculated using various negative binomial regression models, for patients treated for Hirschsprung's disease.

Model		IRR	95% CI	p-value
Unadjusted	Hospital volume	0.99	0.97, 1.02	0.66
	Dispersion	2.69	2.40, 3.06	
Adjusted[1]				
	Hospital volume	0.98	0.96, 1.01	0.18
	Male	0.94	0.84, 1.06	0.31
	Age	0.97	0.95, 0.99	0.0056
	Cardiac anomaly absent	0.38	0.28, 0.54	<0.001
	Dispersion	2.46	2.22, 2.78	
Unadjusted Mixed Effects	Hospital volume	1.00	0.87, 1.16	0.95
Excluding LOS > 30 days				
	Hospital volume	0.99	0.97, 1.00	0.11
	Male	1.05	0.97, 1.14	0.22
	Age	0.99	0.97, 1.00	0.070
	Cardiac anomaly absent	0.94	0.43, 0.68	<0.001
	Dispersion	1.33	1.27, 1.41	
Alternate definition of hospital volume				
	Hospital volume	0.98	0.96, 0.99	0.036
	Male	0.93	0.84, 1.03	0.16
	Age	0.97	0.95, 0.99	0.0013
	Cardiac anomaly absent	0.41	0.30, 0.56	<0.0001
	Dispersion	2.43	2.21, 2.70	

IRR = Incidence rate ratio

1. Negative binomial model adjusted for sex, age at index admission (months), and presence of cardiac anomalies.

Restricted Cubic Spline Regression Analysis

The restricted cubic spline for the probability of blood transfusion is negatively sloped with an inflection point at about 5 procedures per year, after which the probability of transfusion continues to decrease with increasing hospital volume (see *Figure 6a*). Interestingly, all three restricted cubic splines for readmissions (at 1-year, 30-days, and 1-year for HAEC) show a positive slope, indicating that the probability of readmission increases with increasing hospital volume (see *Figures 6 b-d*). In the case of 1-year all cause readmission, an inflection point around 5 procedures

per year was present, after which the probability of readmission increased at a much higher rate with increasing hospital volume. Similarly, a positive relationship was observed between hospital volume and 30-day and 1-year any reoperation, though no inflection points were identified (*Figure 6 e-f*).

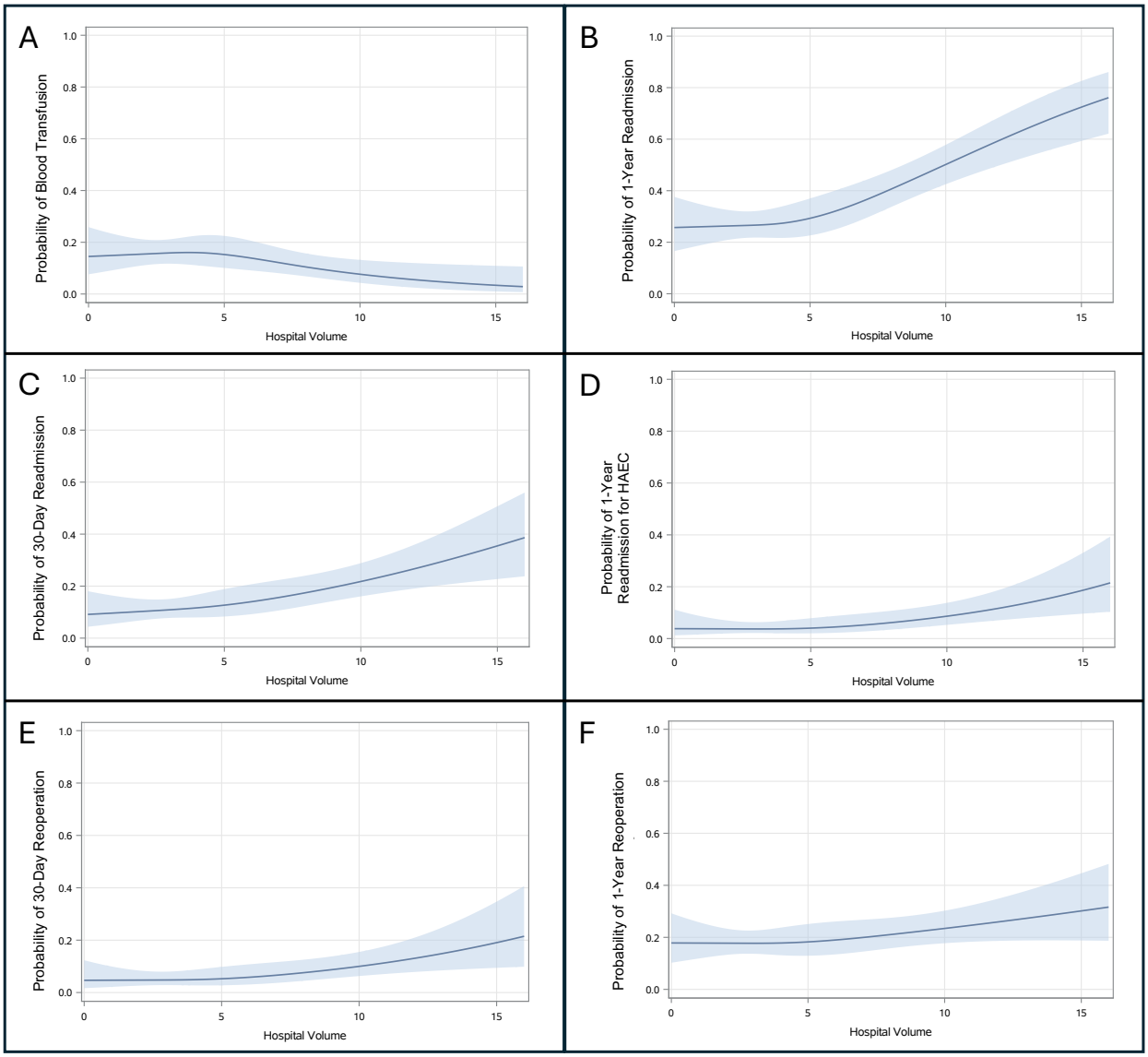


Figure 6. Restricted cubic spline models (three knots) showing the estimated probability of A) blood transfusion at the time of index surgery, B) 1-year readmission for any cause, C) 30-day readmission for any cause, D) 1-year readmission for Hirschsprung's associated enterocolitis, E) 30-day any reoperation, and F) 1-year any reoperation in relation to hospital volume, for patients with Hirschsprung's disease. The solid dark blue line indicates the estimated probability for the spline model and the light blue area represents the 95% confidence intervals.

ROC curves were generated relating hospital volume to the risk for blood product transfusion and 1-year readmission, with cut points of 3, 4, 5, and 6 cases per year (see *Appendix B, Figure C)*. The ideal cut point was found to be 6 cases per year, with an AUC for blood transfusion and 1-year readmission of 0.6232 and 0.6025, respectively (see *Appendix B*, *Figure D)*. Based on these results, hospital volume was dichotomized at 6 cases per year, where LVHs were those that performed < 6 cases per year and HVHs performed ≥ 6 cases per year. A comparison of patients' characteristics treated at LVHs and HVHs is provided in *Table 4*.

Table 4. Comparison of pediatric patients with Hirschsprung's disease treated at high-volume and low-volume hospitals in the study period.

	High volume (≥ 6 cases/year)	**Low volume (<6 cases/year)**	**p-value**
N	165	398	
Age in months (median, IQR)	3 (1, 5)	2 (1, 5)	0.328
GA in weeks (median, IQR)[1]	39 (38, 40)	39 (38, 40)	0.710
Weight in grams (median, IQR)[2]	3510 (2975, 3825)	3528 (3150, 3970)	0.568
Sex			
Male	137 (83)	314 (79)	0.242
Female	28 (17)	85 (21)	
Down's Syndrome	18 (11)	31 (8)	0.228
Premature	5 (3)	6 (1)	0.233
Low birth weight	17 (10)	28 (7)	0.190
Cardiac anomaly	17 (10)	27 (7)	0.154
Fiscal year	2018 (2014, 2020)	2015 (2012, 2019)	<0.0001

1. Due to missing values for gestational age (GA), n=26 treated at HVHs were compared to n=99 treated at LVHs.
2. Missing values for weight, thus comparing n=20 treated at HVHs and n=77 treated at LVHs.

When hospital volume was dichotomized at 6 cases per year, only 6 hospitals were considered HVHs, three of which were in ON, and 399 (71%) patients were treated at LVHs. There were no significant differences in characteristics between patients treated at LVHs and HVHs, however, the fiscal years in which these patients were treated differed significantly.

A comparison of patient outcomes for HVHs and LVHs is presented in *Table 5*. The mean LOS following pull-through procedure was significantly shorter at HVHs than at LVHs. In fact, patients treated at LVHs appear to stay in hospital twice as long as those treated at HVHs. When the median LOS was compared between hospitals, however, this difference was not as great. Patients treated at HVHs had a median LOS of 4 days (IQR 3, 6), whereas those treated at LVHs had a median LOS of 5 days (IQR 3, 8).

Table 5. Comparison of outcomes in pediatric patients with Hirschsprung's disease treated at high-volume and low-volume hospitals in the study period.

	High volume (≥ 6 cases/year)	**Low volume (<6 cases/year)**	**p-value**
N	165	398	
Length of stay, days (mean, SD)	6 (5)	10 (22)	0.0007
Blood transfusion[1]	12 (7)	55 (14)	0.017
1-Year readmission for HAEC	20 (12)	25 (6)	0.0191
1-Year readmission	88 (53)	134 (34)	<0.0001
30-Day readmission	42 (25)	70 (18)	0.033
1-Year reoperation	46 (28)	80 (20)	0.044
30-Day reoperation	20 (12)	28 (7)	0.049

1. Blood transfusion indicator was missing for 21 (3.7%) patients.

All other patient outcomes examined differed significantly between HVHs and LVHs. Seven percent of patients treated at HVHs received a blood transfusion, whereas double (14%) received a transfusion when treated at a LVH. Other patient outcomes occurred at a higher rate at HVHs, in comparison to LVHs, showing that reoperations and readmissions were more common at HVHs.

5.2 Results for Esophageal Atresia with Tracheoesophageal Fistula

A total of 341 patients were identified as having a diagnosis of EA/TEF in the study period. Two-hundred-and-seventy-eight of these patients underwent esophageal and/or tracheal reconstruction. *Figure 7* shows a flow-chart for patient inclusion in the study. Patients who did not undergo a reconstructive procedure in the study period most commonly underwent esophageal

dilatation and gastrostomy-tube insertion. Baseline characteristics of the EA/TEF cohort are shown in *Table 6*. Fifty-seven percent of the cohort was male. An important proportion of this cohort had several risk factors for perinatal morbidity: 29% were born prematurely, 13% had intrauterine growth restriction, and 27% had low birth weight (i.e., < 2,500 g at birth). GA and weight were each associated with 6% missingness. Forty-five percent of patients had a congenital cardiac anomaly and most patients required mechanical ventilation and parenteral nutrition during their index admission (91% and 88%, respectively). As anticipated, the majority (94%) of patients were less than 1 month of age at the time of their index admission.

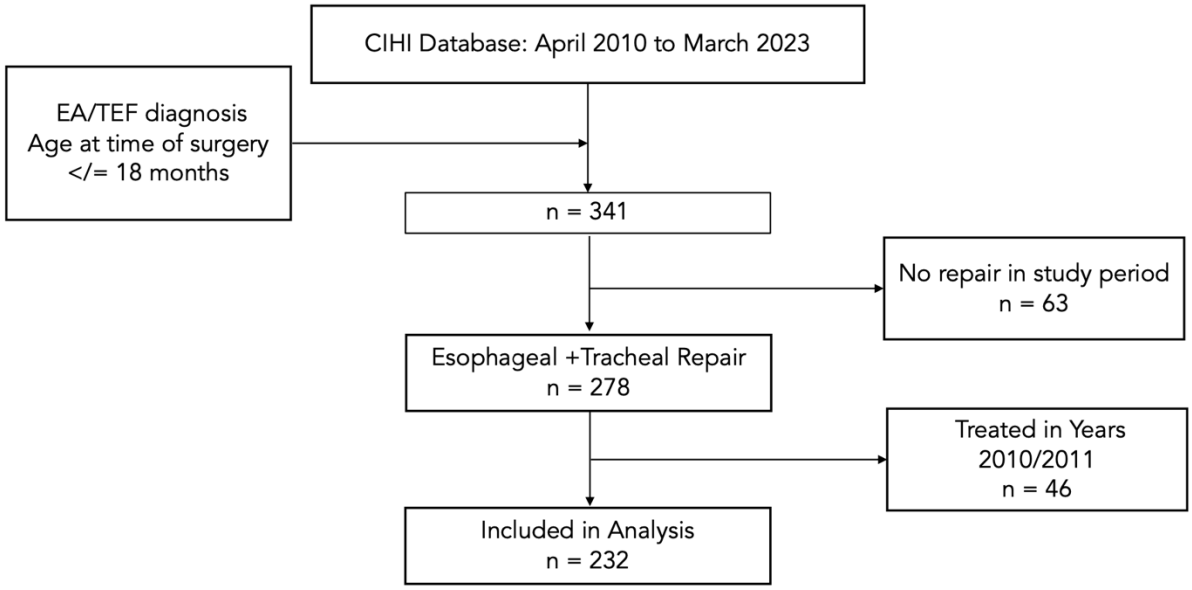


Figure 7. Cohort selection flow chart for patients with esophageal atresia and tracheoesophageal fistula.

Table 6. Characteristics of neonatal patients with esophageal atresia and tracheoesophageal fistula who underwent reconstructive surgery (n=278).

Variable	Median (IQR) or n (%)
Age at index admission	
<1 month	262 (94)
>/= 1 month	16 (6)
Sex	
Male	158 (57)
Female	120 (43)
Weight at index surgery (grams)†	2745 (2190, 3145)
Low birth weight[1]	75 (27)
Gestational age at birth in total completed weeks‡	38 (36, 39)
Premature[1]	80 (29)
Intrauterine growth restriction[1]	92 (33)
Associated diagnoses before or at the time of pull-through[1]	
Congenital cardiac anomaly	125 (45)
Congenital malformation affecting the limbs	105 (38)
Other congenital malformation	4 (1)
Anal atresia or stenosis	12 (4)
Sepsis	19 (7)
Associated treatments at the time of repair[2]	
Mechanical ventilation	254 (91)
Parenteral Nutrition	247 (88)
Admission at which patient underwent index surgery	
1st	274 (98)
2nd	2 (1)
3rd	1 (0.4)
4th	1 (0.4)
Province of treatment	
Newfoundland	Suppressed
Nova Scotia	18 (6)
Ontario	149 (53)
Manitoba	9 (3)
Saskatchewan	6 (2)
Alberta	70 (25)
British Columbia	26 (9)
Hospital Volume (avg. cases performed in previous 2 years)	2.5 (1.2, 7)
Hospital Volume (annual average)	2.3 (1.5, 7.5)

1. Based on ICD-10-CA codes at any admission for patients, except for enterocolitis which was only recorded if documented at index admission.
2. Based on CCI codes recorded at the time of index procedure.
† n= 262; weight was missing for 16 (%) of patients.
‡ n =261; gestational age was missing for 17 (%) of patients.

The mean number of EA/TEF repairs performed annually in Canada was 21 (SD 4, range 15 to 27), and there did not appear to be any temporal trend (See *Appendix C, Figure A*). Patients were treated across 18 hospitals, with six hospitals performing only one EA/TEF repair in the study period. Over half [149, (53%)] of all cases were performed in ON, across 7 hospitals. The median hospital volume was 2.5 (IQR 1.2- 6.5) EA/TEF repairs per year [mean of 3.8 (SD 3.1) cases per year].

The median LOS for index admissions was 25 days (IQR 15, 46) [mean of 43 days (SD 48)]. The distribution of the LOS was right-skewed, as anticipated (see *Appendix C, Figure B*), with a mean that was much smaller than the variance (43 *vs.* 2266). Three patients with the shortest stay were admitted for a single day, while the longest LOS at the time of index admission was 292 days. Two patients documented as having a LOS of 1 day were medically complex and transferred to another institution for ongoing care following EA/TEF repair. One of these patients was treated in 2010 and is therefore excluded from the analysis. Thirty-five (13%) patients had a LOS longer than 90 days. The average GA and weight of these patients were lower than the remainder of the cohort [34 vs 37 weeks ($p < 0.0001$) and 1975 g *vs.* 2716 g ($p < 0.0001$), respectively]. Infants who remained in hospital longer than 90 days were more likely to have had intrauterine growth restriction ($p=0.003$) and a diagnosis of congenital malformation primarily affecting the limbs ($p=0.003$).

Following recovery, 49 (18%) patients were transferred to another hospital and 222 (80%) were discharged home. Seven patients (2%) with EA/TEF died at the time of index admission. All but one of these patients had a congenital cardiac anomaly and/or low birth weight, and 5 were premature.

One hundred and thirteen (41%) patients received a blood transfusion at their index admission. Eighty-six (31%) patients had a readmission within 1 year of their EA/TEF repair, while only 29 (10%) patients had a 30-day readmission. The maximum number of readmissions within 1 year for any single patient was 21. Forty-four percent of patients were documented as having a post-operative complication. Fewer than five patients underwent repeat fistula repair. Most of these patients underwent initial closure of their tracheoesophageal fistula with simple apposition and fibrin glue. They later required reconstruction, repair using local transposition flap, or repeat simple apposition closure of the TEF. Twenty-three percent of the entire cohort required reoperation for any cause within 1 year of their index treatment. See *Table 7* for a comprehensive list of post-operative outcomes.

Table 7. Postoperative complications for patients with esophageal atresia and tracheoesophageal fistula patients who underwent surgical repair (n=278).

Variable	Median (IQR) or n (%)
LOS (days)	25 (16, 47)
In-hospital death	7 (2.5)
1-Year any reoperation	63 (23)
30-Day any reoperation	19 (7)
1-Year readmission for any cause	86 (31)
30-Day readmission for any cause	29 (10)
1- Year readmission for esophageal dilation	32 (11)
Blood transfusion	113 (41)
Post-operative complication†	122 (44)
Post-operative pneumothorax†	40 (14)
Post-operative leak†	13 (5)

† Based on ICD-10-CA codes.

Regression Analysis

The relationship between LOS and hospital volume was visually assessed using a scatterplot (see *Appendix C, Figure C*). On inspection, the distribution of datapoints did not appear

to follow any trend. Forty-six patients were treated in 2010 and 2011 and were therefore excluded from the regression analysis. When a negative binomial regression was adjusted for patient sex, age, GA, and diagnosis of congenital cardiac anomalies, a statistically significant association was detected between LOS and hospital volume [IRR 1.04 (95% CI 1.01, 1.08), p-value = 0.013]. All patients included in this model were <1 month of age, adjustment for age was unnecessary. The model fit was assessed using deviance plots and no problems were detected (see *Appendix C, Figure D*).

When a sensitivity analysis was conducted, excluding patients with a LOS > 90 days, i.e., possible outliers, the model fit improved, though the association was no longer significant and the IRR approached the null [1.02 (95% CI 0.99, 1.05)]. When an alternate definition of hospital volume was used, the association between LOS and hospital volume was significant but the magnitude of effect remained small [IRR 1.05 (95% CI 1.02, 1.09)]. *Figure 8* provides a visual comparison of the IRRs calculated from the various models, and the results of all regression analyses are shown in *Table 8.*

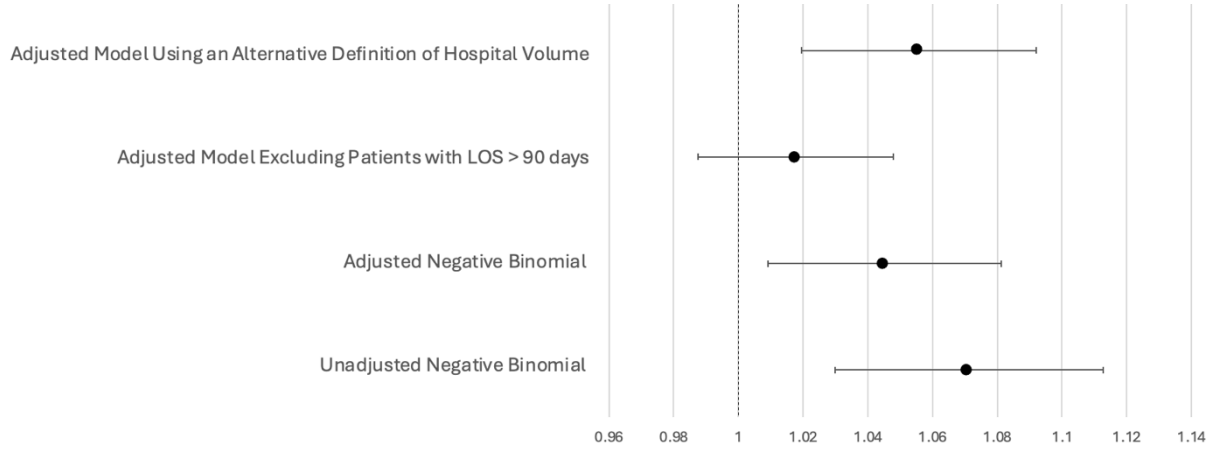


Figure 8. Incidence rate ratios and their 95% confidence intervals for the association between length of stay and hospital volume, for patients with esophageal atresia and tracheoesophageal fistula.

Table 8. Incidence rate ratios for the association between length of stay and hospital volume calculated for patients with esophageal atresia and tracheoesophageal fistula, using various negative binomial regression models.

Model		IRR	95% CI	p-value
Unadjusted	Hospital volume	1.07	1.03, 1.11	0.0006
	Dispersion	2.02	1.80, 2.30	
Adjusted[1]	Hospital volume	1.04	1.01, 1.08	0.013
	Male	0.97	0.79, 1.18	0.74
	Cardiac anomaly absent	0.90	0.74, 1.10	0.32
	Gestational age	0.89	0.86, 0.92	<0.0001
	Dispersion	1.66	1.53, 1.84	
Excluding LOS > 90 days[2]	Hospital volume	1.02	0.99, 1.05	0.26
	Male	0.91	0.77, 1.07	0.25
	Cardiac anomaly absent	1.1	0.92, 1.27	0.32
	Gestational age	0.94	0.91, 0.96	<0.0001
	Dispersion	1.32	1.25, 1.41	
Alternate definition of hospital volume	Hospital volume	1.05	1.02, 1.09	0.0021
	Male	1.00	0.91, 1.09	0.99
	Cardiac anomaly absent	0.91	0.76, 1.08	0.29
	Gestational age	0.89	0.87, 0.92	<0.0001
	Dispersion	1.67	1.53, 1.84	

IRR = Incidence rate ratio

1. Negative binomial regression adjusted for patient age at index admission, sex, gestational age (GA), and diagnosis of congenital cardiac anomalies.
2. Total number of observations included in this model n=188.

Restricted Cubic Spline Regression Analysis

The restricted cubic splines for binary secondary outcomes are shown in *Figure 9a-d*. Not shown is the plot for the probability of death against hospital volume, as this relationship was constant and closely approached zero.

The probability of blood transfusion at index admission appears to be positively sloped (*Figure 9a*), increasing slightly with hospital volume, and reaching a plateau at approximately 3 cases per year. The spline showing the probability of 1-year readmission for any cause against hospital volume is also positively sloped (*Figure 9b*). Interestingly, the restricted cubic splines for 1-year and 30-day reoperation demonstrated higher probability of reoperation at very low and very

high volumes but approached zero between 3 to 7 cases per year. This reflects the raw data, as only 4 (n=4/22, 18%) 30-day readmissions occurred in patients (n= 53) treated at hospitals that performed 3 to 7 cases in the previous 2 years.

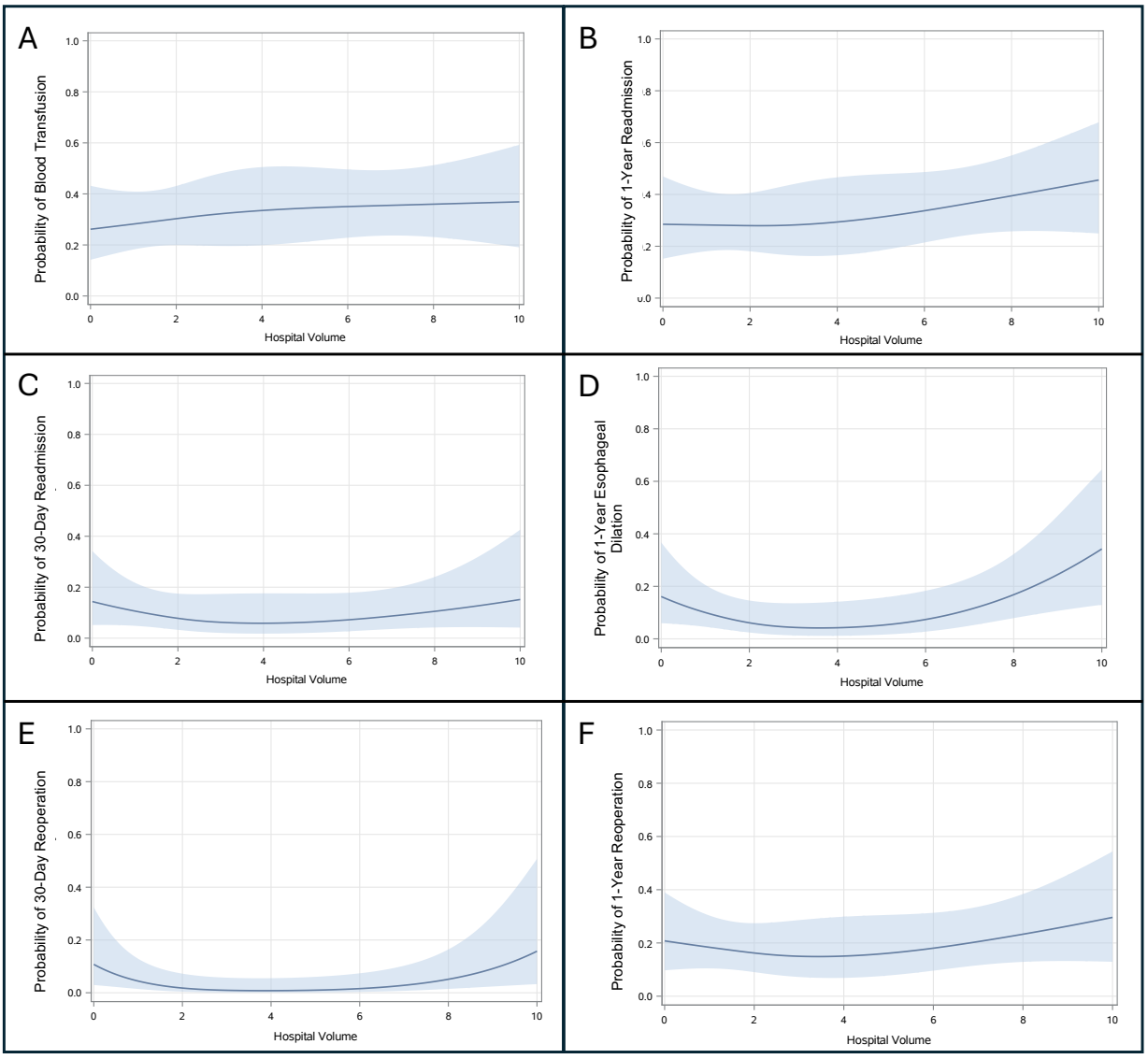


Figure 9. Restricted cubic models (three knots) showing the estimated probability of A) blood transfusion at the time of index surgery, B) 1-year readmission for any cause, C) 30-day readmission for any cause, D) esophageal dilatation within 1 year of index admission, E) 30-day any reoperation, and F) 1-year any reoperation in relation to hospital volume, for patients with esophageal atresia with tracheoesophageal fistula. The solid dark blue line indicates the estimated probability for the spline model and the light blue area represents the 95% confidence intervals.

The spline models in *Figure 9* do not show an inflection point where volume could be meaningfully dichotomized. Rather, the plots for 1-year esophageal dilation, 30-day and 1-year reoperation, appear to be U-shaped, as the probability of the outcome was higher at low and high volumes, and lower in the mid-range. As such, a change in slope at two points was observed in

these spline models. Based on the slope, the cohort could be categorized into three groups: patients with EA/TEF treated at hospitals that performed < 2.5 cases, 2.5 to 7 cases, and >7 cases, in the previous two years. This corresponded to 24%, 23%, and 53% of patients being treated at HVHs, MVHs, and LVHs, respectively. It may be noted these groups differ from what would be observed if the cohort were divided into tertiles based on hospital volume [≤1.5 cases (n=87); 2 to 4.5 cases (n=69); ≥ 5 cases (n=76)]. Characteristics of infants with EA/TEF are presented and compared by hospital volume thresholds identified in the spline plots in *Table 9*.

Table 9. Comparison of pediatric patients with esophageal atresia with tracheoesophageal fistula treated at high-, medium-, and low-volume hospitals in the study period.

	High volume (≥ 7 cases/year)	**Middle volume (2.5-6 cases/year)**	**Low volume (< 2.5 cases/year)**	**p-value**
N	66	65	147	
GA in weeks (median, IQR)[1]	38 (36, 39)	38 (35, 39)	38 (36, 40)	0.3080
Weight in grams (median, IQR)[2]	2575 (2060, 2968)	2910 (2175, 3215)	2749 (2250, 3145)	0.1493
Sex				
Male	42 (64)	34 (53)	82 (56)	0.3958
Female	24 (36)	31 (47)	65 (44)	
Congenital malformation affecting the limbs	32 (48)	29 (45)	44 (30)	0.0153
Intrauterine growth restriction	25 (38)	22 (34)	45 (31)	0.5747
Low birth weight	17 (26)	21 (32)	37 (25)	0.5404
Cardiac anomaly	28 (42)	30 (46)	67 (46)	0.8906
Fiscal year	2017 (2015, 2019)	2016 (2013, 2020)	2016 (2011, 2018)	0.0011

1. Due to missing values for gestational age (GA), n=51 treated at HVHs, n= 61 at MVHs and n=140 at LVHs were compared.
2. Due to missing values for weight, n=51, n=61, and n=142 treated at HVH, MVHs and LVHs, respectively.

Patients with EA/TEF treated across HVHs, MVHs, and LVHs, were similar, though patients treated at LVHs were significantly less likely to have a congenital malformation affecting the limbs.

When outcomes were compared between HVHs, MVHs, and LVHs, using the cut-offs established in the spline analysis, as shown in *Table 10,* MVHs had the longest LOS and differences in LOS were significant between the three hospital volume categories. There was no statistical difference detected for any other outcome between hospital volume groups, though the rate of 1-year readmission for esophageal dilatation and 30-day reoperation seemed much lower at MHV, than at LVHs or HVHs.

Table 10. Comparison of outcomes in pediatric patients with esophageal atresia with tracheoesophageal fistula treated at high-, middle- and low-volume hospitals in the study period, with cut-offs based on restricted cubic spline analysis.

	High volume (≥7 cases/year)	**Middle volume (2.5-6 cases/year)**	**Low volume (< 2.5 cases/year)**	**p-value**
N	66	65	147	
Length of stay, days				
Mean, SD	35 (37)	53 (58)	52 (56)	0.0198
Median, IQR	25 (15, 73)	31(18, 57)	22 (15, 40)	
Blood transfusion[1]	30 (45)	28 (43)	55 (37)	0.5160
1-Year readmission dilation	12 (18)	3 (5)	17 (12)	0.0519
1-Year readmission	23 (35)	18 (28)	45 (31)	0.6703
30-Day readmission	8 (12)	5 (8)	16 (11)	0.6853
1-Year reoperation	16 (24)	12 (18)	35 (24)	0.6509
30-Day reoperation	7 (11)	2 (3)	10 (7)	0.2327

The literature often uses quantiles to categorize hospital volume. When hospital volume was categorized into tertiles, the number of HVHs and MVHs increased (see *Table 11*). Similar results were obtained to when the spline volume cut-offs were applied; LOS was significantly different across tertiles and no other significant difference was identified for the binary outcomes examined. When top-level quartile was used to define HVHs and LVHs, the cut-off value for volume was 7 cases per year (see *Table 12*). In this scenario, 20% of patients were treated at a HVH. In contrast to previous findings, there was no significant difference in LOS between HVHs and LVHs, however 1-year readmission rates for esophageal dilatation were significantly lower at

LVHs than HVHs. These comparisons provide evidence that when the underlying relationship between hospital volume and outcome has not been assessed, arbitrary categorization of volume may not provide an accurate description of the relationship being studied.

Table 11. Comparison of outcomes in pediatric patients with esophageal atresia with tracheoesophageal fistula treated at high-, middle- and low-volume hospitals in the study period, with cut-offs based on tertiles.

	High volume (>4.5 cases/year)	**Middle volume (2-4 cases/year)**	**Low volume (<= 1.5 cases/year)**	**p-value**
N	76	69	133	
Length of stay, days				
Mean, SD	52 (57)	50 (52)	35 (37)	0.0160
Median, IQR	27 (16, 70.5)	30 (18, 58)	22 (15, 40)	
Blood transfusion[1]	35 (46)	30 (43)	48 (36)	0.3415
1-Year readmission dilation	12 (16)	4 (6)	16 (12)	0.1643
1-Year readmission	25 (33)	20 (29)	41 (31)	0.8781
30-Day readmission	8 (10)	6 (9)	15(11)	0.8499
1-Year reoperation	17 (22)	14 (20)	32 (24)	0.8296
30-Day reoperation	7 (9)	2 (3)	10 (7)	0.2937

Table 12. Comparison of outcomes in pediatric patients with esophageal atresia with tracheoesophageal fistula treated at HVHs and LVHs, in the study period, using highest quartile as the volume cut-off.

	High volume (>7 cases/year)	**Low volume (≤7 cases/year)**	**p-value**
N	57	221	
Length of stay, days			
Mean, SD	56 (59)	40 (44)	0.3062
Median, IQR	26 (15, 83)	24 (16, 44)	
Blood transfusion[1]	24 (42)	89 (40)	0.8212
1-Year readmission dilation	11 (19)	21 (9)	0.0388
1-Year readmission	22 (39)	64 (29)	0.1605
30-Day readmission	8 (14)	21 (9)	0.3182
1-Year reoperation	15 (26)	48 (22)	0.4599
30-Day reoperation	7 (19)	12 (5)	0.0676

5.3 Results for Bladder Exstrophy

From April 1st, 2010 to March 31st, 2023, there were 37 patients identified as having a diagnosis of BE. All patients underwent reconstructive surgery at one of 11 hospitals. Notably, no patients underwent treatment in NFLD or Saskatchewan (SK), as shown in *Figure 2C*. A flow-chart of patient inclusion in shown in *Figure 10*. Most (95%) of these patients were carried to term, and few had coexisting congenital anomalies. Sixty percent of patients underwent repair of their exstrophy beyond 1 month of age. Interestingly, over the study period, it appeared that there was a shift in the timing of BE repair. From 2010 to 2014, most patients (83%, n=10/12) underwent repair at less than 1 month of age, suggesting immediate bladder closure in the neonatal period. In subsequent years, from 2015 to 2022, only 20% (n=5/25) of patients underwent immediate repair. In fact, from 2019 to 2022, all patients were older than 1 month of age at the time of BE repair, suggesting that delayed repair is now the favored approach. The baseline characteristics of the BE cohort are shown in *Table 13.*

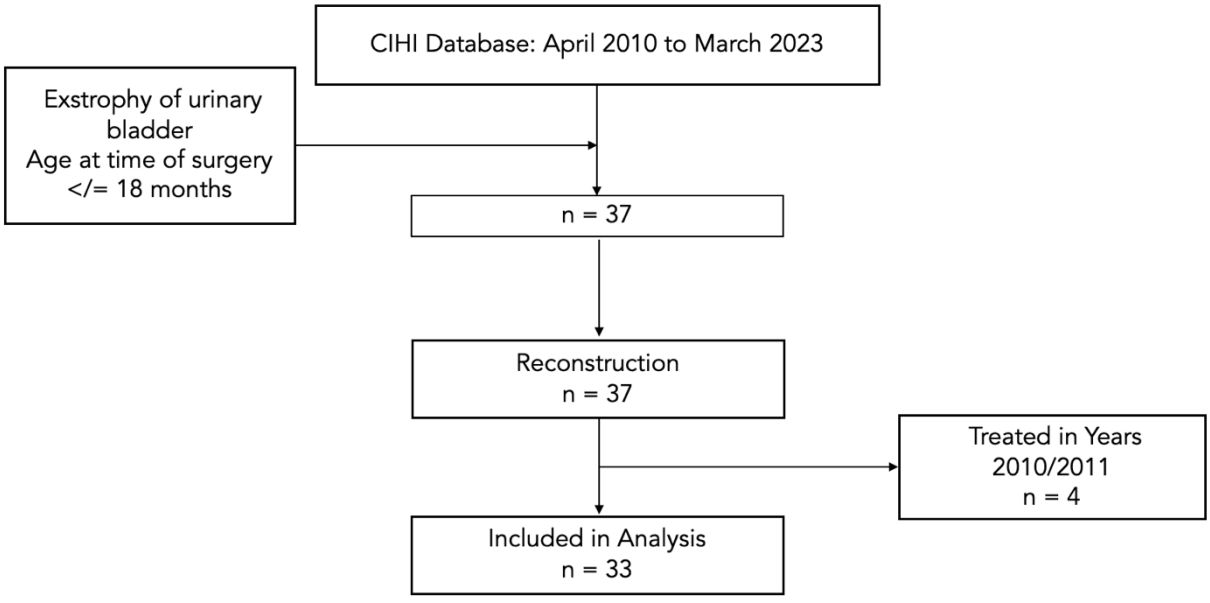


Figure 10. Cohort selection flow chart for patients with bladder exstrophy

The mean number of bladder reconstructions performed annually was 3 (SD 1), with the greatest number of cases (n=5) performed in 2018 (see *Appendix D Figure A*). Individual hospitals performed few cases, with a median hospital volume of zero (IQR 0, 2) cases per year [mean of 0.8 cases per year (SD 1.1)]. When hospital volume was calculated as an average over the study period, the median hospital volume was 0.5 (IQR 0.2, 1.3) cases annually [mean of 0.7 cases per year (SD 0.5)]. When hospital peak volume was examined as an alternate measure of hospital volume, 8 hospitals had a peak volume of 1 case per year, two hospitals had a peak volume of 2 cases per year, and a single hospital had a peak volume of 4 cases per year. Given this distribution, the use of an average annual volume was felt to be more representative of a hospital's experience with BE repairs. *Figure 11* shows the percentage of patients treated in each Canadian province, in comparison to the distribution of treatment of HD and EA/TEF.

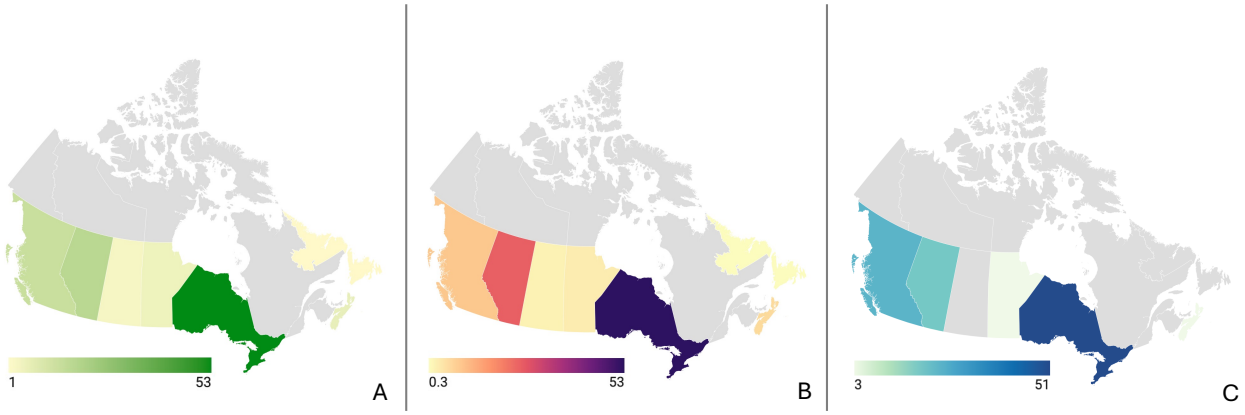


Figure 11. Percentage of patients treated for A) Hirschsprung's disease, B) esophageal atresia with tracheoesophageal fistula, and C) bladder exstrophy, by Canadian province.

The median LOS for index admissions was 27 (IQR 20, 33) days [mean of 26 days (SD 10)]. The distribution of the LOS was right-skewed (see *Appendix D, Figure B*), with a mean that was smaller than the variance (26 *vs.* 100). Two (5%) patients with the shortest stay were admitted

for 2 or fewer days. Neither of these patients was transferred or readmitted to hospital within a year of their index surgery. The longest LOS at the time of index admission was 48 days.

Table 13. Characteristics of neonatal patients with bladder exstrophy who underwent reconstructive surgery (n=37).

Variable	Median (IQR) or n (%)
Age at index admission	
<1 month	15 (40)
>/= 1 month	22 (60)
Sex	
Male	21 (57)
Female	16 (43)
Weight at index surgery (grams)†	3322 (3025, 3732)
Low birth weight[1]	2 (5)
Gestational age at birth in total completed weeks‡	40 (39, 41)
Premature[1]	2 (5)
Associated diagnoses before or at the time of index surgery[1]	
Congenital cardiac anomaly	2 (5)
Congenital malformation affecting the limbs	4 (11)
Indeterminate sex	2 (5)
Urinary tract infection at index admission	9 (24)
Associated treatments at the time of reconstruction[2]	
Mechanical ventilation	10 (27)
Parenteral nutrition	5 (13)
Province of treatment	
Nova Scotia	1 (3)
Ontario	19 (51)
Manitoba	1 (3)
Alberta	7 (19)
British Columbia	9 (24)
Hospital Volume (avg. cases performed in previous 2 years)	0 (0, 2);
Hospital Volume (annual average)	0.5 (0.2, 1.3)

1. Based on ICD-10-CA codes.
2. Based on CCI codes recorded at the time of index procedure.
† n= 15; weight was missing for 23(62%) of patients.
‡ n =15; gestational age was missing for 23(62%) of patients.

No in-hospital deaths occurred for patients with BE. Two (5%) patients were transferred to another hospital, following their index admission, and 35 (95%) were discharged home.

Nineteen (56%) patients received a blood transfusion at their index admission. Twenty-one (57%) patients had a readmission within 1 year of their bladder repair, while only 2 (5%) patients had a 30-day readmission. The maximum number of readmissions within 1 year for any single patient was 7. Sixteen (43%) patients were documented as having a post-operative complication. Four (11%) patients required a second bladder reconstruction, while 14 (38%) required reoperation for any cause within 1 year of their index treatment. See *Table 14* for a comprehensive list of post-operative outcomes.

Table 14. Postoperative complications for neonatal bladder and cloacal exstrophy patients who underwent reconstructive surgery (n=37).

Variable	**Median (IQR) or n (%)**
Length of stay (days)	27 (20, 33)
In-hospital death	0
1-Year any reoperation	14 (38)
30-Day any reoperation	2 (5)
1-Year readmission for any cause	21 (57)
30-Day readmission for any cause	2 (11)
Blood transfusion	19 (56)
Post-operative complication†	16 (43)
Post-operative infection†	8 (22)

† Based on ICD-10-CA codes.

Regression Analysis

The relationship between LOS and hospital volume was visually assessed using a scatterplot (see *Appendix D, Figure C*). On inspection, the distribution of datapoints did not appear to follow any trend. Four patients were treated in 2010 and 2011 and were therefore excluded from the regression analysis.

A negative binomial regression did not detect any statistically significant relationship between LOS and hospital volume. This did not change when the model was adjusted for patient

sex, age, and diagnosis of congenital cardiac anomalies. Nevertheless, the IRR of 1.03 (95% CI 0.87, 1.21) suggested the relationship was positive. The goodness of fit tests for the adjusted model are shown in *Appendix D, Figure D*. Deviance residual plots showed relatively symmetrical distribution and did not display any clear pattern, suggesting the model fit was satisfactory.

Sensitivity analyses showed that when outliers were excluded, i.e., patients with a LOS less than 10 days (n=2), the direction of the relationship between LOS and hospital volume changed [IRR 0.98 (95% CI 0.88, 1.08)] and though the model fit improved, this association was not significant. When hospital volume was calculated as the average number of cases performed over the study period, the IRR increased slightly but the model fit decreased [IRR 1.05 (95% CI 0.77, 1.45)]. *Table 15* provides a comparison of each model's estimates for the association between LOS and hospital volume, and *Figure 10* provides a visual comparison of the IRRs calculated from the various models.

Table 15. Incidence rate ratios for the association between length of stay and hospital volume calculated for patients with bladder exstrophy, using various regression models.

Model		IRR	95% CI	p-value
Unadjusted	Hospital volume	1.02	0.87, 1.21	0.76
	Dispersion	1.22	1.11, 1.45	
Adjusted[1]	Hospital volume	1.03	0.869, 1.21	0.76
	Male	1.04	0.873, 1.24	0.65
	Age <1 month	0.97	0.67, 1.40	0.85
	Cardiac anomaly absent	1.04	0.71, 1.52	0.82
	Dispersion	1.22	1.07, 1.39	
Excluding LOS < 10 days[2]	Hospital volume	0.98	0.88, 1.08	0.68
	Male	1.08	0.97, 1.20	0.16
	Age < 1 month	1.13	0.97, 1.11	0.29
	Cardiac anomaly absent	1.06	0.84, 1.35	0.60
	Dispersion	1.20	1.08, 1.41	
Alternate definition of hospital volume	Hospital volume	1.05	0.77, 1.45	0.74
	Male	1.04	0.89, 1.22	0.61
	Age < 1 month	0.93	0.68, 1.28	0.85
	Cardiac anomaly absent	1.03	0.72, 1.47	0.68
	Dispersion	1.03	1.02, 1.13	

IRR = Incidence rate ratio

1. Negative binomial regression adjusted for patient age, sex, and diagnosis of congenital cardiac anomalies.
2. Total number of observations included in this model n=35.

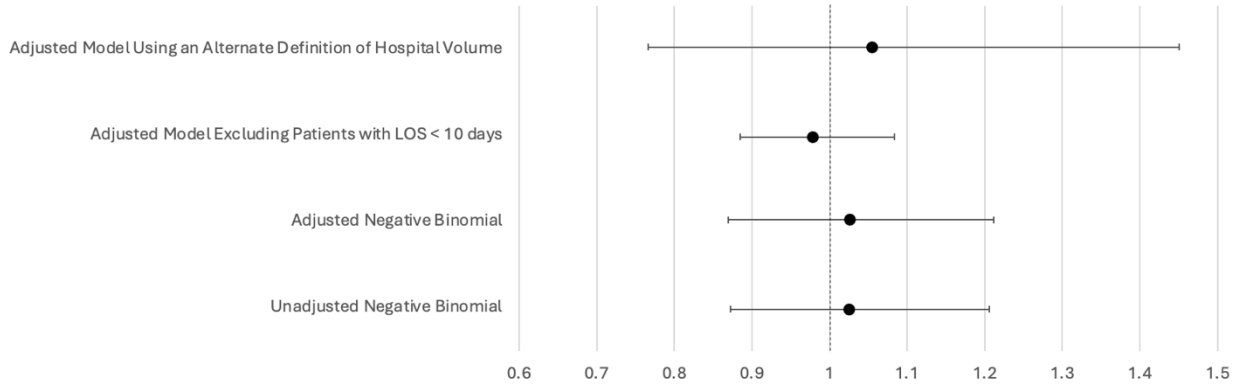


Figure 12. Incidence rate ratios and their 95% confidence intervals for the association between length of stay and hospital volume for patients with bladder exstrophy.

Chapter 6: Discussion

6.1 Discussion of Main Findings

To our knowledge, this work represents the largest Canadian retrospective cohort study on each of the selected conditions. Nearly 900 neonates undergoing high-risk procedures for correction of complex congenital anomalies were included. It offers unique insights into the distribution of pediatric surgical care nationwide. The findings suggest that low procedure volumes are common across most hospitals, and pediatric surgery is conducted in over 18 hospitals across the country. The proportion of patients treated in each province was relatively consistent across the three conditions examined. For all cohorts combined, approximately 6%, 50%, 3%, and 20% of patients were treated in Nova Scotia, Ontario, Manitoba, and Alberta, respectively. While there were variations in the proportion of patients treated for BE compared to other conditions, the small numbers involved limit the conclusiveness of provincial comparisons for this specific condition.

The sample sizes of the three cohorts studied were relatively small. When comparing the sample sizes in this work to the number of cases reported by Statistics Canada from 2011-2020[77], for HD, the numbers are congruent. For EA/TEF and BE, the number of cases reported herein are much lower than those provided by Statistics Canada (341 *vs.* > 507 for EA/TEF and 37 *vs.* >67 for BE). This is due to the rigorous selection criteria applied to these cohorts, along with the exclusion of stillbirths, including spontaneous fetal deaths and elective terminations.

While there has been some evidence of improved outcomes with increased volume and centralization of some pediatric surgical procedures, such as biliary atresia, there has been little evidence regarding the volume-outcome relationships in the treatment of HD, EA/TEF, and BE. Following subspecialization of EA/TEF repair, in the UK, research conducted at a single institution found significant reductions in intensive care LOS and neonatal mortality. However, several other

outcomes were unchanged and trainee experience in EA/TEF repair decreased[78]. In the current study, there were no compelling findings to suggest that pediatric patients requiring surgical treatment for HD, EA/TEF, or BE, would benefit from being treated at higher-volume centers.

Negative binomial regression analysis was employed to determine whether a significant association exits between hospital volume and LOS for three separate cohorts. The results showed that, in patients with EA/TEF who underwent surgical repair, the relationship between hospital volume and LOS was significant, when accounting for patient sex, age, GA, and diagnosis of congenital cardiac anomalies. The same did not hold true for patients with HD or BE; no significant association was detected between hospital volume and LOS for these two cohorts. In all cases, the magnitude of the association was small, though the direction of association varied. These results align with what previous literature has suggested: the volume-outcome relationship in pediatric surgery is not generalizable to all procedures and patient cohorts.

To further explore the volume-outcome relationship for patients with HD and EA/TEF, restricted cubic spline models were used. While use of regression models with categorization of a continuous exposure, in this case hospital volume, is common, categorization has multiple pitfalls, including loss of information, discontinuities in estimated mean outcome values when moving from one category to another, and difficulty comparing results across studies because cut-off points may be data-dependent.[79] Using nonlinear modelling, the work herein demonstrates that the relationship between volume and rates of blood transfusion, readmission and reoperation differ between cohorts. Arbitrary categorization of hospital volume into quantiles would have led to a loss of information, and misinterpretation of the relationships examined. For patients with HD, the restricted cubic spline analysis suggested that hospitals performing more than 6 pull-through procedures per year have decreased rates of blood transfusion and higher rates of 1-year

readmission for any cause. This threshold did not exist for the other outcomes studied, rather, the relationship between hospital volume and 30-day readmission, reoperation, and 1-year reoperation appeared to be nearly linear. For EA/TEF, the restricted cubic spline models for esophageal dilation within 1-year of index admission, 30-day and 1-year reoperation were U-shaped. No clear hospital volume thresholds were observed for any of the outcomes studied for this cohort. Study findings for each of the cohorts are discussed in more detail below.

Hirschsprung's disease

Baseline characteristics of patients with HD included in this work were consistent with what has previously been reported in the literature[76,80,81]: HD more commonly affects males, most of these babies are carried to term with a median GA of 39 (IQR 38, 40) weeks, approximately 8% of patients have an associated cardiac anomaly, and up to 10% have Down syndrome.

As previously mentioned, this study was unable to detect any significant association between hospital volume and LOS at time of pull-through surgery. The median LOS for infants with HD of 5 days (IQR 4,9) was slightly lower than what has previously been reported (8 days, IQR =5),[43,82] despite a number of patients having prolonged (> 1 month) LOS. When an alternative definition of hospital volume was used, allowing all patients (i.e., those treated in 2010 and 2011) to be included in the analysis, the association between LOS and hospital volume was significant, though the magnitude of effect remained small [IRR 0.978 (95% CI 0.958, 0.9999); for every 1 case per year increase in hospital volume, infants with HD had a 2% shorter LOS, when holding sex, age, and the diagnosis of cardiac anomalies constant. As such, this relationship is unlikely to be clinically important.

Mortality was rare event in this cohort (n= 2/563, 0.3%), concordant with previously reported rates of postoperative mortality in infants with HD of less than 1% to 2%.[83,84] Due to the rarity of this outcome, its nonlinear association with hospital volume could not be assessed.

In the analysis of other secondary outcomes, a threshold of hospital volume related to blood transfusion and 1-year readmission was suggested. Above 6 cases per year, the incidence of blood transfusions decreased, and 1-year readmissions increased. Although no inflection points were identified in the restricted cubic spline models 30-day readmissions, 1-year readmission for HAEC, or 1-year and 30-day reoperation, the plots indicated that as hospital volume increased, the probability of these outcomes also increased. This result was unanticipated, as literature has suggested that readmission and reoperations decrease with a hospital's experience and/or expertise.[85] No significant differences in patient characteristics for those who were treated at HVHs versus LVHs were identified to explain this relationship, thus the possibility of an unmeasured confounder, such as a patient's living distance from hospital, is possible. Another possibility is that referral patterns following index admission affect where a patient is readmitted or undergoes reoperation. For example, an infant may be treated at a hospital and if/when they require additional care, they are referred to another, potentially larger, center for a second opinion. This trend may be more prominent in provinces, such as Ontario, where several children's hospitals exist and are located within relatively close proximity of one another.

These results suggest that the associations described in the adult literature between hospital volume and patient outcomes are not generalizable to pediatric surgery. Previous work has drawn similar conclusions. In a 2021 study by Apfeld *et al*., administrative data from 41 American hospitals was used to assess the volume-outcome relationship for patients with HD, following pull-through procedure.[76] These authors defined hospital volume as the average annual number of pull-

through procedures performed by a hospital in patients of any age during the preceding 2 years and found a median annual hospital volume of 9.5 (IQR 7-13) procedures.[76] The latter is a much higher volume than what was found in this study, reflecting that the Canadian population and children's hospitals vary from their American counterparts. Nevertheless, Apfeld *et al.* found that the 30-day readmission and 30-day reoperation rates were 17.2% and 4.5%, respectively[76], consistent with what is described herein. These authors failed to identify any inflection points to categorize operative volumes using restricted cubic splines with quartile knots, therefore dichotomized volume at top patient-level tertiles. No statistically significant relationship between hospital volumes and readmission or reoperation was detected.[76] These results are contrary to what has been observed in the adult volume-outcome literature, though also differ from the results of this work, which show a positive relationship between hospital volume and readmission. Notably, these authors adjusted for patient characteristics in their models, but did not consider patients' socioeconomic status, insurance coverage, or the type of hospital where they were treated, which are factors that limit the comparability of their findings to this work.

Esophageal Atresia with Tracheoesophageal Fistula

This study cohort was unique in its selectivity of patients with EA/TEF, excluding those who had pure EA (Gross Type A), pure TEF (Gross type E), and patients with congenital stricture or stenosis of the esophagus, which are often amalgamated for analyses, despite their pathology representing a wide spectrum of surgical complexity. As such, this work provides a close examination of patients requiring a specific surgical skillset and treatment. Nonetheless, the cohort studied had similar baseline characteristics to those previously reported for infants with EA/TEF.[75]

Previous research has shown that patients who underwent EA/TEF repair had a median LOS of 29 days (range 8-291 days),[80] consistent with the LOS in this study (median 25 days, range

1-292 days). LOS was positively related to hospital volume, though the measure of association was small. Results of the adjusted negative binomial model were significant. With every increase of 1 hospital case per year, patients experienced a 4% increase in their LOS, when controlling for sex, GA, and cardiac anomalies. This relationship was attenuated, and no longer significant, when patients with a LOS greater than 90 days were excluded from the analysis. Despite efforts to address patient risk by adjusting the negative binomial model for patient characteristics, these results suggest that the detected association may be attributable to patient factors. These results are comparable to those reported by Sømme and colleagues, who looked at the volume-outcome relationship in American infants with EA/TEF.[51] They dichotomized hospital volume at 6 cases per year and found the median LOS for patients treated at HVHs to be longer (30 days) than the median LOS of patients treated at LVHs (27 days), though this difference was not significant.[51]

In-hospital mortality for this cohort was 2.5%, which was lower than previous reports of 3.5% to 6.4%, in the literature.[51,75] To date, no significant association between mortality and surgeon or hospital volumes has been identified,[51,75] which was redemonstrated in this study.

Quiroz *et al*. previously reported that 10% (n=212/2179) and 26% of patients with EA/TEF treated in the U.S. were readmitted within 30-days and 1-year, respectively.[54] These results are consistent with rates of readmission in this work. Comparatively, rates of 1-year esophageal dilation, 30-day and 1-year readmission reported herein were lower than those in a 2019 study by Lawrence and colleagues, which aimed to determine whether higher surgeon and hospital volumes are associated with better outcomes after EA/TEF repair.[75] These authors used restricted cubic splines to visually inspect whether any inflection points existed for defining high- and low-hospital and surgeon volumes but found only weak inflection points for some outcomes. Interestingly, the spline models presented in their work for 1-year reoperation showed a positive

relationship with increasing surgeon and hospital volume and strongly resembled the spline for 1-year reoperation in our work (N.B. splines for readmission were described but not provided by the authors for comparison). These authors subsequently dichotomized volume at top tertiles and found no significant association between surgeon or hospital volumes and patient outcomes.

Bladder Exstrophy

This work examined a series of inpatient admissions for patients with BE. Patients with cloacal exstrophy were excluded from this study, to measure the hospital volume-outcome relationship in patients with comparable surgical needs. In doing so, just 37 Canadian patients were identified over the 12-year study period. Results suggest that treatment of these patients may already be centralized, as BE reconstruction took place at only 11 hospitals and no patients were treated in NFLD or SK. Overall hospital volumes were very low, with most hospitals performing 1 or fewer cases annually. Given the rarity of BE, even busy centers may have low or even zero volume years. For this reason, in previous work by Nelson *et al*., hospital peak volume was selected as the exposure when assessing the volume-outcome relationship in 407 patients who underwent treatment of BE.[86] Using 1988 to 2000 data from the Nationwide Inpatient Sample, outcomes for patients undergoing BE repair at high- (n= 6, average of 4.4. cases annually), middle- (n= 13, average 1.8 cases annually), and low-volume hospitals (n= 66, average 0.6 cases annually) were compared.[86] In our study, 72% of hospitals had a peak volume of only 1 BE repair, thus use of peak volumes did not provide much discrepancy across centers.

The management of BE is complex and involves several considerations: timing of the primary closure (immediate vs delayed), the type of BE repair (complete or staged), and the need of symphysis approximation with or without pelvic osteotomy. In the current work, 60% of patients underwent repair at over 1 month of age, consistent with the temporal trend showing that

from 2015 onwards, delayed closure has been favored over early repair. Our study was not designed to evaluate which type of repair patients received. Previously, however, longer LOS and higher rates of transfusion were hypothesized to be associated with higher rates of osteotomy. Nelson *et al.* found the average LOS for patients with BE at the time of repair was 24.6 +/- 22.8 days[86], congruent with what is reported herein. When outcomes were compared by hospital volume, HVHs had significantly longer LOS and transfusion rates than LVHs. In the current work, no significant association between hospital volume and LOS was detected. Rates of transfusion, however, were much higher than what was reported by Nelson and colleagues (56 % vs 6.5-20.2%).

Given the small cohort size, restricted cubic spline analysis could not be employed to assess secondary outcomes in patients with BE. No deaths were documented in the study period, which is consistent with previously reported low rates of mortality (1.5%) in these patients.

This study exemplifies just how rare BE is in Canada and reveals some of the challenges in assessing the volume-outcome relationship, when both the condition and outcomes are rare. Given the observed distribution of care, where surgical treatment of BE is only offered in select provinces, by select hospitals, the question as to whether formal centralization of care would be desirable for care teams and patients requires more investigation.

6.2 Study Limitations

This study has several limitations, many of which may be attributed to its retrospective nature and data source. As previously noted, the DAD provides data from all provinces and territories, except for QC. The exclusion of QC in this dataset means that many cases of HD, EA/TEF, and BE are not captured in this study, and that our results may not be generalizable to infants who receive care in QC.

Patients were identified using a commonly employed method, through the selection of ICD-10-CA codes. Exclusion criteria were applied at the level of data extraction, which may have significantly affected the size of the cohorts, especially for EA/TEF and BE, as several codes exist to characterize variants of those conditions. Notably, the size of both these cohorts was much lower than expected. In work by Dylkowski *et al*., who examined the volume-outcome relationship for EA/TEF repairs from 1993 to 2013, across 4 hospitals in ON, the average number of repairs performed annually by hospital was 5.81 ± 4.41.[87] In a 2014 survey study of Canadian surgeons, the reported average number of EA/TEF cases seen annually by institution ranged from 8-10. Though the latter work was prone to recall bias, and 19 of 70 (27%) surveys did not provide an average number of TEF/EA seen per year, the hospital volume noted in these Canadian studies were much higher than what is reported in our work. Misclassification of patient disease by ICD-10-CA codes is likely to have contributed to the low numbers observed in this study. For example, patients may have been documented as having pure EA, when they in fact had EA with TEF. Misclassification of a patient's disease may also explain why some patients appeared to have undergone EA/TEF repair at over 1 month of age. If they were coded as having pure EA at birth, then that index admission would not have been captured in our dataset and only subsequent admissions documenting EA with TEF would be captured. Ultimately, selection bias may have affected the internal validity of results for the EA/TEF and BE cohorts. Further research on these conditions is required. It may be noted that inconsistent use of ICD-10-CA codes may have led to underreporting of certain patient characteristics and certain outcomes, such as anastomotic leaks.

In this work, we were unable to discern which hospitals were in fact tertiary children's hospitals. Currently, there are 15 hospitals that are known to offer pediatric surgery services: Janeway Children's Health and Rehabilitation Center (NFL), IWK Health Center (NS), Hospital

for Sick Children (ON), Children's Hospital of Eastern Ontario (ON), Children's Hospital at London Health Sciences Centre (ON), McMaster Children's Hospital (ON), Sudbury Infant and Child Development Centre (ON), Montreal Children's Hospital (QC), Centre hospitalier universitaire Sainte-Justine (QC), Children's Hospital of Winnipeg (MB), Royal University Hospital (SK), Jim Pattison Children's Hospital (SK), Stollery Children's Hospital (AB), Alberta Children's Hospital (AB), and BC Children's Hospital (BC). In this study, patients with HD were treated across 18 centers. This suggests that pediatric surgery is at least occasionally offered at centers that are not dedicated pediatric surgery hospitals. Given the lack of information on this topic, the analysis could not be adjusted for hospital type, which may have confounded the volume-outcome relationship for patients with HD and EA/TEF. Additionally, due to the large number of centers that perform the procedures examined, we were unable to account for clustering of patients by hospital, as the negative binomial mixed models did not converge.

Unfortunately, other important measures, i.e, disease-specific clinical information, was not captured in our dataset. For example, in patients with HD, measurement of disease severity remains unknown. This is important, as patients with long-segment HD and total colonic aganglionosis have been linked to higher rates of HAEC and other complications. For patients with BE, we were unable to capture qualifiers on continence following repair, which is an important functional outcome.

Furthermore, we were unable to measure objective outcomes, such as long-term bladder continence, in the treatment of BE, which is often used as a measure of success following repair. Similarly, in HD, postoperative perineal excoriation is a common complication, though not captured in administrative data. Reasons for barriers to healthcare access, which may be

confounders in the relationship between volume and outcome, such as a patient's socioeconomic status and living distance to a hospital, were not captured in our CIHI dataset.

Other sources of measurement error may be attributed to missing data, namely missing MBUN, or data errors. In each of the HD and EA/TEF cohorts, there were admissions that lacked a corresponding MBUN. After close inspection, an MBUN was assigned, however it cannot be known whether these admissions corresponded to a patient already accounted for in the dataset. This would have falsely inflated the number of patients treated with these conditions, though would have led to a nondifferential measurement error, since there was no pattern to their missingness. Surprisingly, several patients in the three cohorts examined had very brief LOS, of only 1 to 2 days. The clinical scenario where a patient would be discharged within that timeframe, following complex surgery, seems highly unlikely. In the BE, these patients were demonstrated to be influential outliers. It is possible that these measurements represent data errors and contribute to a differential measurement error by attenuating the volume-outcome relationship.

Finally, we acknowledge that surgeon volume has been another exposure measured in the literature and may be a more tailored proxy for surgeons' technical ability and skill. Further research on the volume-outcome relationship for HD, EA/TEF and BE, is therefore required.

6.3 Study Strengths

As centralization and subspecialization have become common in the care of adults undergoing complex surgeries, this study is timely in contributing to a body of work that aims to discern whether similar changes to care delivery would benefit pediatric populations. Specifically, this study provides important insight on how care is currently provided to patients with HD, EA/TEF and BE, in Canada. It was carefully designed to study the volume-outcome relationship for these conditions. Importantly, hospital volume was treated as a continuous exposure, which is

uncommon in the literature. This facilitated evaluation of the volume-outcome relationship without loss of information, which is inherent with categorization of continuous variables.

LOS was selected as the primary outcome of interest due to its documented clinical importance and its reliability as a measure. LOS is documented for each patient and unlike other outcomes of interest (e.g., mortality) it is not rare, thus amenable to analyses in a small sample size. Additionally, several important secondary outcomes were examined for each condition. Where restricted cubic spline analysis was possible, the nonlinear modeling of the volume-outcome relationship provided insight that thresholds may only exist for specific outcomes, and trends observed for one condition or procedure are not generalizable to another.

The CIHI dataset proved useful in assessing relevant system-level measures on a national scale. This data was collected using standardized procedures, ensuring consistency across time and regions. Though the data from CIHI does not contain subjective measures (e.g. patient satisfaction scores), the objective nature of the data makes it reliable and comparable. While analysis of this data provides insufficient evidence to support or refute hospital volume as a metric for care delivery, it corroborates previous studies suggesting that governing bodies and policy-makers be judicious in their used of volume as accreditation metrics in pediatric care. This study highlights that low volumes of rare diseases are seen at most institutions in Canada. These results shed light on the importance of determining how surgeons and hospitals maintain competency in the care of complex pediatric conditions.

Chapter 7: Conclusion

Hospital surgical volumes for HD, EA/TEF, and BE are low for the majority of hospitals caring for infants with these conditions, in Canada. Using the largest Canadian health database available, over a 12 -year period, this study found small sample sizes for each condition. Analysis demonstrated that hospital volumes are not significantly associated with LOS in patients who underwent surgical intervention for HD or BE. Conversely, hospital EA/TEF operative volumes were significantly associated with LOS, however the magnitude of this relationship was so small that it was unlikely to be clinically important. Mortality was found to be an exceedingly rare outcome in infants with HD, EA/TEF and BE. This underlines the importance of examining other outcomes in the study of volume-outcome relationships in neonates. In the nonlinear modeling of binary outcomes in relation to hospital volume, a threshold of 6 cases per year was identified for patients treated for HD, whereby risk of blood transfusion decreased and 1-year all cause admissions increased. No thresholds were identified for other outcomes or conditions. These findings suggest that volume may not serve as a reliable metric for guiding pediatric care delivery in Canada, however, further research on this topic is warranted.

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Appendix A: International Classification of Diseases Codes, 10th Edition and Canadian Classification of Intervention Codes used to identify patients for inclusion in this study.

Hirschsprung's Disease:

Q431 (Hirschsprung's disease)

CCI codes: **1**.**NQ87^^** (excision partial, rectum)**, 1.NQ89^^** (excision total, rectum)**, 1NQ74PE** (fixation, rectum perineal approach [includes pull-through, DeLorme, transanal] using plication [imbrication] of anorectal muscle)

Hirschsprung-associated enterocolitis
A047 (Enterocolitis due to C. diff), **A080** (Rotaviral enteritis), **A082** (Adenoviral enteritis), **A083** (other viral enteritis), **A099** (Gastroenteritis and colitis of unspecified origin), **K523** (Indeterminate colitis), **K528** (Other specified noninfective gastroenteritis and colitis), **K529** (Noninfective gastroenteritis and colitis, unspecified)

Esophageal atresia with tracheoesophageal fistula:

Q391 (atresia of esophagus with tracheoesophageal fistula)

CCI codes: **1.NA84^^** (construction or reconstruction, esophagus), **1.GJ86^^** (closure of fistula, trachea) **1.GJ80QB** (repair, trachea with simple apposition [reanastomosis] open thoracic approach [mediastinal, posterolateral thoracotomy]), **1GJ87LA** (excision partial, trachea open approach [e.g. transcervical, collar incision] with simple apposition [anastomosis]).

To identify readmissions: **Q390** (atresia of esophagus without fistula), **Q391**(atresia of esophagus with tracheoesophageal fistula) **Q392** (congenital tracheoesophageal fistula without atresia) **Q393** (congenital stenosis and stricture of the esophagus)

Esophageal Dilation:
1NA50^^ (Dilation, esophagus endoscopic per orifice approach)

Bladder exstrophy:

Q6418 (other exstrophy of urinary bladder)

CCI codes: **1PM80LA** (Repair, bladder using open approach and simple apposition), **1.PM84^^** (reconstruction, bladder)**, 1SY80LA** (Repair, muscles of the chest and abdomen open approach without tissue [e.g. suturing or stapling]), **1.SY84^^** (construction or reconstruction, muscles of the chest and abdomen)**, 1.QE84^^** (construction or reconstruction, penis), **1QE84^^** (Construction or reconstruction, penis).

To identify readmissions: **Q6410** (cloacal exstrophy of urinary bladder), **Q6418** (other exstrophy of urinary bladder)

Urinary tract infection:
N390 (Urinary tract infection, site not specified)

ICD-10-CA codes used to identify patient characteristics and outcomes:

Low birth weight:

P070 (extremely low birth weight), **P071** (other low birth weight)

Prematurity:

P072 (extreme immaturity), **P073** (other preterm infants)

Intrauterine growth restriction:

P0590 (Symmetric intrauterine growth restriction [IUGR]), **P0591** (Asymmetric intrauterine growth restriction [IUGR]), **P0599** (Unspecified intrauterine growth restriction [IUGR])

Down's syndrome:

Q900 (Trisomy 21, meiotic nondisjunction), **Q902** (Trisomy 21, translocation), **Q909** (Down's syndrome, unspecified).

Congenital malformation affecting the limbs:

Q872 (Congenital malformation syndromes predominantly involving the limbs

Congenital Cardiac Anomaly:

Q210 (Ventricular septal defect) **Q211** (Atrial septal defect) **Q212** (Atrioventricular septal defect) **Q213** (Tetrology of Fallot) **Q214** (Aortopulmonary septal defect) **Q218** (Other congenital malformations of cardiac septa) **Q219** (Congenital malformation of cardiac septum, unspecified) **Q220** (Pulmonary valve atresia) **Q221** (Congenital pulmonary valve stenosis) **Q222** (Congenital pulmonary valve insufficiency) **Q223** (Other congenital malformations of pulmonary valve) **Q224** (Congenital tricuspid atresia) **Q225** (Ebstein anomaly) **Q226** (Hypoplastic right heart syndrome) **Q228** (Other congenital malformations of tricuspid valve) **Q229** (Congenital malformation of tricuspid valve, unspecified) **Q230** (Congenital stenosis of aortic valve) **Q231** (Congenital insufficiency of aortic valve) **Q232** (Congential mitral stenosis) **Q233** (Congenital mital insufficiency) **Q234** (Hypoplastic left heart syndrome) **Q238** (Other congenital malformations of aortic and mitral valves) **Q239** (Congenital malformation of aortic and mitral valves, unspecified) **Q240** (Dextrocardia) **Q241** (Laevocardia) **Q242** (Cor triatiatum) **Q243** (Pulmonary infundibular stenosis) **Q244** (Congenital subaortic stenosis) **Q245** (Malformation of coronary vessels) **Q246** (Congenital heart block) **Q248** (Other specified congenital malformations of heart) **Q249** (Congenital malformation of heart, unspecified).

Surgical Complications:

Y832 (Surgical operation with anastomosis, bypass or graft as the cause of abnormal reaction or later complication, without mention of misadventure at the time of the procedure) **Y833** (Surgical operation with formation of external stoma as the cause of abnormal reaction or later complication, without mention of misadventure at the time of the procedure) **Y834 (**Other reconstructive surgery as the cause of abnormal reaction or later complication, without mention of misadventure at the time of the procedure) **Y836 (**Removal of other organ (partial)(total) as the cause of abnormal reaction or later complication, without mention of misadventure at the time of the procedure) **Y838** (Other surgical procedures as the cause of abnormal reaction or later complication, without mention of misadventure at the time of the procedure)

Post-operative Infection:

T814 (Infection following a procedure, not elsewhere classified)

Postoperative leak

T8183 (Postoperative leak)

Appendix B: Additional Figures for Hirschsprung's Disease

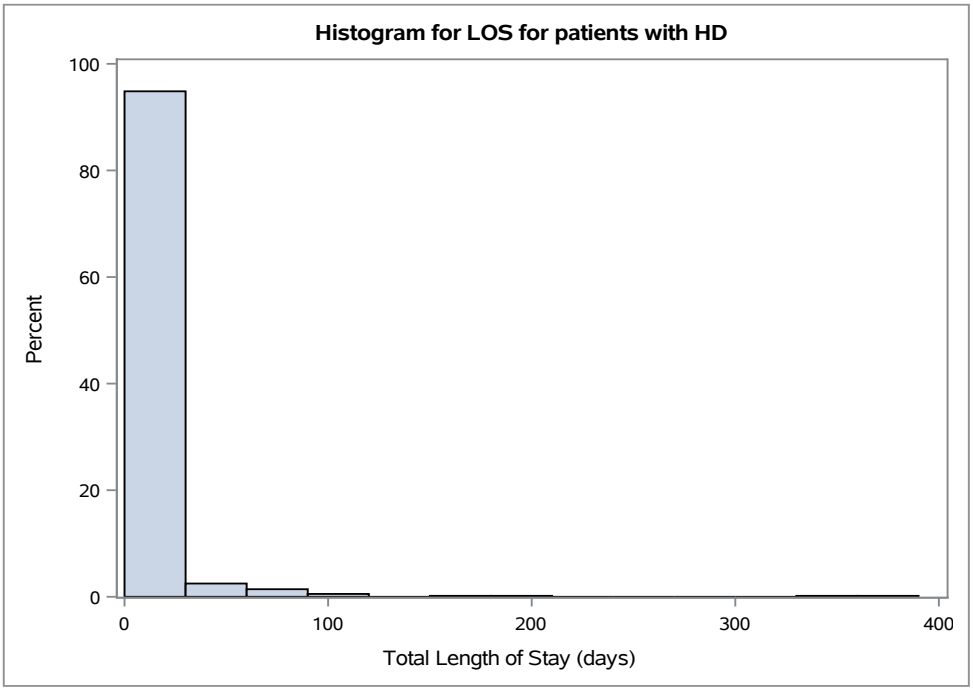

Figure A. Histogram showing the distribution of hospital length of stay for patients with Hirschsprung's disease.

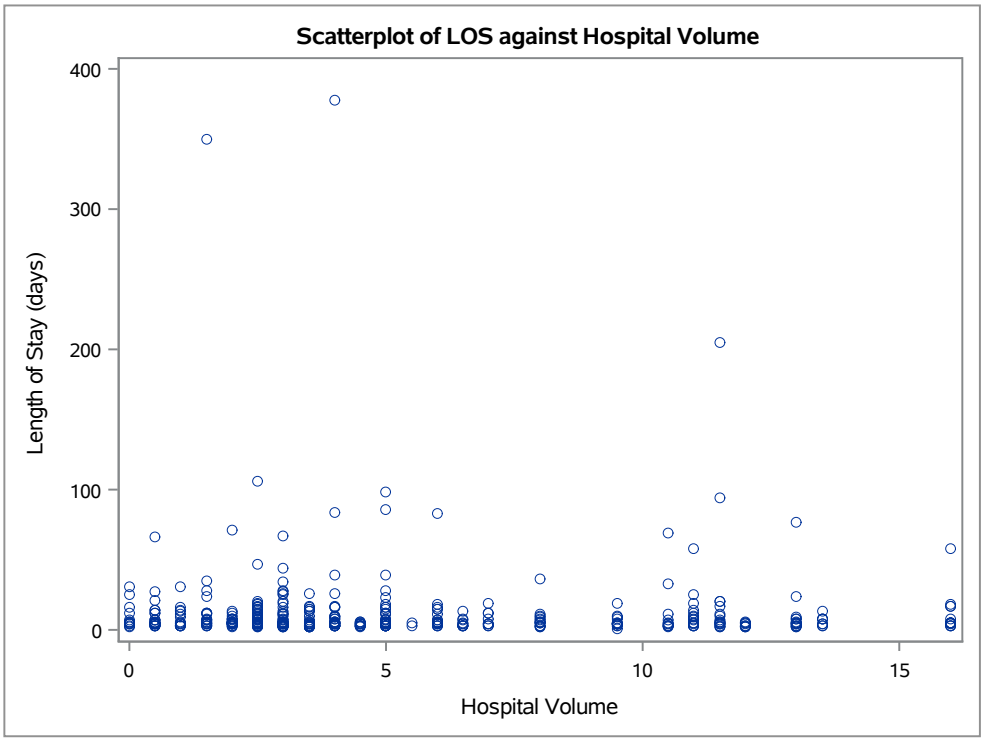

Figure B. Scatter plot showing the length of stay in days against hospital volume, for patients with Hirschsprung's disease.

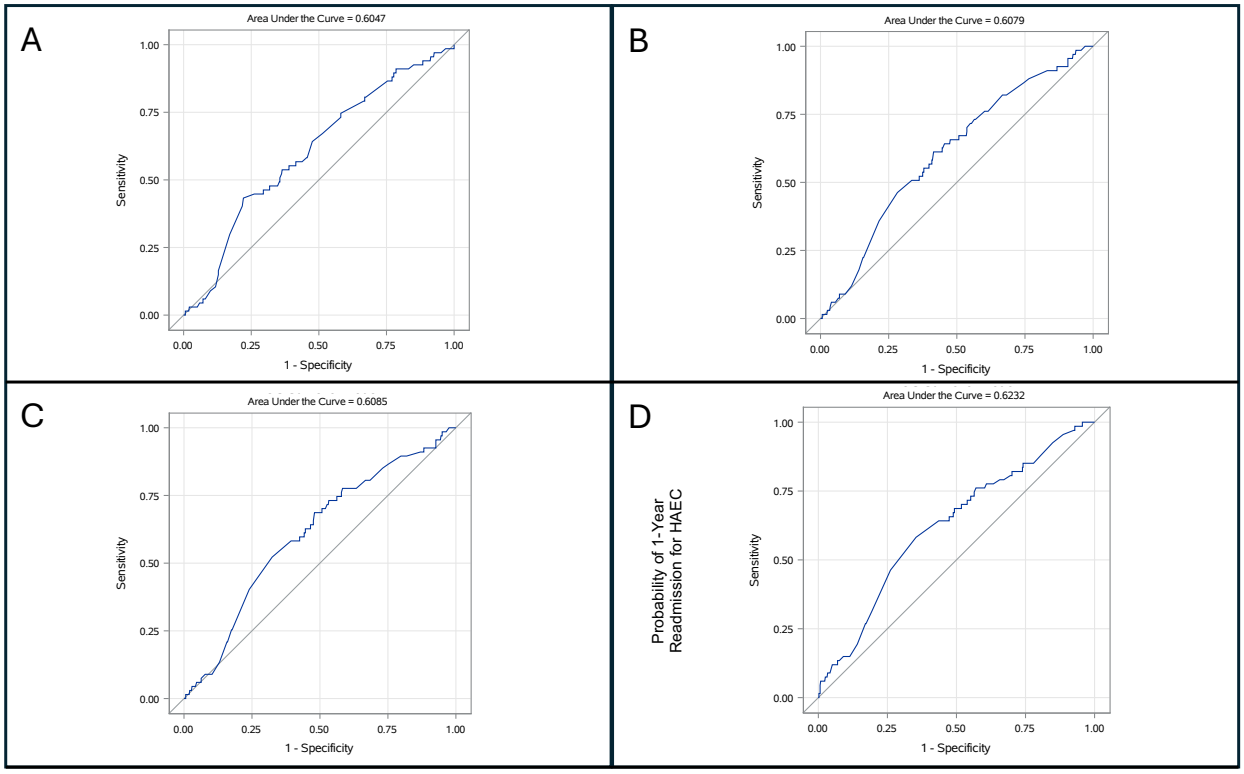

Figure C. Receiver operator curves and corresponding area-under the curve for the association between blood transfusion and hospital volume, when volume was dichotomized at A) 3 cases per year, B) 4 cases per year, C) 5 cases per year and D) 6 cases per year.

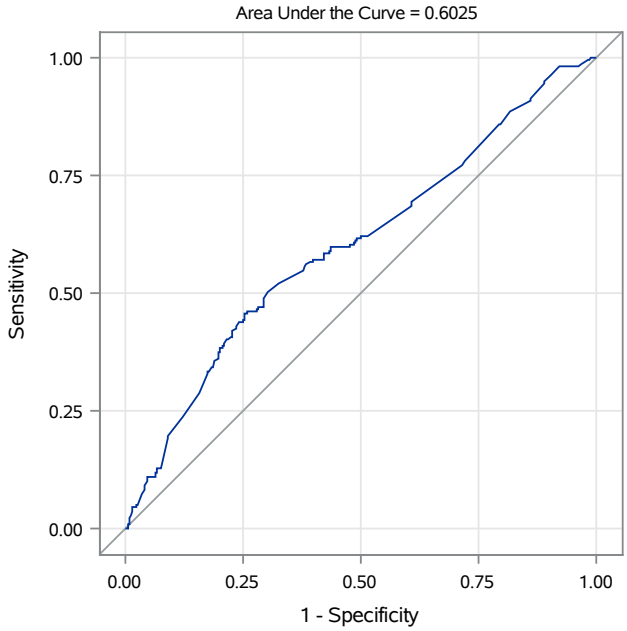

Figure D. Receiver operator curve and corresponding area-under the curve for the association between 1-year readmission for any cause and hospital volume, when volume was dichotomized at 6 cases per year.

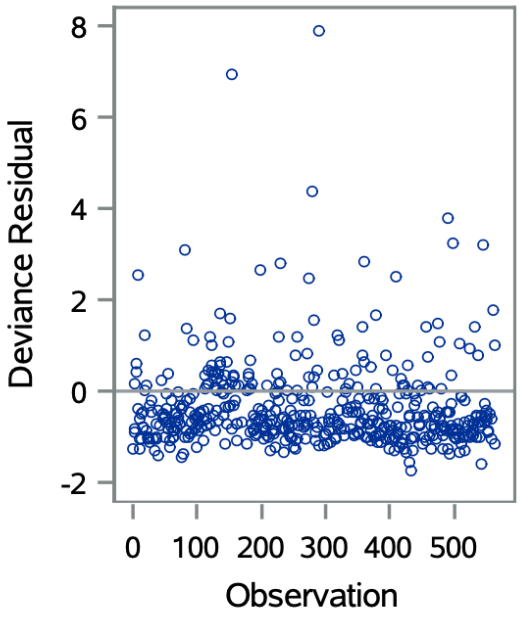

Figure E. Deviance residuals for the adjusted negative binomial regression analysis for the association of hospital volume and length of stay, for patients with Hirschsprung's disease.

Appendix C: Additional Figures for Esophageal Atresia with Tracheoesophageal Fistula

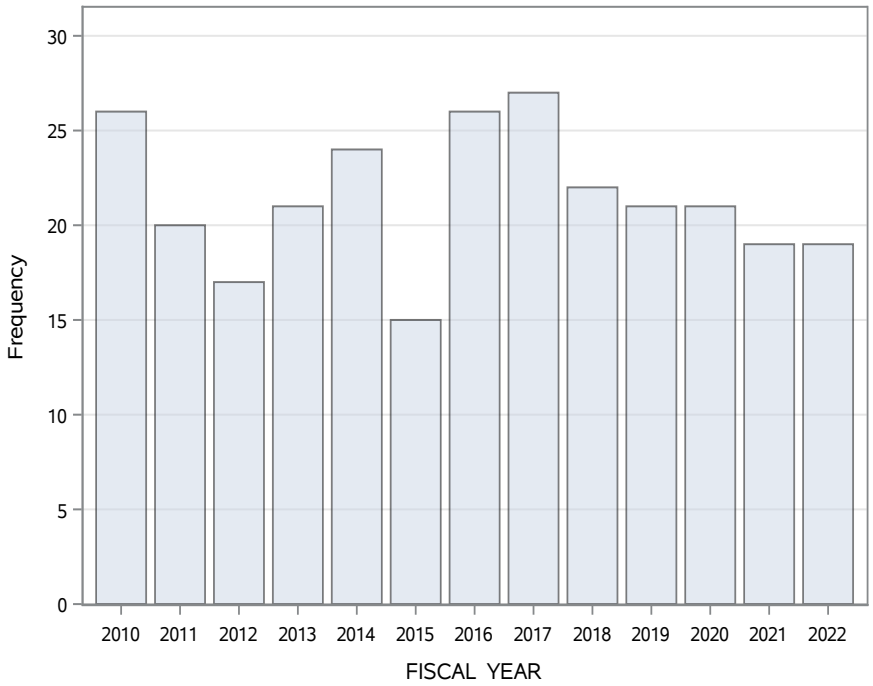

Figure A. Distribution of the number of cases of esophageal atresia with tracheoesophageal fistula across the study period (April 1, 2010 to March 31, 2023).

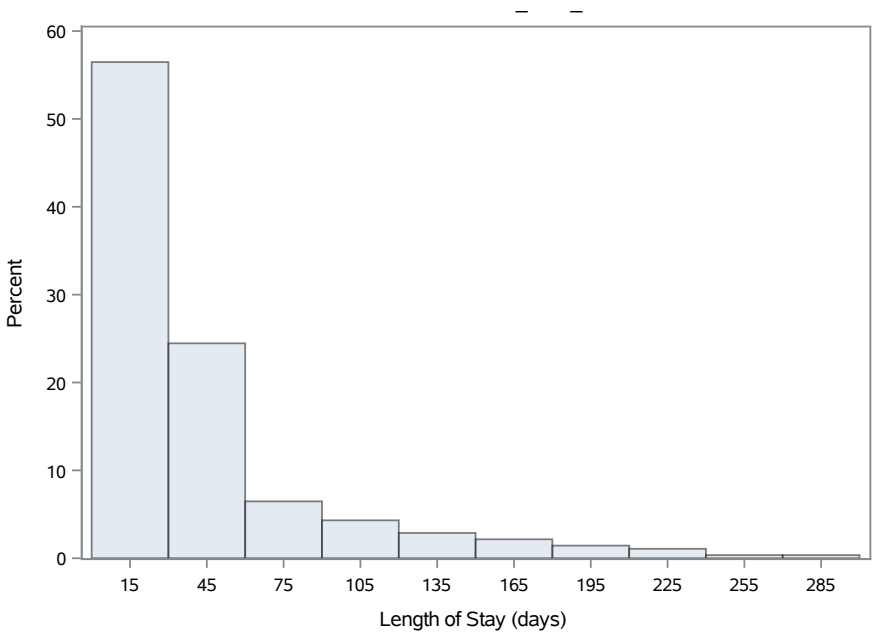

Figure B. Histogram showing the distribution of length of stay in days for patients who underwent repair of esophageal atresia with tracheoesophageal fistula.

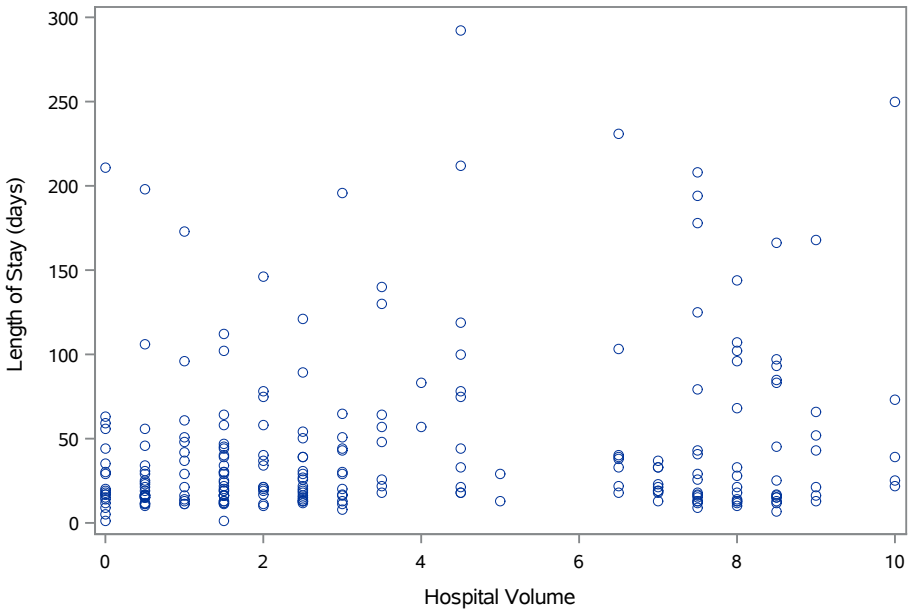

Figure C. Scatterplot showing the length of stay against hospital volume for patients who underwent repair of esophageal atresia with tracheoesophageal fistula.

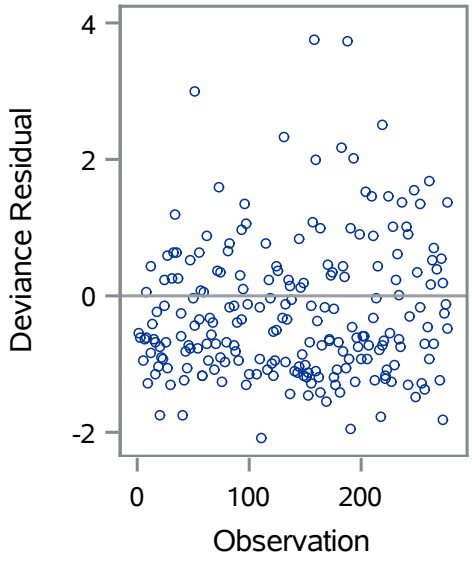

Figure D. Deviance residuals for the adjusted negative binomial regression in the analysis of the association between hospital volume and length of stay, for esophageal atresia with tracheoesophageal fistula.

Appendix D: Additional Figures for Bladder Exstrophy

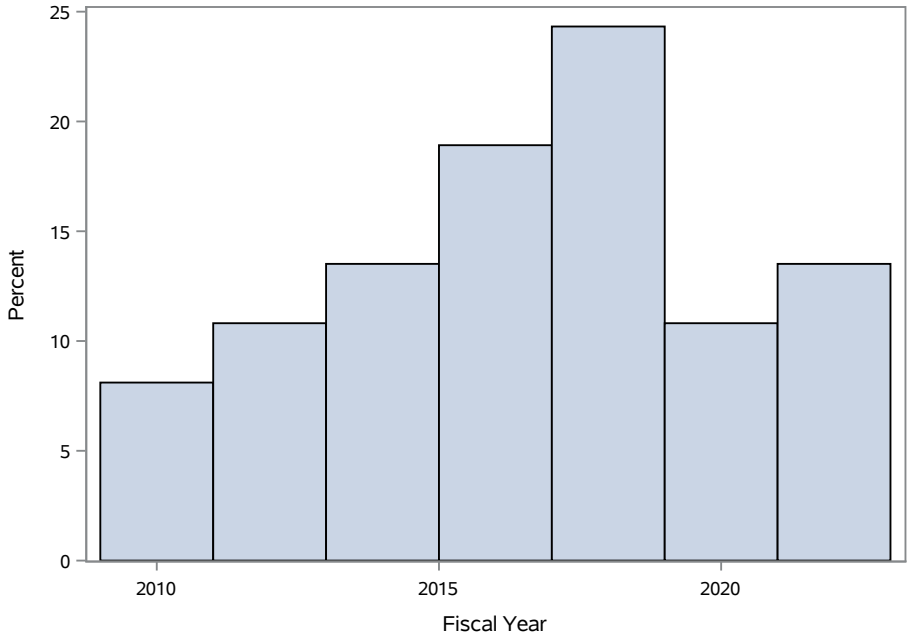

Figure A. Distribution of the number of cases of bladder exstrophy across the study period (April 1, 2010 to March 31, 2023).

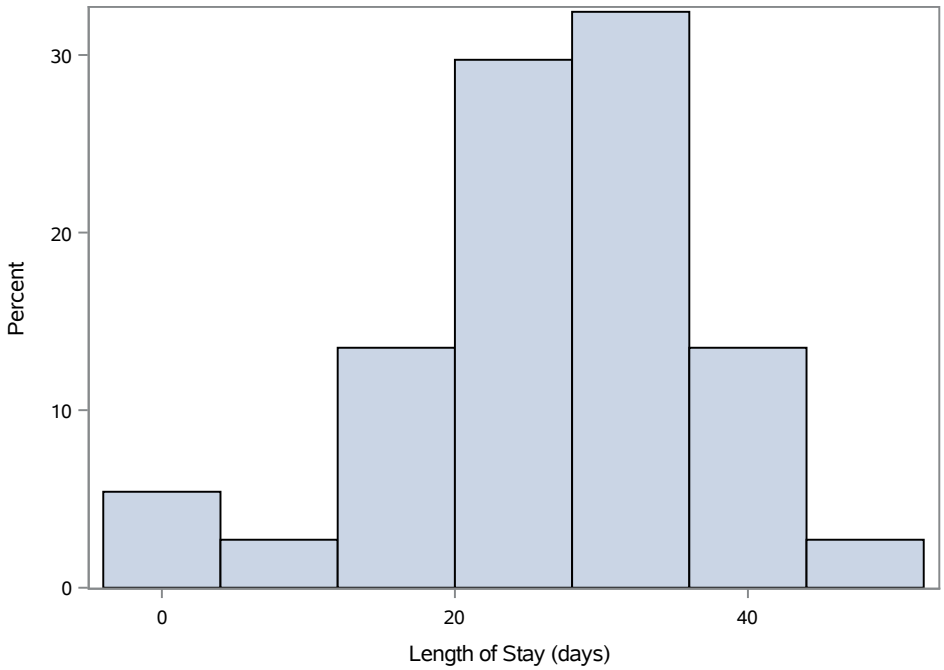

Figure B. Histogram showing the distribution of length of stay in days for patients who underwent reconstruction for bladder exstrophy.

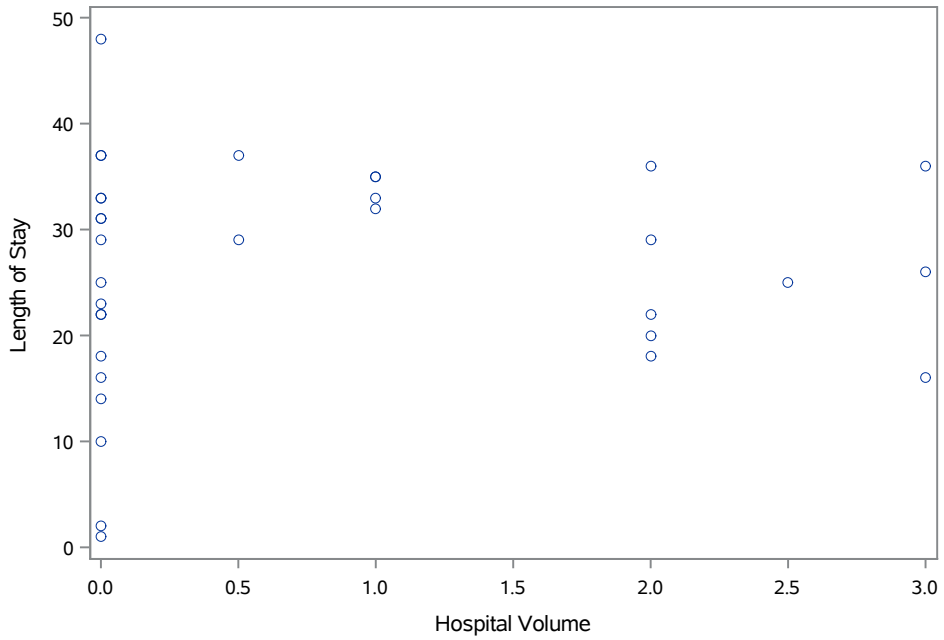

Figure C. Scatterplot showing the length of stay against hospital volume for patients who underwent bladder exstrophy reconstruction.

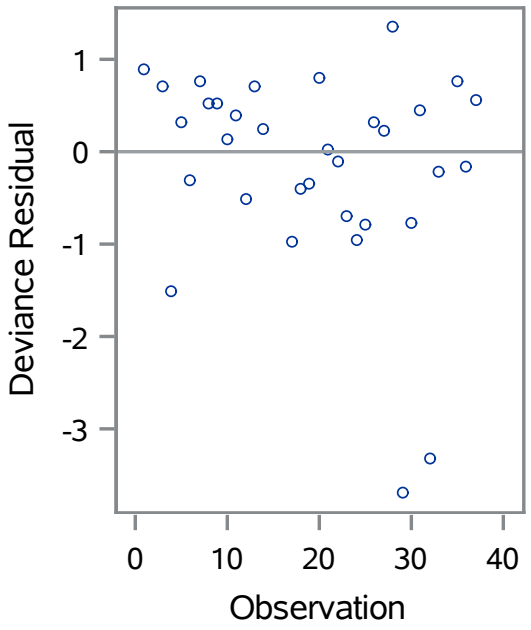

Figure D. Deviance residuals for the adjusted negative binomial regression in the analysis of the association between hospital volume and length of stay, for patients with bladder exstrophy.