Harnessing the potential of big data to investigate outcomes following childhood surgery



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To my family

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ABSTRACT

Background: Globally, it is estimated that 6% of children are born with a congenital anomaly, many of which require surgical treatment. Despite this, determining short-term and long-term outcomes following childhood surgery remains challenging.

Aim: The overall aim of this thesis is to investigate whether it is possible to harness the potential of big data to develop a better understanding of outcomes following childhood surgery, and the factors that influence these outcomes. This thesis focusses on six specific conditions for which childhood surgery is usually required: Hirschsprung's disease, gastroschisis, oesophageal atresia, congenital diaphragmatic hernia, posterior urethral valves, and surgical necrotising enterocolitis.

Methods: A systematic review was conducted to establish long-term outcomes following childhood surgery, as reported in the current literature. A population-based study was undertaken using data from the National Neonatal Research Database to describe the incidence, characteristics and short-term outcomes of surgical neonates. Using this data source, prediction models were developed and internally validated for short-term outcomes. Using data from the Hospital Episode Statistics database, a population-based study was conducted to describe long-term outcomes for all six study conditions. Prediction models for long-term outcomes were developed and internally validated.

Results: A total of 156 studies were included in the systematic review across the six study conditions, encompassing 64,081 children. The pooled proportion for one-year survival was highest amongst children with Hirschsprung's disease 98% (95% confidence interval

[CI] 97-100), followed by 96% for children with gastroschisis (95% CI 95-97), 92% for oesophageal atresia (95% CI 89-95), 77% for congenital diaphragmatic hernia (95% CI 72-82) and 61% for those with surgical necrotising enterocolitis (95% CI 47-76). There was significant heterogeneity between studies and reporting of quality of life and developmental outcomes was notably sparse. The population-based study using National Neonatal Research Database encompassed 8,090 neonates and demonstrated that it is feasible to utilise this data source to explore some short-term outcomes for surgical neonates. However, there were notable limitations including the lack of detailed operative data and condition-specific severity factors. Robust prediction models were developed for the short-term outcomes of survival (area under the receiver operating characteristic curve [AUROC] 0.83, Brier score 0.09), late-onset sepsis (AUROC 0.84, Brier score 0.05) and severe brain injury (AUROC 0.83, Brier score 0.08). The population-based study utilising Hospital Episode Statistics database encompassed 18,824 children across England and demonstrated it was feasible to utilise this database to investigate long-term outcomes of children with one of the six study conditions. Prediction models were developed for the long-term outcomes of one-year survival (AUROC 0.82, Brier score 0.11), operations (AUROC 0.71, Brier score 0.20) and infections (AUROC 0.64, Brier score 0.23).

Conclusion: It is feasible to utilise big data derived from routinely collected databases to explore some short-term and long-term outcomes following childhood surgery. Further research is required to collect and investigate outcomes of interest to patients, parents and clinicians, such as quality of life. Data linkage and the development of multimodal databases may help to ameliorate the limitations of specific databases, as well as provide new opportunities for the updating and enhancement of multivariable prediction models.

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Statement of contribution to work

I completed all the analyses, created the figures and tables, and drafted all chapters of this thesis, with guidance from my supervisors Benjamin Allin, Charles C Roehr, Charles Opondo, Cheryl Battersby and Marian Knight. Rema Ramakrishnan gave statistical guidance. Data was extracted by the data analysts, Julia Lanoue (Neonatal Data Analysis Unit, Imperial College London) and Nick Hall (Unit of Health Care Epidemiology, University of Oxford). For Chapter 2, Emily van Blankenstein, Madura Nandakumar, Marcel Chee, Oliver Arscott and Trishna Desai were second reviewers for the systematic review and were involved in title and abstract screening, full-text screening, assessing risk of bias and data extraction. Nia Roberts (Bodleian librarian) gave guidance for the systematic literature search. Stata packages developed by Giovanni Nattino and Borja M. Fernandez-Felix were used for some analyses, namely generating calibration belt plots and internal validation of prediction models.

List of abbreviations

aHR	Adjusted hazard ratio
AI	Artificial intelligence
AIC	Akaike information criterion
anti-VEGF	Anti-vascular endothelial growth factor
aOR	Adjusted odds ratio
APC	Admitted Patient Care
ARR	Adjusted risk ratio
ASD	Autism spectrum disorder
AUC	Area under the receiver operating characteristic curve
AUROC	Area under the receiver operating characteristic
BAPS-CASS	British Association of Paediatric Surgeons Congenital Anomalies Surveillance System
BIC	Bayesian information criterion
BSID-III	Bayley Scales of Infant Development, Third Edition
CAG	Confidentiality Advisory Group
CDH	Congenital diaphragmatic hernia
CKD	Chronic kidney disease
CI	Confidence interval
CIPS	Continuous InPatient Spells
CITL	Calibration-in-the-large
CROWN	CoRe Outcomes in WomeN's health
CRP	C-reactive protein
COIN	Core Outcomes In Neonatology
COMET	Core Outcome Measures in Effectiveness Trials
COS	Core outcome set
COVID-19	Coronavirus disease 2019
CSOR	Children's Surgery Outcome Reporting programme
DAG	Directed acyclic graph
GORD	Gastroesophageal reflux disease
ECMO	Extracorporeal membrane oxygenation
eGFR	Estimated glomerular filtration rate
ELBW	Extremely low birth weight
EPV	Events per variable
ESRD	End-stage renal disease
ESRF	End-stage renal failure
E:O	Ratio of expected and observed events
FBD	Fluoroscopic balloon dilatation
FCE	Finished consultant episodes
HAEC	Hirschsprung-associated enterocolitis
HD	Hirschsprung's disease
HES	Hospital Episode Statistics
HHI	Herfindahl-Hirschmann Index
HIE	Hypoxic ischaemic encephalopathy
ICD-10	International Statistical Classification of Diseases and Health Related Problems, 10th Edition
IF	Intestinal failure
IFALD	Intestinal failure associated liver disease

IMD	Index of Multiple Deprivation
IQR	Interquartile range
IRR	Incidence rate ratio
IVH	Intraventricular haemorrhage
LBW	Low birthweight
LGOA	Long-gap oesophageal atresia
LHR	Lung-to-head ratio
MAR	Missing at random
MCA	Major congenital anomaly
MDI	Mental Developmental Index
MEN2	Multiple endocrine neoplasia type 2
NBW	Normal birthweight
NDAU	Neonatal Data Analysis Unit
NEC	Necrotising enterocolitis
NHS	National Health Service
NICE	National Institute of Health and Care Excellence
NNAP	National Neonatal Audit Programme
NNRD	National Neonatal Research Database
NOS	Newcastle-Ottawa Scale
OA	Oesophageal atresia
ONS	Office of National Statistics
OPCS-4	Office of Population Censuses and Surveys Classification of Interventions and Procedures Version 4
OR	Odds ratio
PDI	Psychomotor Developmental Index
PICU	Paediatric intensive care unit
PMM	Predictive mean matching
POBF	Postoperative bowel function
PPI	Patient and public involvement
PVL	Periventricular leukomalacia
PUV	Posterior urethral valves
RCT	Randomised controlled trial
ROC	Receiver operating characteristic
ROP	Retinopathy of prematurity
RR	Risk ratio
SBO	Small bowel obstruction
SE	Standard error
SMA	Spinal muscular atrophy
SNHL	Sensorineural hearing loss
SSI	Surgical site infection
TOF	Trachea-oesophageal fistula
TRIPOD	Transparent reporting of multivariable prediction model for individual prognosis or diagnosis
UHCE	Unit of Health Care Epidemiology
UK	United Kingdom
USA	United States of America
UTI	Urinary tract infection
VUR	Vesicoureteral reflux
WHO	World Health Organization
WPPSI	Wechsler Preschool and Primary Scale of Intelligence

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Chapter 1

Introduction

1.1 Challenges in paediatric surgical research

The field of paediatric surgery encompasses operative management of a broad range of body systems and, each year, over half a million children will undergo surgery in the UK.[1] Nonetheless, there exist several unique challenges in conducting research into conditions requiring childhood surgery, the reasons for which are manifold. One of the most significant challenges is that the field of paediatric surgery encompasses many conditions with low population incidences. Although surgical conditions such as inguinal hernia and appendicitis are relatively common, a substantial proportion of the paediatric surgical load comes from rare conditions, often requiring complex and multidisciplinary management. For instance, the incidence of posterior urethral valves and congenital diaphragmatic hernia in the UK is estimated to only be approximately 16 per 100,000 live births and 20 per 100,000 live births respectively.[2 3]

This has important implications, particularly in a research field that is dominated by case studies and smaller institutional series.[4] Conditions with low incidence result in studies with smaller sample sizes, making them more susceptible to bias, producing wider confidence intervals and greater uncertainty in results.[5] Small studies of rare conditions may be underpowered to detect a meaningful difference in results, therefore contributing to research wastage whilst failing to influence clinical practice. A systematic review conducted by Allin et al. found that nearly half (46.8%) of paediatric surgical articles published in 2013 were retrospective case series, with randomised controlled trials (RCTs) comprising only 1.9% of the literature in that year.[4] Furthermore, even when the outcomes are reported for paediatric surgical conditions, they are often measured and reported heterogeneously.[6]

As increasing numbers of infants born with congenital anomalies requiring childhood surgery survive into adulthood, it is important to base management decisions on long-term outcomes, rather than solely neonatal or short-term outcomes.[7] Children with a paediatric surgical condition will often have life-long sequelae following initial surgery.[8 9] Yet despite the importance of long-term information, it can be challenging to obtain such data for children undergoing childhood surgery. The prospective collection of long-term data is often resource-intensive and may be susceptible to attrition as children become lost to follow-up. Furthermore, several years of follow-up may be required, sometimes ten years or more of follow-up time, in order to inform clinical management decisions and provide accurate prognostication for parents. For some conditions, the outcome differences between treatment groups may only appear many years following the initial treatment.[10] Thus, there may be considerable delay between the institution of a new practice or surgical technique and understanding its true long-term implications. This is important to consider when introducing a new surgical practice, particularly amongst children, who may have life-long sequelae. Though short-term outcomes may help surgeons to evaluate their practices, and even provide early signals of long-term outcomes, it is still important to collect long-term outcome data.

Concerns surrounding research for vulnerable populations, including children, present an additional dimension to the challenges in conducting trials and developing a rigorous evidence based for paediatric surgery.[11] Technological and surgical advances may be adopted inappropriately late in the paediatric population compared to the adult population, due to a reluctance of parents and health professionals to perform procedures that may be perceived as being of higher risk or more experimental, even in the absence of evidence supporting a treatment option or where the existing evidence is equivocal.[12] Furthermore,

studies involving children usually also require parental consent, which may result in a reduction in study participation in the paediatric population due to parental caution compared to the adult population, where consent is only required from the adult patient.[7] This preponderance towards risk minimisation in favour of more conservative approaches, even when there is little evidence supporting such approaches as the superior option, comes at the cost of building an adequate evidence base to guide clinical practice. This may inadvertently lead to the perpetuation of suboptimal care for the most vulnerable members of the population.[13]

1.2 Determining outcomes of interest

In order to make meaningful decisions regarding management based upon existing evidence, one must have data on meaningful outcomes. Despite this, study investigators may choose to report outcomes of lesser clinical interest for several reasons. For instance, outcomes may be reported based on availability and ease of data collection, rather than selecting those that are clinically meaningful or important to stakeholders, namely patients, parents, clinicians and the general public.[14] Furthermore, definitions of outcomes and their measurements should be standardised, so that outcome data can be aggregated to draw meaningful and actionable conclusions that can be applied in a clinical setting. This is particularly critical in a field such as paediatric surgery, where it is difficult to amass a substantial number of cases for certain conditions.

Historically, the choice of which outcomes are important have been largely determined by the researcher or clinician conducting the study, with the implication being that what is of interest to the clinician must therefore, by extension, be of interest to the patient and their families. However, in recent years, there has been growing recognition of the importance

of patient-centred models of care, as well as patient and public involvement (PPI) in research.[15 16] A more collaborative approach can help produce research findings that are of meaningful interest to all stakeholders involved and improve efficiency within the research process. In order to address this issue of heterogeneously reported outcomes, a number of core outcome sets (COSs) have been developed to ascertain and explicitly outline the outcomes of greatest importance to stakeholders—generally speaking, patients, parents and clinicians. In this process, candidate outcomes are identified, often through the systematic review of existing literature and primary qualitative research, after which the candidate outcomes are ranked, typically though a modified Delphi technique.[17] Notable examples of COSs include the Core Outcomes In Neonatology (COIN) for infants who receive neonatal care and the CoRe Outcomes in WomeN's health (CROWN) initiative to develop COSs for conditions relating to women's health.[18 19] A database of COSs for specific conditions is held by the Core Outcome Measures in Effectiveness Trials (COMET) initiative.[20] Despite the advantages of utilising COSs, such as easier facilitation of aggregating data, facilitating meaningful comparison between studies, and optimising efficiency of research, COSs may still be underutilised due to notable barriers. Not all conditions have a corresponding COS that has been developed, and even when COSs are developed for a condition, there may be barriers to implementation, such as lack of widespread awareness, incomplete dissemination or study investigators ignoring these predetermined outcomes in favour of outcomes that are more readily available or accessible in their database.[21]

1.3 Addressing the challenges in paediatric surgical research

The combination of small sample sizes, heterogenous outcome reporting and a lack of long-term outcome data makes it challenging to build an evidence base on which to inform clinical practice. In the absence of standardised clinical guidelines based on rigorous

research, variation in management practices will continue to exist. The inevitable outcome is undue variation in clinical outcomes between centres, and the potential for a diminished confidence of parents and the general public in paediatric surgical services. Due to variations in clinical practice, parents may be given conflicting information regarding their child's surgical condition, which can undermine parental trust in the healthcare profession.[22]

Recent developments that may provide novel solutions to the challenges in paediatric surgical research are the rise of big data and increasing use of electronic health records. Where in the past, medical records existed in paper formats, stored in physical archives, the digital era has given rise to new possibilities. There has been an expansion of the amount and range of data that can be captured as the collection and storage of data has become faster, cost-effective, and more convenient.[23] It is now possible to store a wide range of data, in addition to basic electronic medical records, for instance the continuous monitoring of vital signs in intensive care units, pathology results, radiological scans, genomic data and even data from smart watches and electronic wearables. This has given rise to and popularised the areas of data science, machine learning and artificial intelligence in the context of big data. Many of these concepts have already been applied to several fields in healthcare such as radiology, pathology and dermatology, though less commonly in paediatric surgery.[24-26] Whilst the case load of certain neonatal surgical conditions may never reach the numbers typically seen in "big data" articles on diabetes and cancer, there are still lessons that can be drawn from the utilisation of big data in healthcare.[27 28]

1.4 Definition of "big data"

Despite the widespread use of the term "big data", there is no universal definition. Indeed, the meaning and implication of the term "big data" often varies between fields. One framework by Laney that is commonly used is the 3 Vs, which suggests that big data consists of high volume, high variety and high velocity.[29] *High volume* suggests that big data should have a high quantity of data stores or a high number of observations. Though there is no definitive cut-off for how large the data should be, it should typically be larger than previous databases in the field. *High variety* suggest that big data should include different types of data, particularly data collected for different purposes or from different sources. Finally, *high velocity* refers to having a faster and more continuous process for data generation, sometimes even occurring in real-time.[30]

1.5 Utilisation of routinely collected data

Part of the rise of big data can be attributed to the increase in routinely collected data, which is now easier with electronic medical records and the digitalisation of healthcare. One example of this is the National Neonatal Research Database (NNRD), which collects data from all neonatal intensive care units in the UK. This allows for better understanding of practices that influence neonatal outcomes and allows for comparison between centres, along with centre-specific feedback. However, one limitation of the NNRD is that the BadgerNet system from which the NNRD draws its data from is not universally used across all units in the UK. Previous studies have shown that it is feasible to utilise the NNRD and other nationwide routinely collected data to conduct robust nation-wide population-based studies of neonatal care.[31-34] Similarly, the Hospital Episodes Statistics (HES) database contains routinely collected data for all admissions across NHS hospitals

in England and has been used to investigate a broad range of health conditions in England.[35-37]

Therefore, the overall aim of this thesis is to investigate the feasibility and utility of big data to explore outcomes following childhood surgery. To accomplish this, six paediatric surgical conditions were chosen as exemplars of a range of conditions that a paediatric surgeon may encounter: Hirschsprung's disease (HD), gastroschisis, oesophageal atresia (OA), congenital diaphragmatic hernia (CDH), posterior urethral valves (PUV) and surgical necrotising enterocolitis (NEC). These six exemplar conditions were chosen on the basis that they represent a wide range of conditions of differing management options, ages of presentation and affect several body systems. These six surgical conditions are summarised briefly below and their incidences are outlined in **Table 1.1** based on data from the British Association of Paediatric Surgeons Congenital Anomalies Surveillance System (BAPS-CASS).[3 38 39]

Table 1.1: Incidences per 100,000 live births based on data from the British Association of Paediatric Surgeons Congenital Anomalies Surveillance System

Condition	Incidence based on BAPS-CASS data
Hirschsprung's disease	18
Gastroschisis	33.9
Oesophageal atresia	19.8
Congenital diaphragmatic hernia	20.2
Posterior urethral valves	16.2
Surgical necrotising enterocolitis	27.9

1.5.1 Hirschsprung's disease

Hirschsprung's disease (HD), also known as congenital aganglionosis and aganglionic megacolon, is a congenital condition where there is the absence of ganglion cells along the intestine. The condition was described by the Danish physician, Harald Hirschsprung, in

1887.[40] HD may be associated with other genetic anomalies, including the Waardenberg-Shah, multiple endocrine neoplasia type 2 (MEN2), and Goldberg-Shprintzen syndromes.[41-43]

HD usually presents shortly after birth, however it may present and be diagnosed in adulthood in rare cases. Typical clinical features of HD include delay in passing meconium, bilious vomiting and abdominal distension, and a definitive diagnosis of HD can be made on rectal biopsy. Surgical management involves excising the aganglionic section of the bowel and subsequent anastomosis to restore continuity of the bowel, with the most commonly performed procedures being the Duhamel, Swenson and Soave procedures.[44] Depending on the severity of the condition and surgeon preference, repair may be performed as a single-stage or multi-stage procedure. Following surgery, children may experience long-term complications, such as incontinence, constipation and recurrent enterocolitis.[45]

1.5.2 Gastroschisis

Gastroschisis is an abdominal wall defect where there is the protrusion of the intestines through a paraumbilical defect, typically to the right of the umbilicus. In contrast to omphalocele (exomphalos), the intestines are not encased in a membrane. This exposure of the bowel to amniotic fluid in utero may result in intestinal wall thickening, atresia and matting.[46] Uncommonly, stomach and liver herniation may be present in larger defects. Although the exact aetiology of gastroschisis is largely unknown, several studies have identified factors associated with the development of gastroschisis, such as younger maternal age, smoking and alcohol consumption during pregnancy, and environmental exposures to chemicals, such as atrazine.[47-49]

A diagnosis of gastroschisis is often made prenatally from an antenatal scan, normally around 18 to 20 weeks' gestation, demonstrating an abdominal wall defect and free-floating intestinal loops.[50] To stratify condition severity, gastroschisis may be categorised as simple or complex. Simple gastroschisis refers to gastroschisis in the absence of bowel complications, whereas complex gastroschisis is commonly defined as gastroschisis with the presence of intestinal atresia, ischaemia, perforation and/or volvulus.[51] Management of gastroschisis involves returning the eviscerated organs back into the abdominal cavity and repairing the defect. Depending on the size of the defect and the condition of the bowel, there are two management options: primary repair and delayed closure. Although the survival rate of infants with gastroschisis is high, other long-term outcomes, such as quality of life and neurodevelopmental outcomes, are not well described in the existing literature.[46]

1.5.3 Oesophageal atresia

Oesophageal atresia (OA) refers to a congenital anomaly where the continuity of the oesophagus of a newborn is disrupted, with or without the presence of a fistula connecting to the trachea. The aetiology of this condition is mostly unknown, however several genes have been found to be associated with the condition, including the *MYCN*, *FANCB* and *SOX2* genes.[52] Associated anomalies commonly occur with OA, such as CHARGE syndrome and the VACTERL association. OA may be categorised using the Gross classification, which consists of five categories: Type A refers to OA without the presence of a fistula, Type B refers to OA with a proximal trachea-oesophageal fistula (TOF), Type C is the most common and refers to OA with a distal TOF, Type D refers to OA with both

a proximal and distal TOF, and Type E refers to the presence of a TOF only (i.e. in the absence of OA).[53]

OA may be diagnosed antenatally or shortly after birth. Typical signs and symptoms of OA include excessive drooling, as well as coughing, dyspnoea or cyanosis, particularly during feeding. Surgical management of OA usually involves end-to-end anastomosis of the oesophagus and closure of the fistula if present.[54] Early complications following surgery may include recurrent TOF, oesophageal stricture and anastomotic leakage.[55] Children may experience long-term comorbidities associated with OA, such as eosinophilic oesophagitis, gastroesophageal reflux, and respiratory comorbidities, such as severe tracheomalacia and recurrent respiratory infections. Data on other long-term outcomes, such as quality of life and neurodevelopmental outcomes, remain sparse.[56]

1.5.4 Congenital diaphragmatic hernia

Congenital diaphragmatic hernia (CDH) is a condition in which there is a defect of the diaphragm, typically located on the left side, allowing abdominal viscera to herniate into the thoracic cavity and impeding the pulmonary development of the fetus. The Bochdalek hernia is the most common type of CDH and represents a posterolateral defect in the diaphragm, whereas the Morgagni hernia is rare and refers to a retrosternal defect located in the anterior midline posterior to the xiphoid process.[57] CDH often occurs in isolation, but may occur with associated anomalies or as part of a syndrome, for instance the Wolf-Hirschhorn, Fryn, Pallister-Killian and Ghersoni-Baruch syndromes.[58-60] Although the aetiology of CDH has not been fully elucidated, risk factors for the development of CDH identified by some studies include male sex of the fetus, smoking during pregnancy and advanced maternal age.[61 62]

Due to advances in ultrasonography, increasing numbers of cases of CDH are being diagnosed prenatally. Markers of condition severity on antenatal ultrasonography include lung-to-head ratio (LHR), presence of liver herniation, an abnormal position of the stomach and early gestational age at ultrasound diagnosis.[63 64] Following initial cardiorespiratory support and stabilisation of the neonate, surgical management involves returning the herniated abdominal viscera back into the abdomen and repairing the defect of the diaphragm, which may be done minimally invasively or as an open repair.[65]

1.5.5 Posterior urethral valves

PUV is a congenital anomaly that affects males and is one of the most common causes of lower urinary tract obstruction amongst children. First described by Morgagni in 1717, posterior urethral valves are abnormal membranous structures that exist at the posterior section of the urethra, thereby obstructing the flow of urine.[66 67] Depending on the severity of disease, PUV may be diagnosed antenatally or postnatally. Antenatally, PUV may be diagnosed on prenatal ultrasonography. Features consistent with the diagnosis include bladder dilation, bladder wall thickening greater than three millimetres, and the "keyhole sign" representing a distended prostatic urethra. Bilateral hydroureteronephrosis, focal renal cysts and oligohydramnios may also be seen on antenatal ultrasound.[68 69] Postnatally, investigations for PUV typically include blood tests, urinary tract ultrasonography, micturating cystourethrography, renal scintigraphy and urodynamic studies, with micturating cystourethrography considered to be the gold standard investigation for diagnosing children with PUV.

Fetal intervention is often considered but carries significant risk to the fetus and may not be appropriate in many cases.[70] Prenatal interventions may include fetal cystoscopy, in utero ablation of the valves, creation of a vesicostomy and placement of a vesico-amniotic shunt. Postnatally, the initial management of PUV is typically with endoscopic valve ablation. Where valve ablation is not feasible, for instance where the urethra is too small in extremely preterm infants, the surgeon may perform a urinary diversion.[69]

1.5.6 Surgical necrotising enterocolitis

Necrotising enterocolitis is a gastrointestinal condition that mainly affects premature neonates. It is characterised by intestinal inflammation and infection, which may progress to necrosis and perforation of the bowel in more severe cases. The main risk factors for the development of NEC are lower gestational age at birth and lower birthweight. In addition, studies have found that infants fed with human milk have a lower risk of developing NEC compared to infants who are given formula milk.[71] [72] Though the aetiology of NEC has not been fully elucidated, it is thought that hypoxic-ischaemic injury, colonisation of certain bacteria and immaturity of the intestinal tract leading to poor barrier function may contribute to the development of NEC.[73]

Signs and symptoms of NEC may include lethargy, abdominal distension, bilious vomiting, feeding intolerance, and gross blood present in stools. Where the condition of the infant deteriorates despite medical therapy or where bowel perforation or necrosis is present, surgical intervention may be required.[73] [74] As the focus of this thesis is on outcomes following childhood surgery, this thesis will explore the outcomes of infants with NEC requiring surgery, excluding those who only require medical intervention.

1.6 Aims and objectives

The overall aim of this thesis is to investigate whether it is possible to harness the potential of big data to develop a better understanding of outcomes following childhood surgery, and the factors that influence these outcomes. The thesis focusses on six specific conditions for which childhood surgery is usually required: surgical necrotising enterocolitis, posterior urethral valves, congenital diaphragmatic hernia, oesophageal atresia, Hirschsprung's disease and gastroschisis.

There are two main groups of objectives for this thesis:

Group 1: Objectives pertaining to summarising what is already known about outcomes for children undergoing surgery

1. To conduct a systematic literature review to determine the long-term outcomes of children diagnosed with at least one of the six study conditions and identify factors associated with better outcomes.
2. To utilise these identified factors to inform the development of a directed acyclic graph, which will ascertain the factors that will be included in the *a priori* adjustment model for Objective 3.

Group 2: Objectives pertaining to gaining a more reliable understanding of outcomes in the UK using "big data"

3. To describe the incidence, characteristics and short-term outcomes of surgical neonates admitted to neonatal care in England using population-based data held in the National Neonatal Research Database and identify factors associated with variations in short-term outcomes.

4. To assess whether the National Neonatal Research Database can be used to develop a model to predict short term outcomes.
5. To explore the utility of Hospital Episode Statistics data in England to describe the long-term health outcomes of children who have been diagnosed with at least one of the six predetermined surgical conditions and investigate factors associated with variation in long-term outcomes.
6. To investigate whether Hospital Episode Statistics data can be used to develop a model to predict long-term outcomes.

Chapter 2

Systematic review of long-term outcomes following childhood surgery

2.1 Introduction

2.1.1 The importance of understanding long-term outcomes following childhood surgery

Despite challenges in collecting long-term outcome data, this information may be of greater utility to clinicians, patients and their families than short-term outcome data. Due to surgical and medical advancements, larger numbers of preterm neonates and infants born with a surgical condition are surviving to adulthood, and thus, the focus is shifting from short-term survival to long-term morbidity. For instance, the survival rates for children born with gastroschisis and Hirschsprung's disease are now well over 90%.[75 76] Parents should be informed of the likely trajectory and prognosis of their child, however for reasons outlined in **Chapter 1**, it may be difficult to amass significant contemporary cases for rare conditions, such that long-term data for certain outcomes may not be collected or come from smaller case series within a single unit, which are more likely to be unreliable or have limited generalisability.

Long-term data can help elucidate the needs of this population, particularly as they transition into the school environment and adulthood. A greater understanding of long-term morbidity is critical for health service planning, such as establishing a follow-up protocol within a hospital or for the advocacy of additional support services for these children. In particular, the National Institute of Health and Care Excellence (NICE) guidelines have highlighted the importance of planning transitional care for paediatric surgical patients, due to its impact on long-term health and morbidity.[77 78] As the medical and surgical landscape are constantly evolving, contemporary data is needed, as the long-term outcomes of children who were initially operated on many years ago may no longer be informative to clinicians and patients as surgical practices continue to be refined. This

naturally presents a challenge for paediatric surgeons, as it may take several years following the institution of a new practice to truly understand its long-term impact.

Existing literature suggests that the long-term sequelae for these conditions are not insubstantial. Previous studies have reported that children with gastroschisis may require further surgical procedures following the initial operation and have higher rates of bowel obstruction secondary to adhesions.[76 79] Similarly, children with Hirschsprung's disease may suffer from faecal incontinence and soiling in later life, which can affect quality of life.[80 81] Early intervention may be needed in order to mitigate the long-term consequences of a surgical condition, which highlights the importance of understanding factors associated with outcome variation. Long-term data can help to stratify and identify patients at greatest risk of adverse events, such as infections, which can be helpful in parental counselling and prognostication of surgical conditions. Furthermore, understanding factors associated with outcome variation is important in building case-mix adjustment models to allow for meaningful comparisons between centres.

2.2 Aim

The overall aim of this systematic review was to investigate the long-term outcomes for children undergoing surgery for specific neonatal conditions in childhood and identify factors that may affect outcome. From this overarching aim, the following objectives emerged:

1. To describe the outcomes that are commonly reported for the six study conditions.
2. To describe how frequently core paediatric surgical outcomes are reported in the existing literature.

3. To describe the long-term outcomes for these children as reported in the existing literature.
4. To identify factors associated with outcome variation.
5. To develop a directed acyclic graph to depict the relationship between identified factors and outcome variation.

These aims align with the Group 1 objectives for the overall thesis, as outlined in **Chapter 1.**

2.3 Methods

A systematic literature search was performed in MEDLINE, EMBASE, CINAHL Plus, PsycINFO, Web of Science and the Cochrane Library (including the Cochrane Central Register of Controlled Trials (CENTRAL)) from 01 January 2000 to 7th December 2020 for studies published in peer-reviewed journals reporting the long-term outcomes of any of the six specified paediatric surgical conditions (congenital diaphragmatic hernia, oesophageal atresia, gastroschisis, surgical necrotising enterocolitis, Hirschsprung's disease, posterior urethral valves). Free text search terms were combined with subject headings using the appropriate Boolean operators and the final search strategy was developed in conjunction with a specialist medical librarian (N Roberts). There were no restrictions placed on language or study location. Studies with less than 100 cases were excluded as studies with smaller sample sizes may be more susceptible to bias and data from small studies were less likely to meaningfully contribute to overall estimates. Only studies published since 2000 were included, as earlier studies are less likely to be relevant to current practice in paediatric surgery. As this systematic review focussed upon long-term outcomes, studies with a follow-up period of less than 12 months were excluded.

The full search strategy is outlined in **Appendix 2.1**. The protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO) (registration number CRD42021225373).

2.4 Inclusion and exclusion criteria

Inclusion criteria:

- Randomised controlled trials (RCTs), cohort studies, case-control studies, case series and cross-sectional studies that include children undergoing surgery for one of the six predetermined conditions and report on long-term outcomes (outcomes at ≥ 1-year follow-up).
- Studies where ≥ 50% of patients were operated after 1st January 2000 (or ≥ 50% of the study dates were after 1st January 2000).

Exclusion criteria:

- Expert opinion, case reports, conference proceedings, letters to the editor and review articles
- Studies with less than 100 cases
- Studies where ≤ 50% of patients were operated after 1st January 2000 (or ≤ 50% of the study dates were after 1st January 2000)
- Studies where the full text was not available
- Studies with a mean or median follow-up of less than one year

2.5 Selection process

Two reviewers (S Sun and one other reviewer [O Arscott, M Chee, E Van Blankenstein, T Desai, M Nandakumar]) independently screened the titles and abstracts of studies against the eligibility criteria. The full-text papers were sought for all studies that appeared to meet the eligibility criteria or for studies where the title and abstract did not provide sufficient evidence to reach a decision. The full-text papers were then independently screened by two reviewers. Disagreements were discussed and resolved by consensus between the two reviewers. Due to the high number of retrieved articles, data were extracted into Covidence software by a single reviewer (SS) and a selection of 10% of articles were cross-checked by a second reviewer to ensure accurate data extraction. To assess the risk of bias, the Newcastle-Ottawa Scale (NOS) was used for observational studies (**Appendix 2.2**) and the Cochrane Risk of Bias 2 tool was used for randomised controlled trials.

2.6 Data items

The following items were extracted from all included studies: name of authors, year of publication, aim, study design, start date, end date, comparison groups, population description including inclusion and exclusion criteria, country, single or multi-centre study, language, study setting, number of participants, baseline imbalances, participant characteristics, surgical condition, length of follow-up, outcomes reported, factors associated with variation in outcome and measure of effect or association. Factors were considered to be associated with the outcome if there was a statistically significant test result ($p \leq 0.05$) on univariable or multivariable analysis conducted by the study authors. These factors were used to inform the development of a directed acyclic graph (DAG) to depict the relationship between long-term outcomes and associated factors.

Outcomes were reported in six domains: survival, quality of life, developmental outcomes, re-operation, episodes of infection, readmission. These outcome domains were identified in several COSs as outcomes that are important to patients, parents, clinicians and other stakeholders.[18 82]

2.7 Statistical analysis

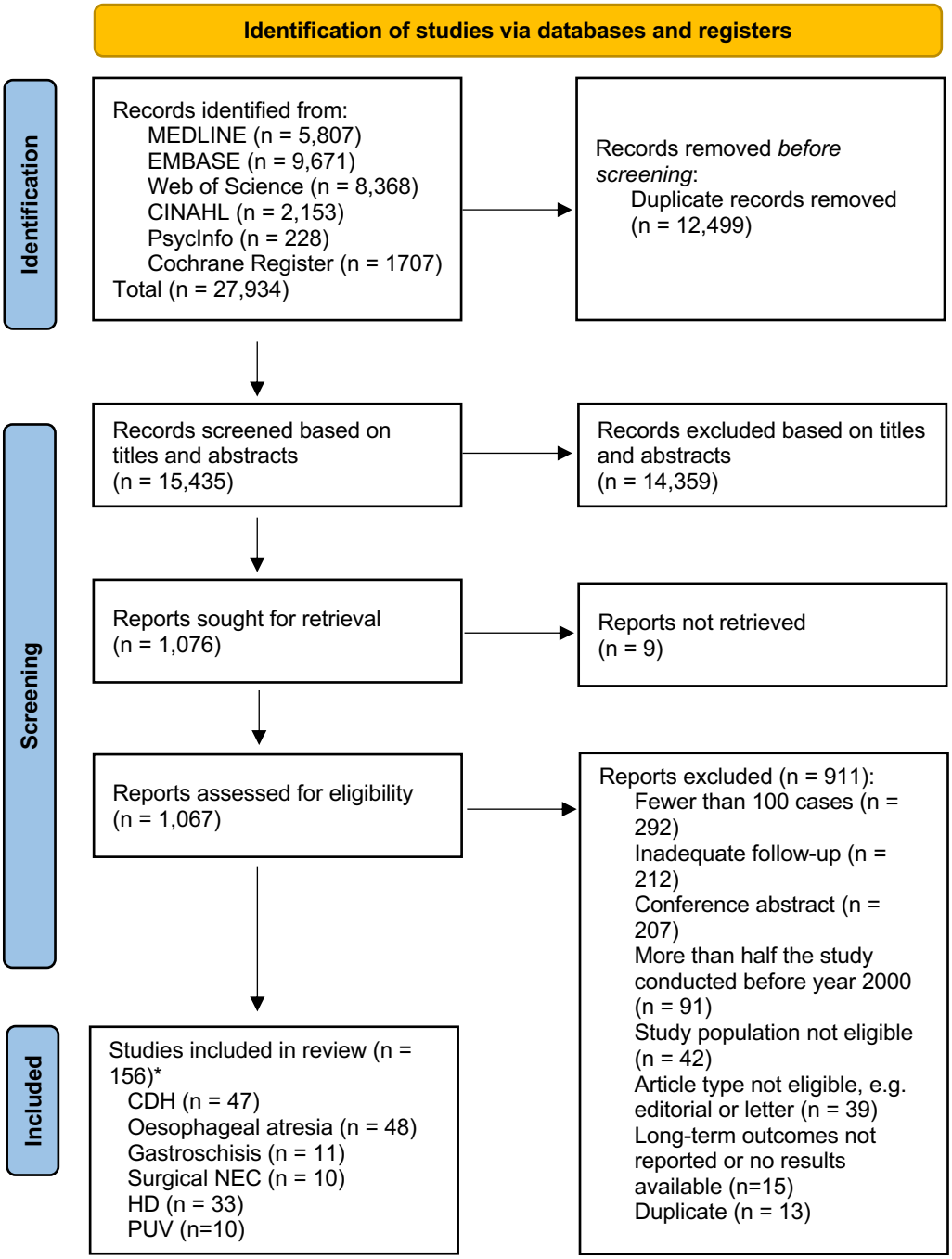
Proportional meta-analysis was conducted using a random-effects model. Where there was an insufficient number of studies for meta-analysis, a narrative review of the evidence was presented. A single meta-analysis was performed encompassing the six study conditions. Following the Cochrane recommendations for assessment of heterogeneity, an I^2 greater than 75% was considered as significant heterogeneity. Statistical analyses were conducted using Stata (StataCorp LLC: Texas, USA) software. The directed acyclic graph (DAG) was constructed using DAGitty software (Version 3.0). A DAG is a causal diagram depicting prior knowledge of the relationships between exposures and outcome, as well as explicitly communicating the *a priori* assumptions that are being made. A DAG can therefore aid in the identification of variables that should be controlled for to minimise the risk of confounding and bias. Firstly, the exposures and outcome were identified, variables that influence both the exposure and outcome were included, and potential causal relationships between these factors were depicted using one-way arrows. As the focus was on identifying common factors across the six surgical conditions that may influence outcomes, only one DAG was produced.

2.8 Results

A total of 27,934 articles were retrieved from the initial search, of which 15,435 remained after removing duplicates. Following title and abstract screening, 1,076 full-text articles

were retrieved and assessed for eligibility. After full-text screening, 911 reports were excluded, with most studies excluded on the basis of having less than 100 cases of at least one of the study conditions (n=292) or due to follow-up of less than one year (n=212). A total of 156 articles were included (**Figure 2.1**), of which 47 studies (30.1%) related to congenital diaphragmatic hernia, 48 (30.8%) related to oesophageal atresia, 11 (7.1%) related to gastroschisis, 10 (6.4%) related to surgical necrotising enterocolitis, 33 (21.2%) related to Hirschsprung's disease and 10 (6.4%) related to posterior urethral valves. Two studies reported on more than one of the study conditions. Sixty-four out of 156 studies (41%) were deemed to have a low risk of bias (**Appendix 2.2**).

Figure 2.1 PRISMA flow diagram of selection of studies



CDH = congenital diaphragmatic hernia; HD = Hirschsprung's Disease; NEC = necrotising enterocolitis; PUV = posterior urethral valves

*Two studies reported on more than one of the six study conditions.

2.8.1 Characteristics of included studies

2.8.1.1 Characteristics of included studies for Hirschsprung's disease

There were 33 studies included that related to Hirschsprung's disease, encompassing a total of 18,767 children across 9 different countries (**Table 2.1**). The highest number of studies were based in China (n=15, 45.5%), followed by the USA (n=9, 27.3%). The duration of follow-up ranged between 12 months to 112 months. Only 7 studies (21.2%) reported gestational age and birthweight of participants, and 5 studies (15.2%) reported the proportion of participants who were of Caucasian ethnicity.

2.8.1.2 Characteristics of included studies for gastroschisis

Eleven articles relating to gastroschisis were included, encompassing 7,251 children with gastroschisis across 6 different countries. Characteristics of included studies are outlined in **Table 2.2**. The majority of studies for gastroschisis were conducted in high-income countries, with the highest number based in the US (n=4). Median duration of follow-up ranged from 12 months to 113.5 months. Five studies (45.5%) reported median or mean gestational age (range 36 to 37 weeks), 4 studies (36.4%) reported birthweight (range 2370g to 2440g) and 3 studies (27.3%) reported the proportion of participants with Caucasian ethnicity (range 65.7% to 91.4%).

2.8.1.3 Characteristics of included studies for oesophageal atresia

Of 156 articles included, 48 studies related to oesophageal atresia, encompassing 19,989 patients across 11 different countries. The greatest number of studies came from the USA (n=10), followed by France (n=8). Duration of follow-up ranged between 12 months and 204 months. Thirty studies (62.5%) reported mean or median gestational age (ranging between 35 weeks to 38.3 weeks), 30 studies (62.5%) reported birthweight (ranging between 2040g to

2944g) and 6 studies (12.5%) reported proportion of participants of Caucasian ethnicity (ranging between 68.2% and 100%). The characteristics of included studies for oesophageal atresia are outlined in detail in **Table 2.3**.

2.8.1.4 Characteristics of included studies for congenital diaphragmatic hernia

A total of 47 studies were identified on congenital diaphragmatic hernia, encompassing 13,725 patients across 12 different countries. The greatest number of studies had participants from the USA (n=22) followed by Japan and the UK (n=6 each respectively). The follow-up duration ranged between 12 months and 204 months. Of 47 studies, 35 studies reported the mean or median gestational age of participants (ranging between 36 weeks and 38.6 weeks), 34 studies reported birthweight (ranging between 2507g and 3890g), and 6 studies reported numbers of participants with Caucasian ethnicity (ranging between 50.3% and 93%). The characteristics of included studies for congenital diaphragmatic hernia are outlined in detail in **Table 2.4**.

2.8.2 Characteristics of included studies for posterior urethral valves (PUV)

A total of 10 papers relating to PUV were included, encompassing 1,668 children across 5 different countries. Most of the studies relating to PUV were conducted in India (n=5), followed by the US (n=2). The mean duration of follow-up ranged between 28.8 months and 102 months and all participants were male due to the nature of the condition. Only 2 studies (20%) reported gestational age, one study (10%) reported the birthweight of participants, and one study (10%) reported the proportion of participants with Caucasian ethnicity. Further details of included studies are outlined in in **Table 2.5**.

2.8.3 Characteristics of included studies for surgical necrotising enterocolitis (NEC)

Of the 156 included studies, 10 studies reported long-term outcomes for surgical necrotising enterocolitis, encompassing 2,681 children across 4 different countries. The greatest number of studies were based in the USA or North America (n=7). The median or mean duration of follow-up ranged between 12 months and 72 months. Of the 10 studies, 8 studies (80%) reported median or mean gestational age (ranging between 25 weeks and 28.8 weeks), 8 studies (80%) reported birthweight (ranging between 730g and 1290g) and 4 studies (40%) reported the number of children with Caucasian ethnicity (ranging between 42% and 61%). The characteristics of included studies for surgical necrotising enterocolitis are outlined in detail in **Table 2.6**.

Table 2.1 Characteristics of included studies for Hirschsprung's disease

Study ID	Country in which the study is conducted	Single vs. multi-centre study	Study design	Total number of participants	Male (%)	Follow-up duration in months (median, unless otherwise stated)	Gestational age in weeks (median, unless otherwise stated)	Birth weight in grammes (median, unless otherwise stated)	Ethnicity: Caucasian (%)
Allin 2020[83]	UK	Multi-centre	Cohort	227	-	81.6	-	-	-
Anderson 2018[84]	USA	Multi-centre	Cohort	2464	67	12	38.29*	3130*	55.6
Apfeld 2020[85]	USA	Multi-centre	Cohort	1268	79.4	24	39	3323.5	61
Bing 2017[86]	China	Single-centre	Cohort	148	-	42*	-	-	-
Bischoff 2017[87]	USA	Single-centre	Cohort	103	76.7	22.8*	-	-	-
Dahal 2011[88]	China	Single-centre	Cohort	131	85.5	29.4*	-	-	-
Elhalaby 2004[89]	Egypt	Multi-centre	Cohort	149	77.9	12	-	-	-
Giuliani 2020[90]	UK	Multi-centre	Cohort	1333	74.6	12	-	-	67.7
Huang 2018[91]	China	Single-centre	Cohort	181	75.1	75.24*	-	-	-
Jiao 2018[92]	China	Single-centre	Cohort	110	76.4	85.2	-	-	-
Khazdouz 2015[93]	Iran	Single-centre	Cohort	161	59	54*	-	3060	-
Kwendakwema 2016[94]	USA	Single-centre	Cohort	207	75.8	35	39	-	-
Li 2006[95]	China	Single-centre	Cohort	252	83.7	12	-	-	-
Liem 2008[96]	Vietnam	Single-centre	Cohort	192	85.9	20*	-	-	-
Lu 2017[97]	China	Multi-centre	Cohort	650	76.5	35.6*	-	-	-
Meng 2020[98]	China	Single-centre	Cohort	204	78.4	57.12*	-	-	-
Miyano 2018[99]	Japan	Single-centre	Cohort	106	69.3	≥12	-	-	-
Nguyen 2009[100]	Vietnam	Single-centre	Cohort	200	78.5	24*	-	-	-
Parahita 2018[101]	Indonesia	Single-centre	Cohort	100	75	17*	-	-	-
Pruitt 2020[102]	USA	Multi-centre	Cohort	1097	76	12	38*	3300*	-

* Mean reported; ^ Range reported

Table 2.1 (continued)

Study ID	Country in which the study is conducted	Single vs. multi-centre study	Study design	Total number of participants	Male (%)	Follow-up duration in months (median, unless otherwise stated)	Gestational age in weeks (median, unless otherwise stated)	Birth weight in grammes (median, unless otherwise stated)	Ethnicity: Caucasian (%)
Pruitt 2020 (2)[103]	USA	Multi-centre	Cohort	2030	76.7	12	38*	3270*	43.2
Quiroz 2020[104]	USA	Multi-centre	Cohort	3635	75	12	-	-	-
Sulkowski 2014[105]	USA	Multi-centre	Cohort	1555	78.3	24*	39	3323*	-
Sun 2015[106]	China	Single-centre	Cohort	286	87.4	24-60^	-	-	-
Taghavi 2020[107]	New Zealand	Multi-centre	Cohort	246	78	88.8	38.9	3396*	-
Tang 2012[108]	China	Single-centre	Cohort	218	69.7	68	-	-	-
Taylor 2020[109]	USA	Multi-centre	Case control	299	76.6	36	-	-	71.4
Yang 2012[110]	China	Single-centre	Cohort	137	67.2	56*	-	-	-
Zhang 2014[111]	China	Single-centre	Cohort	127	70.1	98.4	-	-	-
Zhang 2020[112]	China	Multi-centre	Randomised controlled trial	383	62.9	24*	-	-	-
Zheng 2018[113]	China	Single-centre	Cohort	172	80.2	36-120^	-	-	-
Zhu 2019[114]	China	Single-centre	Cohort	198	79.8	≥12	-	-	-
Zhuansun 2020[115]	China	Single-centre	Cohort	198	75.8	111.96*	-	-	-

* Mean reported; ^ Range reported

Table 2.2 Characteristics of included studies for gastroschisis

Study author and year	**Country**	**Single vs. multi-centre study**	**Study design**	**Total number of participants**	**Male (%)**	**Follow-up duration in months (median, unless otherwise stated)**	**Gestational age in weeks (median, unless otherwise stated)**	**Birthweight in grammes (median)**	**Ethnicity: Caucasian (%)**
Abdelhafeez 2011[116]	Ireland	Dual-centre	Cohort	128	62.5	48	-	-	-
Abdelhafeez 2015[117]	USA	Single-centre	Cohort	142	-	88.8	36	2420	-
Anderson 2018[118]	UK	Multi-centre	Cohort	2527	52.0	12	-	-	67.3
Bradnock 2011[119]	UK	Multi-centre	Cohort	301	45.9	12	-	-	91.4
Cain 2014[120]	USA	Multi-centre	Cohort	324	54.0	≥ 12	36.3*	-	65.7
Chen 2019[121]	Taiwan	Nation-wide	Cohort	179	55.3	113.5	-	-	-
DeBie 2020[122]	USA	Single-centre	Cohort	124	42.0	48	36.4	2440	-
Long 2011[123]	UK	Single-centre	Cohort	170	-	≥ 12	37	2370	-
Minutillo 2013[124]	Australia	Single-centre	Cohort	128	55.6	12	36	2425	-
Schmedding 2020[125]	Germany	Multi-centre	Cohort	316	52.5	12	-	-	-
Ward 2017[126]	USA	Multi-centre	Cohort	2912	-	47.6*	-	-	-

* Mean reported

Table 2.3 Characteristics of included studies for oesophageal atresia

Study ID	**Country in which the study is conducted**	**Single vs. multi-centre study**	**Study design**	**Total number of participants**	**Male (%)**	**Follow-up duration in months** (median, unless otherwise stated)	**Gestational age in weeks** (median, unless otherwise stated)	**Birthweight in grammes** (median, unless otherwise stated)	**Ethnicity: Caucasian (%)**
Allin 2014[127]	UK	Multi-centre	Cohort	151	53	12	37	2600	79
Ax 2021[128]	Sweden	Single-centre	Cross-sectional	114	58.8	24-204^	37	2620	-
Bastard 2018[129]	France	Multi-centre	Cohort	322	-	33*	-	Mean 2580g in those with sequelae and 2620g in those without	-
Baxter 2018[130]	USA	Dual-centre	Cohort	145	61.4	12	37.2*	Mean 2273.5g in patients with a structural airway abnormality and 2613.4g in patients without a structural airway abnormality	-
Coppens 2016[131]	The Netherlands	Single-centre	Cohort	111	63	84	-	2630	-
Dellenmark-Blom 2018[132]	Sweden	Single-centre	Cohort	119	58	108	37	2600	-
Dellenmark-Blom 2019[133]	Sweden	Single-centre	Cohort	103	61.2	24-204^	-	-	-
Dellenmark-Blom 2020[134]	Sweden and Germany	Dual-centre	Cohort	124	60.5	24-204^	-	-	-
Donoso 2016[135]	Sweden	Single-centre	Cohort	129	57.4	63.6	38	Median 2703g in non-LGOA patients and 2184g in LGOA patients	-
Donoso 2017[136]	Sweden	Single-centre	Cohort	128	57.0	≥12	38	Median 2716g in the symptomatic PPI group and 2674g in the prophylactic PPI group	-
Elhattab 2020[137]	France	Dual-centre	Cohort	187	-	12	Mean 38 weeks in the thorascopic group and 36.4 in the open approach group	Mean 2785.2g in the thorascopic group and 2404.9g in the thoracotomy group	-
Fayoux 2018[138]	France	Single-centre	Cohort	158	62	48*	37*	-	-
Flieder 2019[139]	Germany and Sweden	Dual-centre	Cohort	192	60.1	96.8*	-	Mean 2410g in the German group and 2590g in the Swedish group	-
Forster 2019[140]	Canada	Single-centre	Cohort	236	53.8	36.97	37.3*	2696*	-
Francois 2019[141]	France	Multi-centre (nationwide)	Cohort	682	59.9	12	-	-	-
Fung 2019[142]	Canada	Single-centre	Cohort	197	51.3	15.1*	38	2645	-
Fusco 2018[143]	USA	Single-centre	Cohort	110	-	112.9*	-	-	-

* Mean reported; ^ Range reported. LGOA = long-gap oesophageal atresia; PPI = proton-pump inhibitors

Table 2.3 (continued)

Study ID	**Country in which the study is conducted**	**Single vs. multi-centre study**	**Study design**	**Total number of participants**	**Male (%)**	**Follow-up duration in months** (median, unless otherwise stated)	**Gestational age in weeks** (median, unless otherwise stated)	**Birthweight in grammes** (median, unless otherwise stated)	**Ethnicity: Caucasian (%)**
Garabedian 2015[144]	France	Multi-centre (nationwide)	Cohort	469	-	12	Median 36 weeks in the prenatal diagnosis group and 38 weeks in the postnatal diagnosis group	Median 2352g in the prenatal group and 2680g in the postnatal group	-
Garabedian 2015-2[145]	France	Multi-centre	Cohort	408	-	12	Median 36 weeks in the prenatal diagnosis group and 38 weeks in the postnatal diagnosis group	Median 2340g in the prenatal group and 2700g in the postnatal group	-
Hsieh 2017[146]	Canada (Montreal), Australia (Sydney) and France (Lille)	Multi-national	Cohort	542	-	20.4*	-	-	-
Jones 2020[147]	UK	Single-centre	Cohort	114	67.5	58.8	39	2800	-
Jones 2020-2[148]	UK	Single-centre	Cohort	120	68.3	60	39	2800	-
Koivusalo 2013[149]	Finland	Single-centre	Cohort	130	-	105.6	-		-
Kovesi 2018[150]	Italy	Single-centre	Cohort	105	-	42.5	36.1*	2465.6*	-
Lal 2017[151]	USA	Multi-centre	Cohort	396	61	≥12	37	2600	77.8
Lal 2018[152]	USA	Multi-centre	Cohort	292	60	12	37	2650	78
Lawrence 2019[153]	USA	Multi-centre	Cohort	3085	54.7	12	37	2590	69.3
Mawlana 2018[154]	Canada	Single-centre	Cohort	253	49.4	24-36^	36.7*	2745.3*	-
Nurminen 2019[155]	Finland	Single-centre	Cohort	104	54	60	-	-	-
Oztan 2020[156]	Turkey	Multi-centre	Cohort	389	53.4	12	Median 35 weeks in the low birthweight group and 38 weeks in the normal birthweight group	Mean 2040g in the low birthweight group and 2944g in the normal birthweight group	-

* Mean reported; ^ Range reported. LGOA = long-gap oesophageal atresia; PPI = proton-pump inhibitors

Table 2.3 (continued)

Study ID	**Country in which the study is conducted**	**Single vs. multi-centre study**	**Study design**	**Total number of participants**	**Male (%)**	**Follow-up duration in months** (median, unless otherwise stated)	**Gestational age in weeks** (median, unless otherwise stated)	**Birthweight in grammes** (median, unless otherwise stated)	**Ethnicity: Caucasian (%)**
Paramalingam 2013[157]	UK	Single-centre	Cohort	107	68.2	42	38	2597	-
Porcaro 2017[158]	Italy	Single-centre	Cohort	105	54	26.4*	36.9	2579.6	100
Pruitt 2020-2[102]	USA	Multi-centre	Cohort	673	56.5	12	37*	2600*	-
Quiroz 2020-2[159]	USA	Multi-centre	Cohort	3157	54	12	34*	-	-
Raitio 2016[160]	UK	Single-centre	Cohort	137	-	58.8	-	-	-
Schmedding 2020-2[161]	Germany	Multicentre	Cohort	287	52.6	12	-	-	-
Schneider 2014[162]	France	Multi-centre (nationwide)	Cohort	307	55	12	37*	2591*	-
Shah 2015[163]	Australia	Single-centre	Cohort	100	45	≥12	36.4	2702.5	-
SinghSodhi 2013[164]	India	Single-centre	Cohort	210	60	36*	-	2800*	-
Soliman 2019[165]	Canada	Single-centre	Cohort	106	58.5	84	-	-	-
Sulkowski 2014-2[166]	USA	Multi-centre	Cohort	3479	55.6	24	37	2582	68.2
Tambucci 2020[167]	Italy	Single-centre	Cohort	370	66.7	108	-	-	-
Thyoka 2014[168]	UK	Single-centre	Cohort	103	59	22.8	-	-	-
Vergouwe 2017[169]	The Netherlands	Single-centre	Cohort	126	61.9	≥24	38.3	2830	86.5
Vergouwe 2019[170]	The Netherlands	Multi-centre	Cohort	454	61	79.2	38	2780	-
Yasuda 2019[171]	USA	Single-centre	Cohort	310	49	44	-	-	-
Yasuda 2020[172]	USA	Single-centre	Cohort	171	48.5	24	-	-	-
Zhu 2018[173]	China	Single-centre	Cohort	172	57	34.2*	38*	2852*	-

***** Mean reported; ^ Range reported
LGOA = long-gap oesophageal atresia; PPI = proton-pump inhibitors

Table 2.4 Characteristics of included studies for congenital diaphragmatic hernia (CDH)

Study ID	**Country in which the study is conducted**	**Single vs. multi-centre study**	**Study design**	**Total number of participants**	**Male (%)**	**Follow-up duration in months** (median, unless otherwise stated)	**Gestational age in weeks** (median, unless otherwise stated)	**Birthweight in grammes** (median, unless otherwise stated)	**Ethnicity: Caucasian (%)**
Abramov 2020[174]	USA	Multi-centre	Cohort	588	57.4	24	37.8*	-	-
Ali 2019[175]	UK	Single-centre	Cohort	191	54.5	-	36	Median 2590g in the LCDH group and 2670g in the RCDH group	-
Aydin 2019[176]	USA	Single-centre	Cohort	223	58.5	-	37.7*	Mean 3111.8g in the hernia sac group and 3890.1g in the absent hernia sac group	-
Aydin 2020[177]	USA	Single-centre	Cohort	171	53.8	60	37.3*	Mean 2908g in the patch group and 2853g in the flap group	-
Bairdain 2015[178]	USA	Single-centre	Cohort	110	67	12	-	-	-
Barriere 2018[179]	France	Multi-centre	Cohort	158	51.1	12	-	2908	-
Burgos 2017[180]	Sweden	Single-centre	Cohort	251	60.3	≥12	-	-	-
Cauley 2015[181]	USA	Single-centre	Cohort	201	63.7	61.2	38	Median 3000g in the invasive support group and non-invasive support group, 3200g in the room air group	-
Chen 2019[182]	China	Single-centre	Cohort	152	-	12-108^	-	-	-
Cioci 2020[183]	USA	Multi-centre	Cohort	511	52	12	-	-	-
Costerus 2016[184]	The Netherlands and Germany	Dual-centre	Cohort	108	52.3	12	38	Median 3045g in the thoracoscopic group and 2950g in the open group	-
Danzer 2016[185]	USA	Single-centre	Cohort	135	56.3	13	38	3283	75
Danzer 2018[186]	USA	Single-centre	Cohort	212	56.6	-	37.5*	Mean 3033g in the no ECMO group and 3089g in the ECMO group	73% in the no ECMO group and 56% in the ECMO group
Danzer 2018-2[187]	USA	Single-centre	Cohort	183	62.7	-	37.7*	Mean 2507g in the ASD group and 3074g in the non-ASD group	93% in the ASD group and 79% in the non-ASD group

* Mean reported; ^ Range reported. LCDH = left-sided congenital diaphragmatic hernia; RCDH = right-sided congenital diaphragmatic hernia; ECMO = extracorporeal membrane oxygenation; ASD = autism spectrum disorder; UK = United Kingdom; USA = United States of America

Table 2.4 (continued)

Study ID	Country in which the study is conducted	Single vs. multi-centre study	Study design	Total number of participants	Male (%)	Follow-up duration in months (median, unless otherwise stated)	Gestational age in weeks (median, unless otherwise stated)	Birthweight in grammes (median, unless otherwise stated)	Ethnicity: Caucasian (%)
DeBie 2020[188]	UK and Belgium	Dual-centre	Cohort	117	64.1	12	Median 37.5 weeks in the thoracotomy group and 38.5 weeks in the laparotomy group	Median 2830g in the thoracotomy group and 3000g in the laparotomy group	-
Dennett 2014[189]	USA	Single-centre	Cohort	122	63.1	47	38*	3000	-
Garcia 2013[190]	USA	Single-centre	Cohort	106	-	26.6	37.8*	2946*	-
Garriboli 2012[191]	UK and Ireland	Dual-centre	Cohort	234	55.1	12	39	3000	-
Haliburton 2015[192]	Canada	Single-centre	Cohort	116	68.1	60-204^	38*	-	-
Heiwegen 2020[193]	The Netherlands	Single-centre	Cohort	197	61.9	24-192^	38.3	2991.2*	-
Heiwegen 2020-2[194]	The Netherlands	Single-centre	Cohort	183	62.4	132	38.3	Mean 2911g in the no true defect group and 3004g in the true defect group	-
Jancelewicz 2013[195]	Canada	Single-centre	Cohort	157	59.9	68.4	38	Mean 3200g in the primary repair group and 3100g in the non-primary repair group	-
Janssen 2018[196]	The Netherlands	Single-centre	Cohort	112	62	87.6^	38.5*	2997*	-
Kadir 2017[197]	USA	Single-centre	Cohort	113	53.1	30	38	Median 3192g in the early time period and 3215 in the later time period	-
Lee 2018[198]	Australia	Multi-centre	Cohort	215	54	12	37.2	-	-
Liem 2011[199]	Vietnam	Single-centre	Cohort	139	65.5	26.3*	-	-	-
Long 2019[200]	UK	Multi-centre		219	60.8	12	39	Median 3080g in survivors and 2735g in non-survivors	85% of survivors and 91% of non-survivors
Masi 2010[201]	Italy	Single-centre	Cohort	116	-	≥12	-	-	-
Nagata 2015[202]	Japan	Multi-centre	Cohort	180	54.4	55.0*	37.8*	Mean 2533g in the recurrence group and 2703g in the nonrecurrence group	-

* Mean reported; ^ Range reported. LCDH = left-sided congenital diaphragmatic hernia; RCDH = right-sided congenital diaphragmatic hernia; ECMO = extracorporeal membrane oxygenation; ASD = autism spectrum disorder; UK = United Kingdom; USA = United States of America

Table 2.4 (continued)

Study ID	**Country in which the study is conducted**	**Single vs. multi-centre study**	**Study design**	**Total number of participants**	**Male (%)**	**Follow-up duration in months** (median, unless otherwise stated)	**Gestational age in weeks** (median, unless otherwise stated)	**Birthweight in grammes** (median, unless otherwise stated)	**Ethnicity: Caucasian (%)**
Okuyama 2011[203]	Japan	Multi-centre	Cohort	117	53.9	≥18	38	2780	-
Partridge 2014[204]	USA	Single-centre	Cohort	112	51.5	24-36^	37.8*	3007*	-
Pruitt 2020-3[102]	USA	Multi-centre	Cohort	500	57.4	12	38*	3000*	-
Ruano 2015[205]	USA	Single-centre	Cohort	139	-	12	38*	2917*	-
Russell 2014[206]	USA	Single-centre	Cohort	236	-	132	-	-	-
Short 2018[207]	USA	Single-centre	Cohort	127	64.6	20.4	-	-	-
Style 2019[208]	USA	Single-centre	Cohort	107	61.7	12	37.2*	2900*	50.5
Suply 2020[209]	UK	Single-centre	Cohort	203	60.6	19.1	39	3000	-
Takayasu 2016[210]	Japan	Multi-centre	Cohort	159	-	51.6*	37.9*	2702.5*	-
Terui 2014[211]	Japan	Multi-centre	Cohort	182	54.4	≥18	37.8*	2680*	-
Terui 2016[212]	Japan	Multi-centre (nationwide)	Cohort	174	55.2	50.4	38	2745	-
Tsai 2012[213]	USA	Single-centre	Cohort	149	59.7	18	Median 38.6 weeks in the primary repair group and 38 weeks in the patch repair group	Median 3060g in the primary repair group and 3020g in the patch group	-
Verla 2020[214]	USA	Single-centre	Cohort	191	54	45.6	38.1	2935	-
Wang 2019[215]	UK	Multi-centre (nationwide)	Cohort	2336	58.6	12	-	-	67.4
Ward 2017-2[126]	USA	Multi-centre	Cohort	3051	-	47.6*	-	-	-
Weaver 2016[216]	USA, Germany and Japan	Multi-national	Cohort	109	57.8	18.2	-	Mean 3080g in the no recurrence group and 2800g in the recurrence group	-
Wong 2018[217]	Canada	Single-centre	Cohort	153	62.6	≥12	38.4*	Mean 3160g in the prenatally diagnosed group and 3100g in the postnatally diagnosed group	-
Wong 2019[218]	Canada	Single-centre	Cohort	160	-	≥12	38	Median 3000g in the tube feeds group and 3200g in the oral feeds group	-

* Mean reported; ^ Range reported. LCDH = left-sided congenital diaphragmatic hernia; RCDH = right-sided congenital diaphragmatic hernia; ECMO = extracorporeal membrane oxygenation; ASD = autism spectrum disorder; UK = United Kingdom; USA = United States of America

Table 2.5 Characteristics of included studies for posterior urethral valves (PUV)

Study author and year	Country	Single vs. multi-centre study	Study design	Total number of participants	Follow-up in months (mean)	Gestational age in weeks	Birthweight in grammes	Ethnicity: Caucasian (%)
Akhtar 2014[219]	Pakistan	Single-centre	Cohort	100	36	-	-	-
Amirzargar 2020[220]	Iran	Single-centre	Cohort	110	36	-	-	-
Ansari 2010[221]	India	Single-centre	Cohort	227	86.4	-	-	-
Ansari 2018[222]	India	Single-centre	Cohort	270	102	-	-	-
Bhadoo 2014[223]	India	Single-centre	Cohort	152	60	-	-	-
Bilgutay 2016[224]	USA	Single-centre	Cohort	104	28.8	33% born before 37 weeks' gestation	-	15.4%
Chatterjee 2020[225]	India	Single-centre	Cohort	272	93.6	-	-	-
Menon 2010[226]	India	Single-centre	Cohort	181	30	-	-	-
Sarhan 2017[227]	Saudi Arabia	Dual-centre	Cohort	112	62.5	Mean 33 weeks in the preterm/LBW group and 38 weeks in the full-term/NBW group	Mean 1950g in the preterm/LBW group and 3200g in the full-term/NBW group	-
Tourchi 2014[228]	USA	Single-centre	Cohort	140	45.6	-	-	-

VUR = vesicoureteral reflux; CKD = chronic kidney disease; ESRD = end-stage renal disease; eGFR = estimated glomerular filtration rate; ESRF = end-stage renal failure; LBW = low birthweight; NBW = normal birthweight; USA = United States of America
Note: all participants were male.

Table 2.6 Characteristics of included studies for surgical necrotising enterocolitis (NEC)

Study ID	Country	Single vs. multi-centre study	Study design	Total number of participants	Male (%)	Follow-up duration in months (median, unless otherwise stated)	Gestational age in weeks (median, unless otherwise stated)	Birthweight in grammes (median, unless otherwise stated)	Ethnicity: Caucasian (%)
Allin 2018[229]	UK	Multi-centre	Cohort	236	57	12	27	1013	42
Calvert 2020[230]	UK	Single-centre	Cohort	243	62	12	28	1030	-
Cole 2008[231]	USA	Multi-centre	Cohort	131	60.3	18-22^	-	-	43.5
Elfvin 2015[232]	Canada	Single-centre	Cohort	153	-	12	28.8*	1290*	-
Fredriksson 2019[233]	Canada	Single-centre	Cohort	131	61.1	72	27	788	-
Fullerton 2018[234]	North America	Multi-centre	Cohort	449	58	18-24^	25*	752*	61
Hong 2018[235]	North America	Multi-centre	Cohort	462	58	18-24^	25	730	-
Shah 2012[236]	USA	Multi-centre	Cohort	121	51	18-22^	25.7*	753*	-
Sung 2019[237]	Korea	Multi-centre	Cohort	283	-	18-24^	-	-	-
Wadhawan 2014[238]	USA	Multi-centre	Cohort	472	58.3	18-22^	25.6*	736*	50.2

* Mean reported; ^ Range reported
IFALD = intestinal failure associated liver disease; NEC = necrotising enterocolitis; IF = intestinal failure

2.8.4 Reported long-term outcomes for each of the six study conditions

Out of the six outcome domains (survival, quality of life, developmental outcomes, re-operation, episodes of infection, readmission), only survival was consistently reported across the six study conditions (**Table 2.7**).

Table 2.7 Frequencies of reported outcomes by condition

Legend: Red = 0% of studies reported the outcome; Orange = <20% of studies reported the outcome; Yellow = 20-49% of studies reported the outcome; Green ≥50% reported the outcome

	Long-term survival	**Quality of life**	**Developmental outcomes**	**Re-operation**	**Sepsis/ episodes of infection**	**Re-admission**
Congenital diaphragmatic hernia	27/47 (57.4%)	0/47 (0.0%)	15/47 (31.9%)	11/47 (23.4%)	0/47 (0.0%)	4/47 (8.5%)
Oesophageal atresia	18/48 (37.5%)	3/48 (6.3%)	9/48 (18.8%)	21/48 (43.75%)	8/48 (16.7%)	10/48 (20.8%)
Gastroschisis	10/11 (90.9%)	0/11 (0.0%)	2/11 (18.2%)	5/11 (45.5%)	0/11 (0.0%)	3/11 (27.3%)
Surgical necrotising enterocolitis	7/10 (70%)	0/10 (0%)	5/10 (50%)	6/10 (60%)	2/10 (20%)	3/10 (30%)
Hirschsprung's disease	10/33 (30.3%)	2/33 (6.1%)	0/33 (0.0%)	9/33 (27.3%)	24/33 (72.7%)	5/33 (15.2%)
Posterior urethral valves	3/10 (30%)	0/10 (0%)	0/10 (0%)	2/10 (20%)	3/10 (30%)	0/10 (0%)

2.8.5 Reported long-term outcomes for Hirschsprung's disease

Of the 33 included studies, the most frequently reported outcome domain for studies on Hirschsprung's disease was episodes of infection (72.7%, n=24), including Hirschsprung's-associated enterocolitis. The next most frequently reported outcome domains were long-term survival (30.3%, n=10) and re-operation (27.3%, n=9). Other commonly reported outcomes for Hirschsprung's disease included bowel function, such as soiling, constipation and stool frequency. The reported outcomes are mapped and outlined in **Table 2.8**.

2.8.6 Reported long-term outcomes for gastroschisis

Of the 11 included studies, the most frequently reported outcome domain amongst articles on gastroschisis was long-term survival (90.9%, n=10), followed by re-operation (45.5%, n=5). No studies reported on episodes of infection or quality of life. Other commonly reported outcomes for gastroschisis included volvulus, long-term parenteral nutrition and liver failure. The reported outcomes are mapped and outlined in **Table 2.9**.

2.8.7 Reported long-term outcomes for oesophageal atresia

Of the 48 studies relating to oesophageal atresia, the most frequently reported outcome domain was long-term survival (57.4%, n=27), followed by developmental outcomes (31.9%, n=15). Other commonly reported outcomes included anastomotic stricture, gastro-oesophageal reflux, vocal cord paralysis and respiratory complications. The reported oesophageal atresia outcomes are mapped and outlined in **Table 2.10**.

2.8.8 Reported long-term outcomes for congenital diaphragmatic hernia

Out of 47 studies, the most frequently reported outcome domain for congenital diaphragmatic hernia was long-term survival (57.4%, n=27), followed by developmental outcomes (31.9%, n=15). No studies reported on long-term quality of life. Other frequently reported outcomes included respiratory outcomes, hernia recurrence, musculoskeletal conditions such as pectus deformity, and gastro-oesophageal reflux. The reported outcomes are mapped and outlined in further detail in **Table 2.14**.

2.8.9 Reported long-term outcomes for PUV

Out of the 10 included studies, the most frequently reported outcome domains were long-term survival and episodes of infection, though only 30% (n=3) reported these outcomes.

No studies reported on re-admission, quality of life or developmental outcomes. All studies also reported renal outcomes, such as chronic kidney disease, nocturnal enuresis and vesicoureteral reflux. The reported outcomes for PUV are mapped and outlined in **Table 2.17**.

2.8.10 Reported long-term outcomes for surgical necrotising enterocolitis

The most frequently reported outcome domain for articles relating to surgical necrotising enterocolitis was long-term survival (70%, n=7), followed by re-operation (60%, n=6). No studies reported long-term quality of life. The reported outcomes are mapped and outlined in further detail in **Table 2.18**.

Table 2.8 Reported long-term outcomes by domain for Hirschsprung's disease

Study ID	Long-term survival	Sepsis/ episodes of infection	Re-admission	Re-operation	Quality of life	Developmental outcomes	Other reported long-term outcomes
Allin 2020	✓	HAEC		✓	✓		Permanent stoma, faecal incontinence, urinary incontinence, bowel movements without enemas or rectal or colonic washouts, psychological stress, objective measure of bowel function
Anderson 2018	✓						
Apfeld 2020		HAEC	✓	✓			
Bing 2017		HAEC					Faecal soiling, recurrent constipation, bowel function score
Bischoff 2017				✓			Damaged anal canal
Dahal 2011	✓	HAEC					Soiling, constipation, stool frequency
Elhalaby 2004	✓	HAEC					Anastomotic stricture, recurrent constipation, complete anorectal continence, adhesive obstruction, rectal prolapse, anastomotic leak
Giuliani 2020	✓		✓	✓			Perianal excoriation
Huang 2018	✓	HAEC					Soiling/incontinence, constipation, anastomotic stenosis, bowel obstruction, anal prolapse
Jiao 2018							Constipation, soiling
Khazdouz 2015	✓	HAEC					Constipation, incontinence, diarrhoea
Kwendakwema 2016		SSI, HAEC					Anastomotic leak, anastomotic stricture, bowel obstruction
Li 2006							Complete anorectal continence
Liem 2008	✓	HAEC					>4 bowel movements, incontinence, constipation, anorectal function (modified Wingspread score)
Lu 2017							Incontinence/constipation scores
Meng 2020		HAEC			✓		Constipation, soiling, incontinence, invisible scar
Miyano 2018							Postoperative bowel function (POBF) evaluation scores
Nguyen 2009		HAEC					Erectile dysfunction, defecations per day, incontinence, constipation, anastomotic stenosis
Parahita 2018		HAEC					

HAEC = Hirschsprung-associated enterocolitis; POBF = postoperative bowel function; SSI = surgical site infection

Table 2.8 (continued)

Study ID	Long-term survival	Sepsis/ episodes of infection	Re-admission	Re-operation	Quality of life	Developmental outcomes	Other reported long-term outcomes
Pruitt 2020			✓	✓			
Pruitt 2020 (2)	✓	HAEC		✓			
Quiroz 2020		HAEC	✓				Hospital costs
Sulkowski 2014		SSI, HAEC	✓	✓			Anal dilations, anastomotic leak, stricture, small bowel obstruction
Sun 2015		HAEC					Soiling
Taghavi 2020	✓			✓			Appendicostomy, defunctioning stoma
Tang 2012		HAEC					Soiling, functional results (Windspread score), postoperative adhesive bowel obstruction, anastomotic stricture, recurrent constipation
Taylor 2020		HAEC		✓			Anastomotic stricture
Yang 2012		HAEC					Functional results (Windspread score), perianal dermatitis, recurrent constipation, soiling
Zhang 2014		HAEC					Constipation, anastomotic stricture
Zhang 2020		HAEC					Soiling, anastomotic stricture, constipation, adhesive intestinal obstruction, time to obtain normal defecation
Zheng 2018		HAEC					Stooling score, anastomotic stricture, incidence of soiling, constipation, incontinence
Zhu 2019		HAEC					Anastomotic stenosis, anastomotic leakage, constipation recurrence, soiling
Zhuansun 2020		HAEC					Adhesive bowel obstruction, anastomotic strictures, rectal prolapse, constipation, incidence of soiling, incontinence, anastomotic leakage, urinary retention, school absence, unhappy or anxious, peer rejection, food restriction

HAEC = Hirschsprung-associated enterocolitis; POBF = postoperative bowel function; SSI = surgical site infection

Table 2.9 Reported long-term outcomes by domain for gastroschisis

Study ID	Long-term survival	Sepsis/ episodes of infection	Re-admission	Re-operation	Quality of life	Developmental outcomes	Other reported long-term outcomes
Abdelhafeez 2011	✓						Volvulus
Abdelhafeez 2015	✓			✓			Midgut volvulus
Anderson 2018	✓						
Bradnock 2011	✓			✓			Long-term parenteral nutrition or liver failure
Cain 2014	✓		✓				
Chen 2019	✓			✓			
DeBie 2020	✓	Short-term only		✓		✓	Gastroesophageal reflux disease, constipation, incontinence
Long 2011	✓			✓			Long-term parenteral nutrition or liver failure
Minutillo 2013	✓					✓	
Schmedding 2020	✓		✓				
Ward 2017			✓				

Table 2.10 Reported long-term outcomes by domain for oesophageal atresia

Study ID	Long-term survival	Sepsis/ episodes of infection	Re-admission	Re-operation	Quality of life	Developmental outcomes	Other reported long-term outcomes
Allin 2014	✓						Stricture, recurrent fistula, anastomotic leak
Ax 2021		Sepsis during first hospital stay only		✓			At least one feeding difficulty
Bastard 2018							Thoracic skeletal sequelae from surgery
Baxter 2018				✓			Dysphagia defined by the need for tube feeding (either via nasogastric or gastrostomy tube), functional oral intake scale
Coppens 2016				✓			Gastroesophageal reflux (GORD), dysphagia
Dellenmark-Blom 2018				✓		Special school for children with learning disabilities	Gastrostomy feeding at follow-up, oesophageal dilation, special school support, educational support, doctor diagnosed asthma, severe tracheomalacia/tracheobronchomalacia, support with nutritional intake issues, school absence, reasons for school absence
Dellenmark-Blom 2019					Eating-QOL		Problem-focused coping and emotion-focused coping
Dellenmark-Blom 2020		Airway infection		✓	✓		Digestive symptoms the past month: difficulty swallowing food, heartburn, vomiting. Respiratory symptoms the past month: wheezing, cough, airway infection, breathlessness at rest/physical activity, chest tightness.
Donoso 2016	✓			✓			Anastomotic stricture, anastomotic leakage, recurrent TOF
Donoso 2017							Anastomotic stricture
Elhattab 2020	Reports neonatal deaths			✓			Anastomotic strictures that required at least one endoscopic dilatation
Fayoux 2018	✓			✓			Acute life-threatening events (ALTE)
Flieder 2019					PedsQL		Physical health summary score, psychosocial health summary score, school functioning, social functioning, physical functioning, emotional functioning

GORD = gastroesophageal reflux disease; TOF = tracheo-oesophageal atresia; FBD = fluoroscopic balloon dilatation

Table 2.11 (continued)

Study ID	Long-term survival	Sepsis/ episodes of infection	Re-admission	Re-operation	Quality of life	Developmental outcomes	Other reported long-term outcomes
Forster 2019	✓						
Francois 2019	✓	Recurrent lung infections (though grouped under "respiratory complications)		✓		Nutrition status at 1 year: oral nutrition, enriched oral nutrition, enteral nutrition, weight gain	GORD, respiratory complications, PPI treatment, feeding difficulty, prokinetic treatment, recurrent TOF, stricture, acute life-threatening event
Fung 2019	Short-term only	Pneumonia	✓				Aspiration recovery
Fusco 2018		Short-term sepsis only					Stricture, anastomotic leak, musculoskeletal complications
Garabedian 2015	✓		✓			Weight outcomes	Anastomotic strictures, recurrent fistula, stenosis, composite variable (including neonatal morbidity [anastomotic oesophageal leaks, recurrent fistula, stenosis] and death)
Garabedian 2015-2	✓		✓			Weight outcomes	Composite variable (anastomotic oesophageal leaks, recurrent fistula stenosis), oesophageal stricture, anastomotic leaks, recurrent fistula
Hsieh 2017							Intestinal metaplasia
Jones 2020							Stricture
Jones 2020-2							Anastomotic leak, recurrent TOF, stricture
Koivusalo 2013	✓			✓		Children thriving with oral intake of food	Anastomotic leakage, anastomotic stricture, recurrent TOF, GOR
Kovesi 2018							Vocal cord paresis or paralysis
Lal 2017	✓						Overall morbidity, anastomotic stricture, anastomotic leak, vocal cord dysfunction (paralysis/paresis), recurrent fistula
Lal 2018	✓	Pneumonia					Anastomotic stricture, anastomotic leak, recurrent fistula, vocal cord paresis or paralysis

GORD = gastroesophageal reflux disease; TOF = tracheo-oesophageal atresia; FBD = fluoroscopic balloon dilatation

Table 2.12 (continued)

Study ID	Long-term survival	Sepsis/ episodes of infection	Re-admission	Re-operation	Quality of life	Developmental outcomes	Other reported long-term outcomes
Lawrence 2019	In-hospital mortality only	Pneumonia	✓	✓			
Mawlana 2018	✓					Hearing impairment, visual impairment, neurodevelopmental outcome, cognitive delay, language delay, motor delay, growth delay	Services involved: speech and language therapy, occupational therapy, physiotherapy
Nurminen 2019	✓	Pneumonia and non-pneumonia respiratory infections					
Oztan 2020	✓					Weight and height at 1-year	
Paramalingam 2013							Oesophageal stricture
Porcaro 2017		Recurrent pneumonia					GORD, oesophagitis, oesophageal stenosis, respiratory symptoms, vocal cord paresis
Pruitt 2020-2	Short-term mortality only		✓	✓			
Quiroz 2020-2	Short-term mortality only		✓				
Raitio 2016	✓			✓			Symptom recurrence requiring repeat dilation, fluoroscopic balloon dilatation (FBD) yielding complete resolution of symptoms, oesophageal perforation (radiological leak)
Schmedding-2 2020	✓		✓				

GORD = gastroesophageal reflux disease; TOF = tracheo-oesophageal atresia; FBD = fluoroscopic balloon dilatation

Table 2.13 (continued)

Study ID	Long-term survival	Sepsis/ episodes of infection	Re-admission	Re-operation	Quality of life	Developmental outcomes	Other reported long-term outcomes
Schneider 2014	✓		✓	✓		Undernourished, weight/age z-score	Respiratory symptoms, anastomotic leaks (radiological leaks), recurrent TOF, anastomotic stenosis, dysphagia
Shah 2015		Recurrent chest infections		✓			Respiratory complications: chronic cough and/or wheeze, dysphagia, oesophageal strictures, GORD, oesophageal oesophagitis, tracheomalacia, cyanotic spells
SinghSodhi 2013							Oesophageal motility problems, gastroesophageal reflux, anastomotic leak, stricture, persistent fistula, anastomotic site diverticulae, hiatus hernia
Soliman 2019							Scoliosis
Sulkowski 2014-2		Pneumonia	✓	✓			
Tambucci 2020							Eosinophilic oesophagitis
Thyoka 2014	✓			✓			Requiring further intervention after fluoroscopic balloon dilatation (FBD), multiple strictures, complete resolution of symptoms after the first FBD
Vergouwe 2017		Pulmonary infections (though unclear at which time-point measured)	✓	✓		Growth outcomes including stunting (chronic malnutrition), wasting (acute malnutrition), height-for-age, distance-to-target-height, weight-for-height	
Vergouwe 2019	✓			✓			Anastomotic leakage, recurrent TOF, antireflux medical therapy, history of GORD, refractory stricture
Yasuda 2019				✓			Erosive oesophagitis, histologic oesophagitis, abnormal biopsy
Yasuda 2020				✓			
Zhu 2018	Short-term mortality only	Sepsis (likely only short-term)					Gastroesophageal reflux (GOR), any postoperative complication, anastomotic stricture, anastomotic leakages, recurrent TOF, tracheomalacia

GORD = gastroesophageal reflux disease; TOF = tracheo-oesophageal atresia; FBD = fluoroscopic balloon dilatation

Table 2.14 Reported long-term outcomes by domain for congenital diaphragmatic hernia

Study ID	Long-term survival	Sepsis/ episodes of infection	Re-admission	Re-operation	Quality of life	Developmental outcomes	Other reported long-term outcomes
Abramov 2020	Short-term only					✓	
Ali 2019	✓			Fundoplication			Hernia recurrence, pectus deformity, scoliosis, chronic cough
Aydin 2019	✓						
Aydin 2020	✓						Hernia recurrence
Bairdain 2015	✓					Weight outcomes	Malnutrition
Barriere 2018	✓					Abnormal neurologic status	Oral disorder (defined as GORD and/or swallowing disorders), requiring nutritional support
Burgos 2017	✓						
Cauley 2015	✓		✓	✓		Referred for developmental therapy	Pulmonary outcomes, developmental outcomes, any ipsilateral V/Q mismatch, severe ipsilateral V/Q mismatch, G or J tube placed, Nissen procedure, surgery for hernia recurrence, surgery for bowel obstruction
Chen 2019	✓						Knots unravelled
Cioci 2020			✓	✓		Failure to thrive	
Costerus 2016							Hernia recurrence
Danzer 2016						✓	
Danzer 2018						✓	
Danzer 2018-2						Autism spectrum disorder (ASD), BSID-III outcomes	Wechsler Preschool and Primary Scale of Intelligence (WPPSI)
DeBie 2020	✓			✓			Acute gastrointestinal complications, volvulus, perforation, obstruction, recurrence
Dennett 2014						Sensorineural hearing loss (SNHL)	
Garcia 2013	✓						Long-term pulmonary hypertension

GORD = gastroesophageal reflux disease; ASD = autism spectrum disorder; BSID-III = Bayley Scales of Infant Development, Third Edition; WPPSI = Wechsler Preschool and Primary Scale of Intelligence; SBO = small bowel obstruction; CDH = congenital diaphragmatic hernia; SNHL = sensorineural hearing loss

Table 2.15 (continued)

Study ID	Long-term survival	Sepsis/ episodes of infection	Re-admission	Re-operation	Quality of life	Developmental outcomes	Other reported long-term outcomes
Garriboli 2012	✓						
Haliburton 2015						Failure to thrive, stunting	
Heiwegen 2020	✓						Malrotation diagnosed during follow-up, small bowel obstruction (SBO)
Heiwegen 2020-2	✓						Hernia recurrence
Jancelewicz 2013	✓						Operation for bowel obstruction, hernia recurrence, multiple recurrences, major chest deformity, scoliosis
Janssen 2018	Short-term only			✓			CDH recurrence, SBO, thoracic deformities (including scoliosis/asymmetry, pectus excavatum, flaring of ribs, pectus carinatum)
Kadir 2017	✓						
Lee 2018	✓						
Liem 2011	✓						Hernia recurrence
Long 2019	✓			✓			Postoperative chylothorax, recurrence, receiving medical therapy for GOR
Masi 2010						SNHL, progressive hearing loss	Type 2 or type 4 hearing loss with a delay in speech and language development
Nagata 2015	✓						Hernia recurrence
Okuyama 2011	Short-term only					✓	
Partridge 2014						SNHL, BSID-II/BSID-III outcomes, developmental delay, speech delay	Occupational therapy, speech therapy
Pruitt 2020-3	Short-term only		✓	✓			

GORD = gastroesophageal reflux disease; ASD = autism spectrum disorder; BSID-III = Bayley Scales of Infant Development, Third Edition; WPPSI = Wechsler Preschool and Primary Scale of Intelligence; SBO = small bowel obstruction; CDH = congenital diaphragmatic hernia; SNHL = sensorineural hearing loss

Table 2.16 (continued)

Study ID	Long-term survival	Sepsis/ episodes of infection	Re-admission	Re-operation	Quality of life	Developmental outcomes	Other reported long-term outcomes
Ruano 2015	✓						
Russell 2014	✓						Pectus deformity
Short 2018	✓						Hernia recurrence
Style 2019	✓						Resolution of pulmonary hypertension by 12 months of age
Suply 2020	✓						Hernia recurrence
Takayasu 2016	Short-term only						Orthopaedic abnormalities, pectus excavatum, chest asymmetry
Terui 2014				Surgery for GORD		Developmental delay	Medical therapy for GORD
Terui 2016				✓		✓	Hernia recurrence
Tsai 2012				✓			Pectus deformity, scoliosis, SBO, recurrence (operative, nonoperative, total)
Verla 2020				✓			Other abdominal surgery, receiving supplemental enteral tube feeding at 12 months of age, GORD, gastroparesis, SBO
Wang 2019	✓		Short-term only				Total bed-days
Ward 2017-2			Volvulus readmission				
Weaver 2016	✓	Infection (central venous line or wound) – short-term only					Hernia recurrence, SBO/ ischaemic bowel
Wong 2018	Mortality time-point not specified						Right ventricular systolic pressure on serial echocardiography, lung perfusion scan outcomes
Wong 2019	✓						Long-term tube feeds

GORD = gastroesophageal reflux disease; ASD = autism spectrum disorder; BSID-III = Bayley Scales of Infant Development, Third Edition; WPPSI = Wechsler Preschool and Primary Scale of Intelligence; SBO = small bowel obstruction; CDH = congenital diaphragmatic hernia; SNHL = sensorineural hearing loss

Table 2.17 Reported long-term outcomes by domain for posterior urethral valves (PUV)

Study ID	Long-term survival	Sepsis/ episodes of infection	Re-admission	Re-operation	Quality of life	Developmental outcomes	Other reported long-term outcomes
Akhtar 2014	✓						Vesico-ureteric reflux resolution, serum creatinine levels, chronic kidney disease (CKD), renal scarring
Amirzargar 2020	✓			✓			CKD
Ansari 2010		UTI					CKD, end-stage renal disease (ESRD)
Ansari 2018		UTI					CKD stage IIIB or more, vesicoureteral reflux (VUR), renal scarring, serum creatinine
Bhadoo 2014							Chronic renal failure
Bilgutay 2016		UTI		✓			CKD of at least stage IIIA, ESRD
Chatterjee 2020							Upstaging of CKD, ESRF
Menon 2010		UTI					Nocturnal enuresis
Sarhan 2017	✓						CKD, daytime frequency
Tourchi 2014		UTI					VUR resolution during follow-up

CKD = chronic kidney disease; UTI = urinary tract infection; ESRD = end-stage renal disease; VUR = vesicoureteral reflux

Table 2.18 Reported long-term outcomes by domain for surgical necrotising enterocolitis

Study ID	Long-term survival	Sepsis/ episodes of infection	Re-admission	Re-operation	Quality of life	Developmental outcomes	Other reported long-term outcomes
Allin 2018	✓			✓			Intestinal failure associated liver disease (IFALD), parenteral nutrition dependency at 1 year, liver transplant at 1 year
Calvert 2020	✓						
Cole 2008	✓	Short-term only	✓	✓			Vitamin/mineral/nutrition supplements, tube feeding
Elfvin 2015	✓			✓			Long-term parental nutrition (at 12 months), cholestasis, liver failure
Fredriksson 2019	✓			✓			Intestinal failure, IFALD, stricture, stoma complications, NEC recurrence, short bowel syndrome
Fullerton 2018	✓	✓	✓	✓		✓	Any type of tube feeds, bilateral blindness, hearing impairment requiring amplification, inability to walk 10 steps without support, cerebral palsy
Hong 2018	✓	✓	✓	✓		✓	
Shah 2012	Only reports survival to discharge					✓	
Sung 2019						✓	
Wadhawan 2014	Only reports survival to discharge					✓	Cerebral palsy, blindness

IFALD = intestinal failure associated liver disease; NEC = necrotising enterocolitis

2.9 Factors associated with outcome variation

The factors associated with outcome variation in each domain are outlined below.

2.9.1 Factors associated with long-term survival

2.9.1.1 Factors associated with long-term survival in Hirschsprung's disease

Five studies (15.2%) reported one-year survival outcomes. Reported one-year survival was high, ranging from 96.7% to 99.7%. Only one study examined potential risk factors associated with one-year survival and found that recurrent post-operative HAEC was not associated with increased odds of one-year mortality (adjusted odds ratio [aOR] 3.3, 95% CI 0.88-12.1, p-value 0.08).[103] A study by Taghavi et al. found that total colonic aganglionosis was significantly associated with increased long-term mortality on univariable analysis (12.5% vs 0.5%, p <0.0005).[107]

2.9.1.2 Factors associated with long-term survival in gastroschisis

Six of 11 articles on gastroschisis reported one-year survival. The one-year survival rate of infants with gastroschisis ranged from 93.9 to 96.8%. Factors associated with decreased odds of survival on univariable analysis conducted by the study authors were birthweight <1500g, lower gestational age, complex gastroschisis, volvulus, abnormal vascular supply to the small intestine, high C-reactive protein (CRP) levels within 72 hours of life and prolonged hospital stay.[124] [125] Only one study performed multivariable analysis and found that complex gastroschisis was the only independent predictor of death or severe disability.[124]

2.9.1.3 Factors associated with long-term survival in oesophageal atresia

Out of 48 oesophageal atresia related studies, 9 studies (18.8%) reported one-year survival outcomes. One-year survival ranged from 81.0% to 98.1%. Congenital heart disease and low birthweight were significantly associated with lower one-year survival on univariable analysis.[151 152 156] Independent predictors of decreased one-year survival included pulmonary hypoplasia, trisomy 18 and 21, lower birthweight, heart defects and persistent pulmonary blood circulation.[161]

Eleven studies (22.9%) reported on long-term survival (but not one-year survival). Multi-gestational patients were associated with lower long-term survival compared to singleton patients on univariable analysis (18% vs. 6%, p=0.049).[140] Although one study by Mawlana et al. found that lower birthweight, lower gestational age, and presence of cardiac defect were associated with decreased long-term survival, only presence of cardiac defect was significantly associated with survival following multiple regression analysis ($p<0.0001$).[154]

2.9.1.4 Factors associated with long-term survival in congenital diaphragmatic hernia

There were 15 studies (31.9%) that reported one-year survival outcomes. One-year survival ranged between 53.0% and 94.0%, though the latter only reported survival outcomes for neonates with isolated, left-sided Bochdalek CDH and excluded those who received ECMO or were prenatally treated.[188]

On univariable analysis, one factor that was significantly associated with lower one-year survival was the presence of a major heart anomaly compared to isolated CDH (40.0% vs. 77.1%, p=0.04). Factors associated with increased one-year survival included postnatally

diagnosed infants compared to prenatally diagnosed infants (70.6% vs. 32.9%, p<0.001) and having isolated CDH compared to patients with at least one other anomaly (55.5% vs. 11.9%, p=0.01).[194 198 205]

Independent predictors of lower one-year survival included use of vasodilators after birth, female sex, use of inotropes, prenatal diagnosis, use of surfactant and being small for gestational age.[200] Another study by Wang et al. found that independent predictors of increased one-year mortality included lower birthweight, lower gestational age, black ethnicity, belonging to the most deprived socioeconomic quintiles (4 and 5), primary pulmonary hypertension, congenital pulmonary hypoplasia, chromosomal abnormalities and requiring ECMO, whereas older age at admission and chronic lung disease were independent predictors for increased one-year mortality.[215]

In addition to the studies reporting one-year survival, 13 studies (27.7%) also reported long-term survival (other than one-year survival). Use of ECMO (p=0.01) and prenatal lung-to-head ratio (LHR) <0.85 (p=0.001) were significantly associated with increased mortality. Independent predictors of increased long-term survival included presence of a hernia sac.[176] Independent predictors of decreased long-term survival included presence of an accompanying syndrome, thoracic herniation of the liver, lower birthweight, lower Apgar score and prenatal diagnosis.[176 197]

2.9.1.5 Factors associated with long-term survival in PUV

There were no studies that reported one-year survival outcomes for PUV. Of 3 studies (30%) that reported long-term (but not one-year survival), none reported patient factors that were associated with long-term survival in PUV.

2.9.1.6 Factors associated with long-term survival with necrotising enterocolitis

There were 3 studies (30%) that reported one-year survival, ranging from 44.4% to 70.9%.[229 230 232] Factors associated with one-year survival on univariable analysis included birthweight, gestational age and area of bowel region involved.[230] Infants with surgical necrotising enterocolitis had lower one-year survival than infants with medical necrotising enterocolitis.[232] Independent risk factors associated with higher one-year survival included increasing gestational age, increasing age at presentation to hospital and more anatomically localised disease according to area of bowel region involved. Independent risk factors associated with lower one-year survival included being small for gestational age, needing inotropes at the time of decision for surgery, presence of free air and presence of a non-cardiac congenital anomaly.[229 230]

Another study by Fredriksson et al. also found that lower gestational age was an independent risk factors for long-term survival and that survival rates for infants with surgical necrotising enterocolitis have decreased over time, after adjusting for gestational age.[233]

2.9.2 Factors associated with long-term quality of life

2.9.2.1 Factors associated with long-term quality of life in Hirschsprung's disease

There were only 2 studies that reported on long-term quality of life for children with Hirschsprung's disease. The PedsQL scores for children with Hirschsprung's disease was found to be significantly lower than the general reference population (i.e. children without a diagnosis of Hirschsprung's disease), with the mean score for the study population being 68.1 for children with Hirschsprung's disease (standard deviation 20.62).[83] One study by Zhuansun et al. found that quality of life scores were higher in children who underwent a laparoscope-assisted heart-shaped anastomosis compared with children who underwent a laparoscope-assisted Soave procedure, specifically in the quality of life scoring criteria related to soiling, being unhappy or anxious and peer rejection.[115]

2.9.2.2 Factors associated with long-term quality of life in oesophageal atresia

Only 3 studies (6.3%) reported upon long-term quality of life for children with oesophageal atresia and all 3 studies used different quality of life measurement tools. Using the Paediatric Quality of Life Inventory 4.0 Generic Core Scale (PedsQL 4.0), one study by Flieder et al. found that independent predictors of lower quality of life scores included German residency, having a single parent, severe oesophageal atresia and prenatal diagnosis of oesophageal atresia.[139] Oesophageal atresia was deemed severe if one or more of the following criteria were present: major revision following primary repair, presence of severe tracheomalacia, presence of an additional congenital anomaly causing disability, and delayed primary anastomosis or oesophageal replacement.[139] Studies by Dellenmark-Blom et al. found that independent predictors of lower Esophageal-Atresia-Quality-of-Life (EA-QOL) scores included gastrostomy insertion, no primary anastomosis, female sex, at least one oesophageal dilatation, lower gestational age at birth, presence of

an associated anomaly, and severe oesophageal atresia.[134] Having a "confronting approach" (i.e. attempting to mimic other children in situations involving eating) was correlated with higher Eating-QOL scores, whereas coping strategies such as expressional of emotional concerns, distancing, problem solving and avoidance were correlated with poorer Eating-QOL scores.[133]

2.9.2.3 Factors associated with long-term quality of life for the other study conditions

There were no included studies that reported on long-term quality of life for children with gastroschisis, CDH, PUV or surgical NEC.

2.9.3 Factors associated with long-term developmental outcomes

2.9.3.1 Factors associated with long-term developmental outcomes in gastroschisis

There were 2 studies (18.2%) that reported on long-term developmental outcomes in children with gastroschisis. Both reported percentage of infants with a weight below the 10th percentile at one-year follow-up, which ranged between 22.6% to 28% for infants with simple gastroschisis, and 44% for infants with complex gastroschisis.[122 124] On univariable analysis, factors associated with failure to thrive at 12 months of age (i.e. weight below the 10th percentile) included birthweight (OR 0.99 95%CI 0.99-1.00, p=0.002), maximum CRP within 72 hours (OR 1.01 95%CI 1.003-1.02, p=0.007), age at commencing enteral feeds (OR 1.12 95%CI 1.01-1.23, 0.021), and hospital stay greater than 60 days (OR 4.1 95%CI 1.18-14.4, p=0.026). However, on multivariable analysis, none of these factors remained significant.[124]

2.9.3.2 Factors associated with long-term developmental outcomes in oesophageal atresia

There were 9 studies (18.8%) that reported long-term developmental outcomes in children with oesophageal atresia. There were a wide range of outcomes reported and measurements used, such as neurodevelopmental score using the Bayley Scales of Infant Development (III), weight outcomes, nutritional status at one year, need for special school support, and undernourishment. Differences in outcome reporting made it difficult to aggregate the data or produce a meaningful summary estimate. Independent predictors of need for educational support included low birthweight of less than 2500 g (OR 3.31 95%CI 1.15-9.53, p=0.026) and associated anomaly (OR 3.35 95%CI 1.00-11.20, p=0.049), whereas gastrostomy insertion was an independent predictor of need for support with nutritional intake (OR 5.42 95%CI 1.79-16.37, p=0.0028).[132] Long-gap OA was an independent predictor of insufficient oral intake.[149]

2.9.3.3 Factors associated with long-term developmental outcomes in congenital diaphragmatic hernia

There were 15 studies (31.9%) that reported on long-term developmental outcomes in patients with congenital diaphragmatic hernia. There were a variety of outcomes reported, including growth outcomes, autism spectrum disorder, sensorineural hearing loss, and neurodevelopmental outcomes measured using the Vineland Adaptive Behaviours Scale and the Bayley Scales of Infant Development. The rate of sensorineural hearing loss ranged between 2.7% to 39%. On multivariable analysis, independent predictors of lower weight-for-age Z-scores at one year included birthweight less than 2500g, patch repair and protein intake less than 2.3g/kg/day during PICU admission.[178]. Length of aminoglycoside treatment (aOR 1.44 95%CI 1.13-1.83, p<0.001) was an independent predictor for sensorineural hearing loss and ongoing neurocognitive delay was an independent predictor for autism spectrum disorder (aOR 25.15 95%CI 0.95-664.81, p=0.05).[187 189]

2.9.3.4 Factors associated with long-term developmental outcomes in Hirschsprung's disease and posterior urethral valves

There were no included studies that reported long-term developmental outcomes for children with Hirschsprung's disease and posterior urethral valves.

2.9.3.5 Factors associated with long-term developmental outcomes in surgical necrotising enterocolitis

There were 5 studies (50%) that reported on long-term developmental outcomes in children with surgical necrotising enterocolitis. Four of the 5 studies used the Bayley

Scales of Infant Development to measure neurodevelopmental outcomes at 18 to 22 months, though growth outcomes such as severe growth failure were also reported. Two studies reported the proportion of children with a Mental Developmental Index (MDI) or Psychomotor Developmental Index (PDI) below 70, which ranged between 16% to 50.6% for an MDI below 70, and 20% to 46.3% for a PDI below 70.[234 238] Surgical necrotising enterocolitis was found to be a risk factor for neurodevelopmental disability or impairment, when compared to infants without necrotising enterocolitis or infants with medical necrotising enterocolitis.[234 237 238] One study by Hong et al. found that independent predictors of severe growth failure included small for gestational age (adjusted risk ratio [ARR] 1.91 95%CI 1.62–2.25), severe intraventricular haemorrhage or cystic periventricular leukomalacia (ARR 1.21 95% CI 1.02–1.43), chronic lung disease (ARR 1.13 95%CI 1.02–1.26), tube feeding post-discharge (ARR 1.46 95%CI 1.27–1.68) and severe growth failure at discharge (ARR 1.98 95%CI 1.64–2.39).[235]

2.9.4 Factors associated with re-operation

2.9.4.1 Factors associated with re-operation in Hirschsprung's disease

There were 9 studies (27.3%) that reported re-operation amongst children with Hirschsprung's disease. Re-operation within the first year of follow-up ranged between 8% to 11.9%.[90 102] On univariable analysis, factors associated with re-operation included damaged anal canal (OR 6.90 95%CI 1.86-25.6, p<0.004), multi-stage procedure compared to those who had a single-stage procedure (38.7% vs. 26.0%, p<0.0001), and those who had a history of postoperative enterocolitis (9.3% vs. 3.8%, p=0.06).[87 105 109] On multivariable analysis, recurrent postoperative HAEC was associated with increased odds of needing condition-specific re-operation (OR 5.2 95%CI 3.3-8.1, p<0.001).[103]

2.9.4.2 Factors associated with re-operation in gastroschisis

There were 5 studies (45.5%) that reported on re-operation amongst children with gastroschisis. The re-operation rate ranged from 3% to 17.5%. The only factor that was found to be associated with unplanned laparotomy rate was whether the infant had simple gastroschisis or complex gastroschisis (0.5% vs. 6%, p=0.03).[119]

2.9.4.3 Factors associated with re-operation in oesophageal atresia

There were 21 studies (43.8%) that reported on re-operation or additional operations amongst children with oesophageal atresia. Fundoplication or anti-reflux surgery at 12 months ranged between 7.5% to 16.5%. On univariable analysis, factors associated with need for antireflux surgery included birthweight, prematurity, associated malformation, anastomotic tension, gastrostomy, anastomotic stricture, acute life-threatening event, feeding difficulty, GORD, nutritional status at 1 year, cyanotic spells and severe tracheomalacia.[141 163] On multivariable analysis, independent predictors of antireflux

surgery during the first year of life included anastomotic tension (aOR 2.49 95%CI 1.34-4.59, p<0.004), birthweight per z-score increase (aOR 0.79 95%CI 0.65-0.96, p=0.018), and associated malformation (aOR 2.18 95%CI 1.13-4.17, p=0.019), and gastrostomy.[141] [163] Independent predictors for aortopexy included fundoplication and severe tracheomalacia. [163]

On univariable analysis, factors associated with stricture resection included ≥7 therapeutic endoscopies, type of surgery, fundoplication, history of leak, long-gap oesophageal atresia and stricture length ≥10mm. However, on multivariable analysis, the only independent predictor of stricture resection was history of leak (adjusted hazard ratio [aHR] 3.64 95%CI 1.49-8.93, p=0.005).[172]

2.9.4.4 Factors associated with re-operation in congenital diaphragmatic hernia

There were 11 studies (23.4%) that reported on re-operation in patients with congenital diaphragmatic hernia. Surgical intervention for CDH recurrence within the first year ranged between 11.4% to 18%, whereas surgery for GORD in the first year of follow-up ranged between 1.6% to 19.2%.[181] [183] On univariable analysis, there was a significant difference between infants who required invasive support, noninvasive support and room air for the following outcomes: placement of a gastric or jejunal feeding tube (65.7% vs. 34.0% vs 10.6%, p<0.001), Nissen fundoplication performed (40.0% vs 23.4% vs 8.2%, p<0.001) and surgery for hernia recurrence (20.6% vs 17.0 vs 4.7, p=0.02).[108] There was a significant difference between grades of stomach displacement in left-sided CDH in terms of fundoplication (Grade 1-4: 4% vs. 11% vs. 28% vs. 18%, p=0.05).[181] [214] Repair by thoracotomy compared to repair by laparotomy was associated with higher surgical reintervention (29.1% vs. 6.5%, p=0.001). On multivariable analysis, independent

predictors of surgery for GORD were diaphragmatic defect greater than 75% (HR 4.3 95%CI 1.6-12.9, p=0.005) and gestational age (HR 4.78 95%CI 1.5-21.1, p=0.006).[211]

2.9.4.5 Factors associated with re-operation in posterior urethral valves

There were 2 studies (20%) that reported on re-operation for children with posterior urethral valves. Need for more than one surgical intervention ranged between 15.3% and 42%.[220 224] On multivariable analysis, the only independent predictor of multiple surgical interventions was recurrent UTIs. On univariable analysis, factors associated with requiring more than one operation included prematurity, prenatal diagnosis, recurrent UTIs, symptomatic presentation, bilateral loss of corticomedullary differentiation, and bilateral pre-op vesicoureteral reflux.[224]

2.9.4.6 Factors associated with re-operation in surgical necrotising enterocolitis

There were 6 studies (60%) that reported on long-term re-operation in children with surgical necrotising enterocolitis. Need for additional surgery ranged between 48% to 60.2% at mean follow-up of 12 to 22 months, whilst need for liver transplant ranged between 0.65% to 0.9%.[229 234] Infants with surgical NEC had a higher risk of postdischarge surgery compared to infants without NEC (adjusted risk ratio [ARR] 1.65 95%CI 1.41-1.92, p<0.001).[234]

2.9.5 Factors associated with long-term episodes of infection

2.9.5.1 Factors associated with long-term episodes of infection in Hirschsprung's disease

Most studies (n=24/33, 72.7%) reported on Hirschsprung-associated enterocolitis (HAEC), though the time-point at which this outcome was measured varied significantly. The proportion of children who had at least one episode of HAEC within 12 months of follow-up ranged between 3.7% to 17.6%.[104 114] On univariable analysis, factors associated with HAEC included bowel preparation time (p=0.015), diet control (p=0.048), pathologic type (p=0.013), having a Duhamel procedure compared to a Soave procedure (28% vs. 10%, p=0.03), and having long-segment aganglionosis compared to short-segment HD (amongst those who had a Soave pull-through) (OR 24.4 95%CI 1.9-318.1), having a stoma takedown during pull-through procedure compared to those who underwent pull-through without a levelling stoma, having a multi-stage pull-through procedure (p<0.001), private insurance (OR 0.47 95%CI 0.26-9.84, p=0.01) and rectosigmoid original transition zone (OR 0.47 95%CI 0.26-0.84, p=0.01). [91 101 104 105 109 112] On multivariable analysis, factors associated with recurrent HAEC included congenital neurologic anomalies (aOR 4.5 95%CI 1.4-14.4, p=0.01), pre-operative HAEC (aOR 95%CI 2.2-5.8, p<0.001), history of CNS system infection (aOR 2.5 95%CI 1.0-6.0, p=0.05), and rectosigmoid original transition zone (aOR 0.46 95%CI 0.26-0.84, p=0.01).[103]

2.9.5.2 Factors associated with long-term episodes of infection in gastroschisis

There were no included studies that reported on long-term episodes of infection for children with gastroschisis.

2.9.5.3 Factors associated with long-term infection in oesophageal atresia

There were 8 studies (16.7%) that reported long-term episodes of infection for children with oesophageal atresia, all of which reported respiratory infections. The one-year pneumonia rate ranged between 3% to 17.5%.[152 153] On univariable analysis, significant risk factors for pneumonia were formation of early strictures (OR 3.33 95%CI 1.26-8.77), major anastomotic re-operation (RR [95%CI] 2.2 [1.3-3.7], p=0.028), fundoplication (RR [95%CI] 2.0 [1.2-3.3], p=0.022), the occurrence of respiratory infections other than pneumonia (RR [95%CI] 3.4 [1.5-7.5], p<0.0001), number of respiratory infections other than pneumonia (RR [95%CI] 1.4 [1.1-1.7], p=0.002), and number of oesophageal atresia anastomosis dilatations (RR [95%CI] 1.1 [1.0-1.2], p=0.007).[155 163] On multivariable analysis, significant predictors of pneumonia included number of oesophageal atresia anastomosis dilatations (aRR [95%CI] 1.1 [1.0-1.2], p<0.0001) and occurrence of respiratory infections other than pneumonia (aRR [95%CI] 3.4 [1.5-7.5], p=0.017).[155]

2.9.5.4 Factors associated with long-term episodes of infection in congenital diaphragmatic hernia

There were no studies that reported on long-term episodes of infection requiring hospital admission for children with congenital diaphragmatic hernia.

2.9.5.5 Factors associated with long-term episodes of infection in posterior urethral valves

There were 3 studies (30%) that reported on long-term infections for children with posterior urethral valves, all of which reported on urinary tract infections (UTIs) at various time-points. One study by Menon et al. found that in children who had persistent vesicoureteral reflux, those who underwent Deflux injection had a longer UTI-free period

than those who received prophylactic antibiotics and those who underwent ureteroneocystostomy ($p<0.001$).[226]

2.9.5.6 Factors associated with long-term episodes of infection in surgical necrotising enterocolitis

There were 2 studies (10%) that reported long-term episodes of infection for children with surgical necrotising enterocolitis. It is likely that both these studies had an overlap of patients, as Fullerton et al. reported upon extremely low birth weight (ELBW) neonates born between 1999 to 2012 from 47 Vermont Oxford Network member centres, whilst Hong et al. reported upon ELBW neonates born between 2000 to 2013 at 46 Vermont Oxford Network centres.[234 235] The rate of rehospitalisation for any infection at follow-up of 18-24 months was 11% for children with necrotising enterocolitis. There were no factors identified that were associated with episodes of infection.

2.9.6 Factors associated with readmission

2.9.6.1 Factors associated with readmission in Hirschsprung's disease

There were 5 studies (15.2%) that reported on all-cause readmission for children with Hirschsprung's disease. The reported one-year readmission rate ranged between 35.5% to 70.2%. The two studies that reported two-year readmission both reported a readmission rate of 42.6%. Children who had stoma takedowns during their pull-through procedure had significantly higher one-year readmission rates compared to those who underwent pull-through without a levelling ostomy (47% vs. 33%, $p<0.01$) and both Giuliani et al. and Sulkowski et al. found that children with HD who underwent a single-stage procedure had a significantly lower readmission rates than those who underwent a multiple-staged repair.[90 104 105] Although Apfeld et al. found no association between hospital volume or surgeon volume with readmission rate, one study by Pruitt et al. found that high-concentrated hospitals with an HHI≥0.24 was associated with a reduction in unplanned readmissions compared to weakly/moderately concentrated hospitals with an HHI<0.25 (aRR [CI] 0.8 [0.69-0.97], $p<0.02$).[85 102] Hospital concentration was measured using the Herfindahl-Hirschman Index, which was calculated from the number of cases performed at a single hospital and the number of surgeons performing those operations.

2.9.6.2 Factors associated with readmissions in gastroschisis

There were 3 studies (27.3%) that reported readmissions amongst children with gastroschisis. One study reported a one-year readmission rate of 59% amongst gastroschisis survivors.[125] There were no factors identified that were significantly associated with readmission.

2.9.6.3 Factors associated with long-term re-admission in oesophageal atresia

There were 10 studies (20.8%) that reported on readmission amongst children with oesophageal atresia. Readmission within 1 year ranged between 26% to 75.3%. Only one study by Quiroz et al. found factors associated with one-year readmission on univariable analysis, which included being VLBW, LBW, premature, having any additional anomaly, additional anomaly, central nervous system anomaly, major cardiac anomaly, small bowel atresia, anorectal malformation, genitourinary anomaly, congenital diaphragmatic hernia, chromosomal anomaly, VACTERL, Spitz II/III, surgical site dehiscence, respiratory distress syndrome, meconium obstruction, GORD, and intraventricular haemorrhage.[159] Other studies examined the differences between children with vocal cord dysfunction and those without vocal cord dysfunction, children with prenatal diagnosis compared to postnatal diagnosis, and highly concentrated hospitals compared to weakly or moderately concentrated hospitals, though none of the studies found any significant difference between the groups in terms of readmission rates.[102 142 144 145]

2.9.6.4 Factors associated with long-term re-admission in congenital diaphragmatic hernia

There were 3 studies (6.4%) that reported readmission rates, and one other study that reported readmission for volvulus.[102 126 181 183] Readmission rate within one year ranged considerably, from 31.7% to 97%. The only factor found to be associated with one-year readmission was hospital concentration based on the Herfindahl-Hirschmann Index (HHI), which is often used to measure market concentration. Pruitt et al. found that highly concentrated hospitals (i.e. hospitals with an HHI ≥0.25) were significantly associated with reduced risk of unplanned readmissions, compared with weakly/moderately concentrated

hospitals, i.e. those with an HHI<0.25 (adjusted risk ratio [aRR] [CI] 0.4 [0.28-0.71], p<0.001).[102]

2.9.6.5 Factors associated with readmission in posterior urethral valves

There were no included studies that reported on readmission for children with posterior urethral valves.

2.9.6.6 Factors associated with readmission in surgical necrotising enterocolitis

There were 3 studies (30%) that reported upon readmission amongst infants with surgical necrotising enterocolitis. As previously mentioned, two of the studies by Fullerton and Hong appear to have similar cohorts.[234 235] Readmission prior to follow-up at 18-22 months for infants with surgical necrotising enterocolitis ranged between 54% and 58%.[231 234 235] ELBW infants with surgical NEC had significantly higher risk of readmission compared to ELBW infants without NEC (adjusted risk ratio [ARR] [95%CI] 1.41 [1.27–1.57], p<0.001). Interestingly, EBLW infants with medical NEC did not have a significantly increased risk of readmission (ARR [95%CI] 1.10 [0.97-1.26], p<0.15).[234]

2.9.7 Summary of factors associated with outcome variation

Of the factors that were associated with long-term outcome variation, common factors that were associated with multiple outcomes across conditions included gestational age, birthweight, sex, and major congenital anomaly (including chromosomal anomalies and major cardiac anomalies). A summary of factors associated with outcome variation is displayed in **Table 2.19**).

Table 2.19 Summary of factors associated with variations in long-term outcomes (either poorer or better outcomes)
Factors identified in the systematic review that were associated on univariable analysis or multivariable analysis with long-term outcomes

	Congenital diaphragmatic hernia	**Oesophageal atresia**	**Gastroschisis**	**Surgical necrotising enterocolitis**	**Hirschsprung's disease**	**Posterior urethral valves**
Factors associated with variations in long-term survival	Presence of a true defect, major cardiac anomaly, prenatal diagnosis, isolated CDH, use of vasodilators after birth, female sex, use of inotropes, use of surfactant, small for gestational age, black ethnicity, belonging to the most deprived socioeconomic quintiles (4 and 5), primary pulmonary hypertension, congenital pulmonary hypoplasia, chromosomal abnormalities, requiring ECMO, chronic lung disease, prenatal lung-to-head ratio, presence of hernia sac, thoracic herniation of the liver, and Apgar score	Congenital heart disease, birthweight, pulmonary hypoplasia, trisomy 18 and 21, persistent pulmonary foetal blood circulation, and multi-gestational patients	Complex gastroschisis, birthweight <1500g, lower gestational age, volvulus, abnormal vascular supply to the small intestine, high C-reactive protein (CRP) levels within 72 hours of life and prolonged hospital stay	Birthweight, gestational age, area of bowel region involved, small for gestational age, needing inotropes at time of decision for surgery, presence of free air, and presence of a non-cardiac congenital anomaly	Total colonic aganglionosis	Not reported
Factors associated with variations in long-term quality of life	Not reported	Gastrostomy insertion, no primary anastomosis, gestational age, gender, at least on oesophageal dilatation, presence of associated anomaly, coping strategies (expression of emotional concerns, distancing, problem solving, avoidance, confronting approach, severe oesophageal atresia (defined as the presence of at least one of the following: major revisional surgery, another congenital disabling anomaly, delayed anastomosis or oesophageal replacement, or severe tracheomalacia), country of residency, having a single parent, prenatal diagnosis of OA	Not reported	Not reported	Type of operation (laparoscope-assisted heart-shaped anastomosis vs. laparoscope-assisted Soave procedure)	Not reported

CRP = C-reactive protein; CDH = congenital diaphragmatic hernia; ECMO = extracorporeal membrane oxygenation; OA = oesophageal atresia

Table 2.20 (continued)

	Congenital diaphragmatic hernia	Oesophageal atresia	Gastroschisis	Surgical necrotising enterocolitis	Hirschsprung's disease	Posterior urethral valves
Factors associated with variations in long-term developmental outcomes	Gestational age, gender, birthweight, birth height, defect size of diaphragm, age of child, repair type (primary or patch), on oxygen at discharge, GORD therapy at discharge, and protein intake during PICU admission, need for ECMO, length of stay, requiring prolonged resuscitation prior to CDH repair, use of nitric oxide, prolonged ventilatory support, need for nutritional support, neuromuscular hypotonicity, right-sided CDH, IVH, abnormal brainstem auditory evoked responses, and ongoing neurodevelopmental delay, length of aminoglycoside, administration of vasodilator at discharge	Birthweight, associated anomaly, gastrostomy insertion, antireflux surgery, prenatal diagnosis, long-gap OA, Down's syndrome/ CHARGE syndrome/ neurological disorder, Spitz class	Birthweight, maximum CRP within 72 hours, age at commencing enteral feeds, length of hospital stay	Small for gestational age, severe intraventricular haemorrhage or cystic periventricular leukomalacia, chronic lung disease, tube feeding post-discharge, and severe growth failure at discharge	Not reported	Not reported
Factors associated with variations in long-term re-operation	Gestational age, type of respiratory support (invasive support, noninvasive support and room air), type of repair (thoracotomy vs laparotomy), diaphragmatic defect greater than 75%, grade of stomach displacement in left-sided CDH	Birthweight, prematurity, associated malformation, anastomotic tension, gastrostomy, anastomotic stricture, acute life-threatening event, feeding difficulty, GORD, nutritional status at 1 year, long-gap OA, cyanotic/dying spells, severe tracheomalacia, prior fundoplication, ≥7 therapeutic endoscopies, type of surgery, history of leak, stricture length ≥10mm.	Simple gastroschisis vs complex gastroschisis	Not reported	Damaged anal canal vs. intact anal canal, recurrent postoperative HAEC, multi-stage procedure vs. single-stage	Prematurity, prenatal diagnosis, symptomatic presentation, recurrent UTIs, bilateral loss of corticomedullary differentiation, and bilateral pre-operative vesicoureteral reflux

HAEC = Hirschsprung-associated enterocolitis; CRP = C-reactive protein; CDH = congenital diaphragmatic hernia; ECMO = extracorporeal membrane oxygenation; OA = oesophageal atresia; GORD = gastro-oesophageal reflux disease; IVH = intraventricular haemorrhage; HHI = Herfindahl-Hirschmann Index

Table 2.21 (continued)

	Congenital diaphragmatic hernia	Oesophageal atresia	Gastroschisis	Surgical necrotising enterocolitis	Hirschsprung's disease	Posterior urethral valves
Factors associated with variations in long-term episodes of infection	Not reported	Major anastomotic re-operation, fundoplication, the occurrence of respiratory infections other than pneumonia, number of respiratory infections other than pneumonia, formation of early strictures, and number of oesophageal atresia anastomosis dilatations	Not reported	Not reported	Bowel preparation time, diet control, pathologic type (e.g. short, common, long), Duhamel vs. Soave procedure, long-segment aganglionosis, pre-operative HAEC, history of CNS system infection, congenital neurologic anomalies, ostomy takedowns during pull-through procedure vs. those who underwent pull-through without a levelling ostomy, multi-stage pull-through procedure, rectosigmoid original transition zone, and private insurance	Deflux injection
Factors associated with variations in long-term re-admission	Concentration of hospitals (measured using HHI)	Birthweight, gestational age, any additional anomaly (e.g. central nervous system anomaly, major cardiac anomaly, small bowel atresia, anorectal malformation, genitourinary anomaly, CDH, chromosomal anomaly, VACTERL), Spitz class, surgical site dehiscence, respiratory distress syndrome, meconium obstruction, GORD, and intraventricular haemorrhage	Not reported	Not reported	Single-stage vs multiple-staged repair, age of child, ostomy takedowns during pull-through procedure vs. pull-through without a levelling ostomy, concentration of hospitals (measured using HHI)	Not reported

HAEC = Hirschsprung-associated enterocolitis; CRP = C-reactive protein; CDH = congenital diaphragmatic hernia; ECMO = extracorporeal membrane oxygenation; OA = oesophageal atresia; GORD = gastro-oesophageal reflux disease; IVH = intraventricular haemorrhage; HHI = Herfindahl-Hirschmann Index

2.10 Meta-analyses of one-year outcomes

The most common time-point at which outcomes were described were at one-year and the most reported outcome across the six surgical conditions was one-year survival. Proportional meta-analysis using a random-effects model was conducted for one-year outcomes where there were sufficient studies. Due to differences in outcome reporting and follow-up length, meta-analyses could only be conducted for one-year survival, anti-reflux surgery amongst children with congenital diaphragmatic hernia and oesophageal atresia, HAEC amongst children with Hirschsprung's disease, and readmission (**Figure 2.2**, **Figure 2.3**, **Figure 2.4**, and **Figure 2.5**). Notably, the estimates are highly heterogenous for most outcomes, which warrants caution when interpreting the results.

Figure 2.2 Proportional meta-analysis using a random-effects model depicting one-year survival by surgical condition

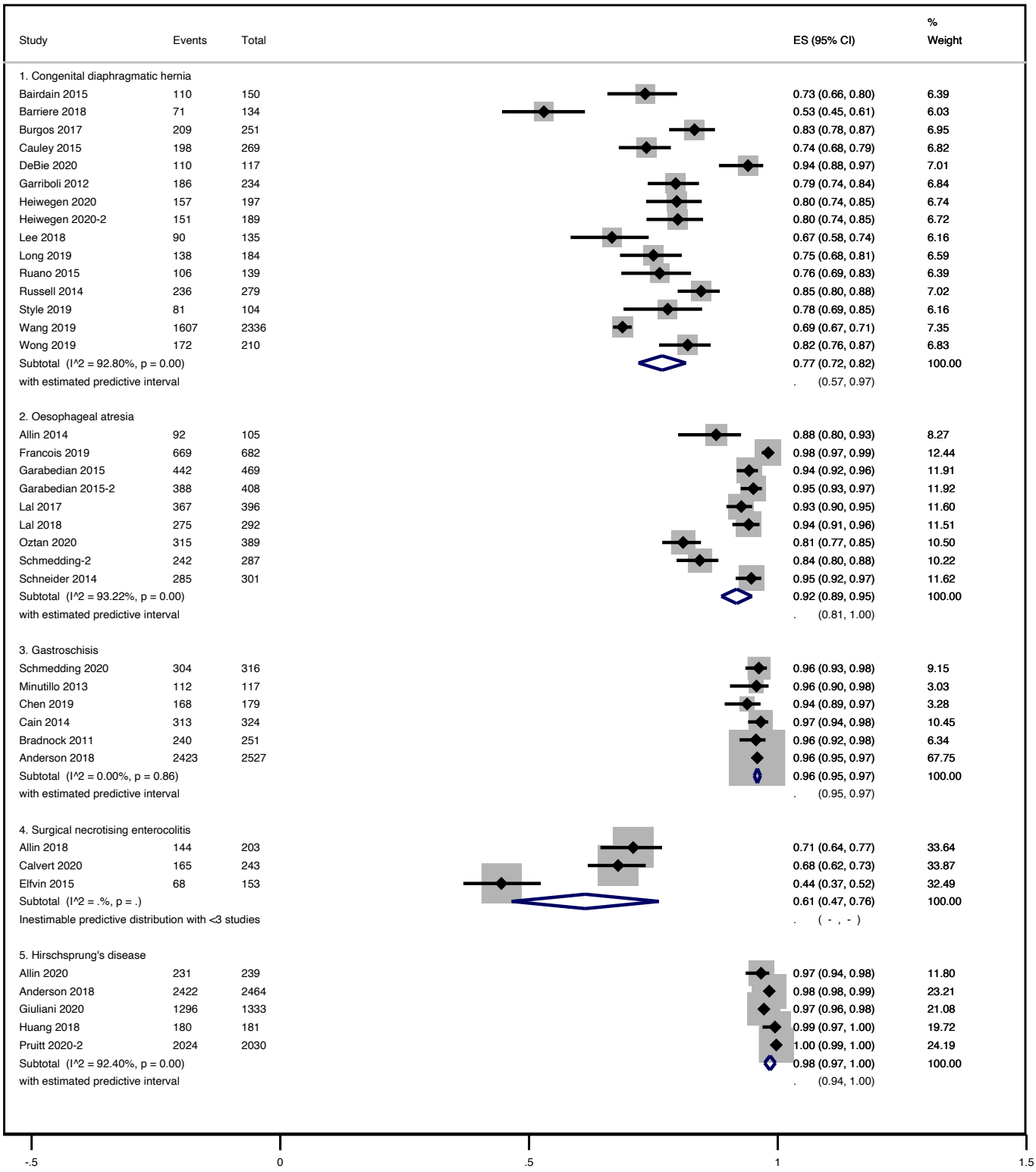


Figure 2.3 Proportional meta-analysis using a random-effects model depicting one-year anti-reflux surgery amongst children with congenital diaphragmatic hernia, oesophageal atresia, HD and gastroschisis

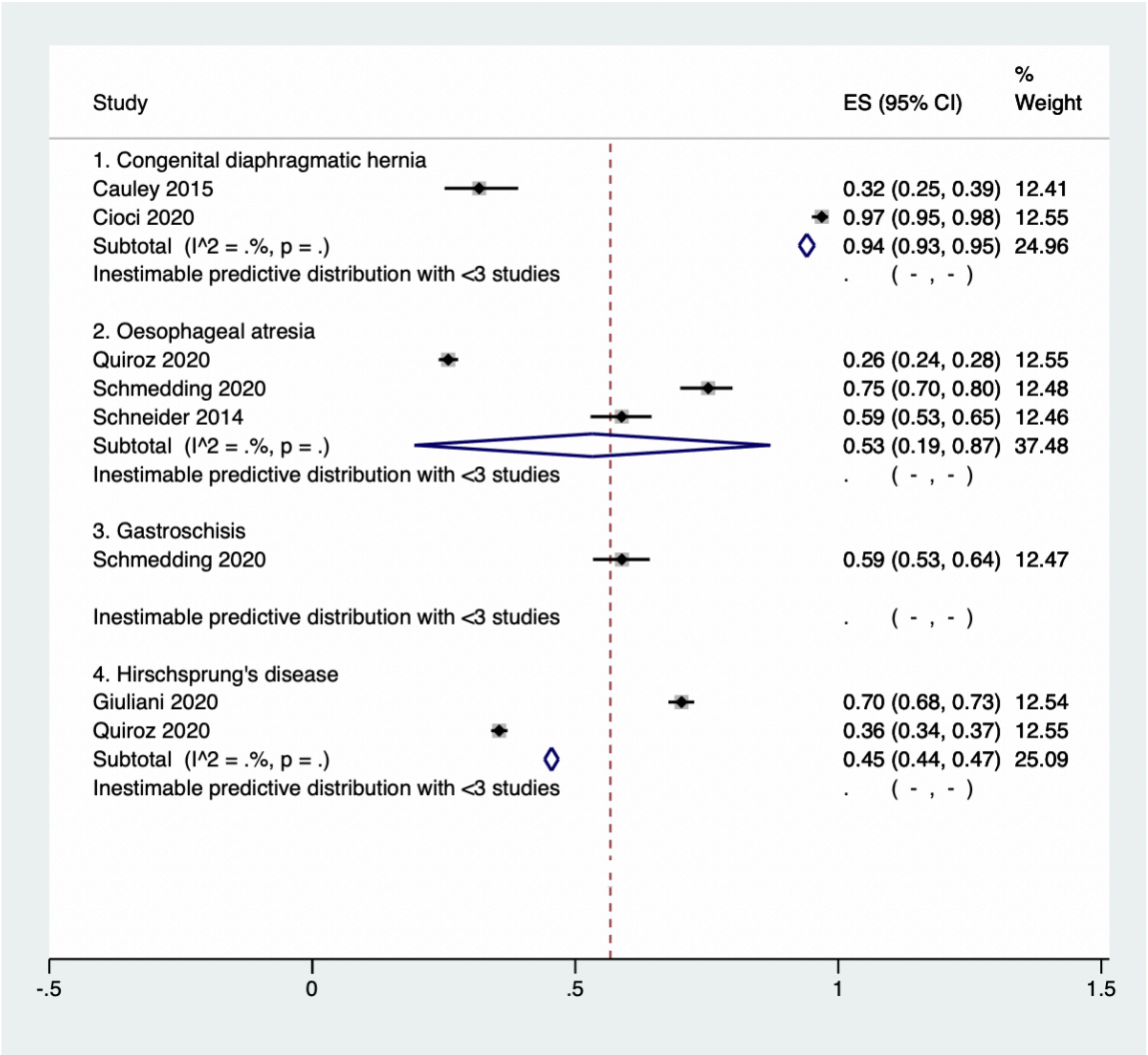


Figure 2.4 Proportional meta-analysis using a random-effects model depicting one-year HAEC amongst children with Hirschsprung's disease

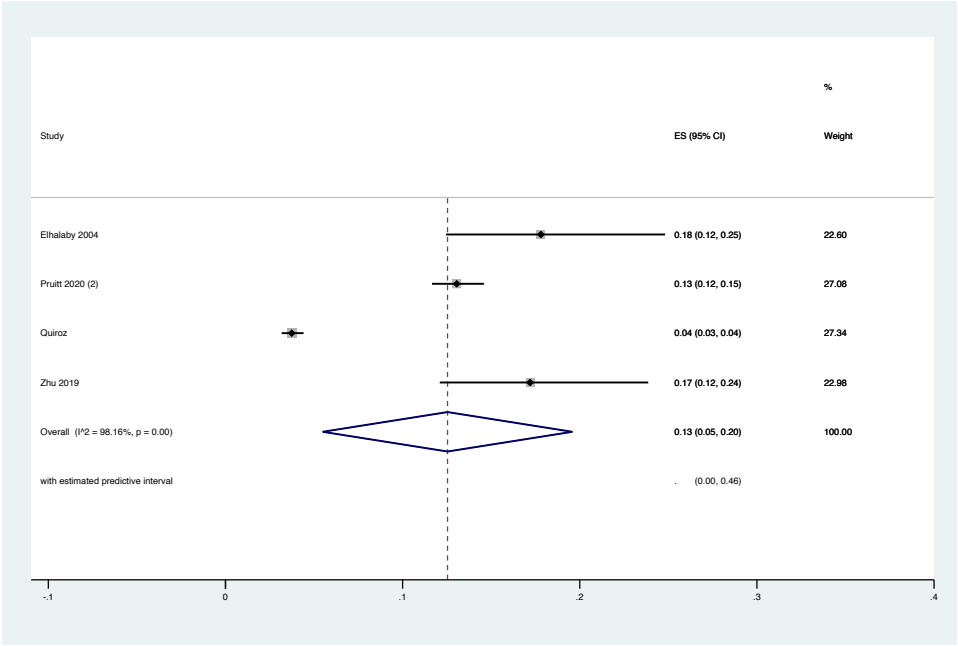
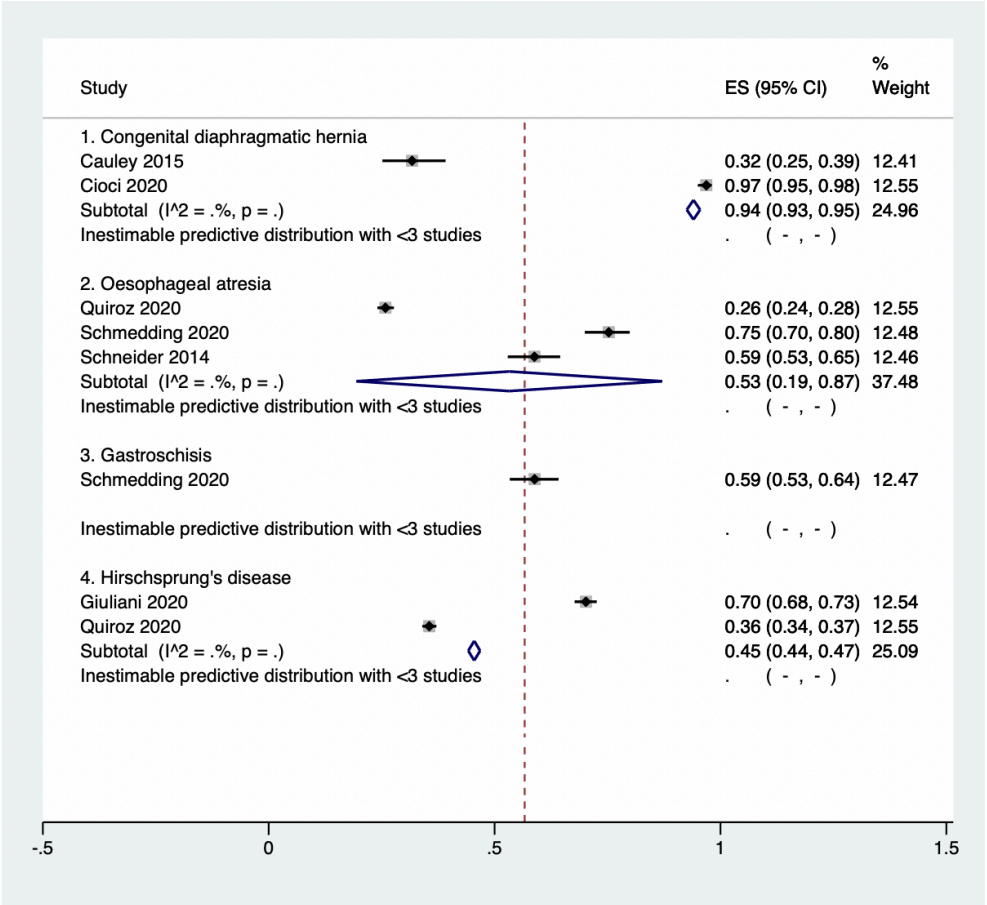


Figure 2.5 Proportional meta-analysis using a random-effects model depicting one-year readmissions by surgical condition



An overview of study characteristics and results are outlined in **Table 2.22**. Congenital diaphragmatic hernia and oesophageal atresia had the highest number of studies. Survival was the most reported outcome domain and the USA was the country with the highest number of studies.

Table 2.22 Summary of results

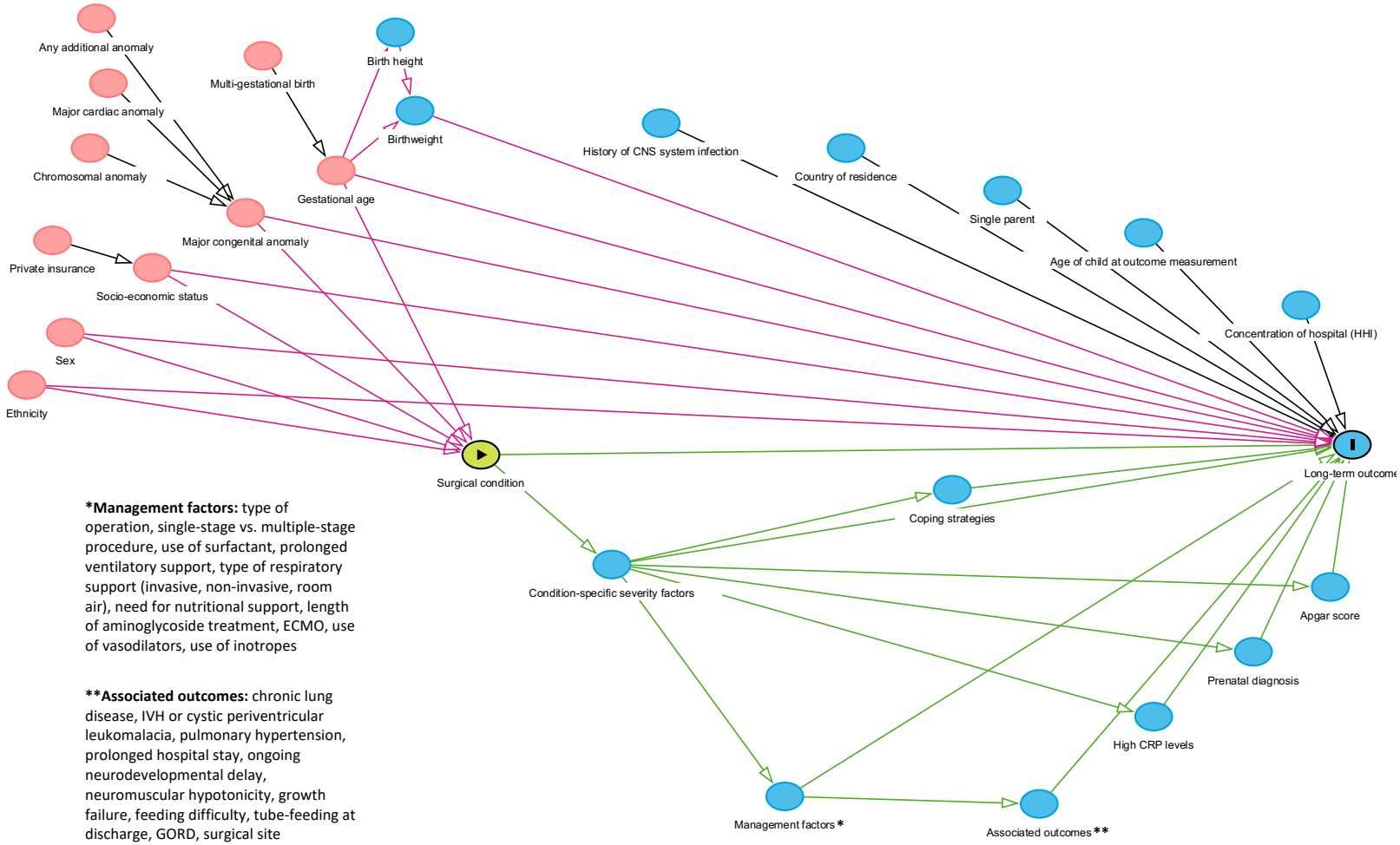
	Congenital diaphragmatic hernia	**Oesophageal atresia**	**Gastroschisis**	**Surgical necrotising enterocolitis**	**Hirschsprung's disease**	**Posterior urethral valves**
Number of studies	47	48	11	10	33	10
Total number of cases	13,725	19,989	7,251	2,681	18,767	1,668
Country with highest number of studies	USA (n=22)	USA (n=10)	USA (n=4)	USA or North America (n=4)	China (n=15)	India (n=5)
Most reported outcome domain	Survival	Re-operation	Survival	Survival	Episodes of infection (Hirschsprung's associated enterocolitis)	Episodes of infection (urinary tract infection)
One-year survival (range)	53.0% - 94.0%	81.0% - 98.1%	93.9 - 96.8%	44.4% - 70.9%	96.7 - 99.7%	Not reported

2.11 Development of a directed acyclic graph

Using the findings from the systematic review, a directed acyclic graph (DAG) was developed to depict the relationship between the outcome of long-term survival and associated factors that were identified through the systematic review (**Figure 2.6**). The DAG was constructed using DAGitty software (Version 3.0). From this DAG, the minimal sufficient adjustment set for estimating the *total* effect of surgical condition on long-term survival is as follows: ethnicity, gestational age, major congenital anomaly, sex, and socioeconomic status. The minimum sufficient adjustment set for estimating the *direct* effect of surgical condition on long-term outcome includes: condition-specific severity factors, ethnicity, gestational age, major congenital anomaly, sex, and socio-economic status. Condition-specific severity factors are outlined in **Table 2.23**.

Figure 2.6 Directed acyclic graph depicting the causal relationship between long-term survival and factors identified in the systematic review

Legend: *The causal pathway is represented by the green arrows. The confounding pathway is represented by the pink arrows. The exposure is surgical condition, and the outcome is long-term survival. The pink bubbles represent confounders, whilst the blue bubbles represent mediators. Condition-specific severity factors are outlined in* ***Table 2.23****.*



***Management factors:** type of operation, single-stage vs. multiple-stage procedure, use of surfactant, prolonged ventilatory support, type of respiratory support (invasive, non-invasive, room air), need for nutritional support, length of aminoglycoside treatment, ECMO, use of vasodilators, use of inotropes

****Associated outcomes:** chronic lung disease, IVH or cystic periventricular leukomalacia, pulmonary hypertension, prolonged hospital stay, ongoing neurodevelopmental delay, neuromuscular hypotonicity, growth failure, feeding difficulty, tube-feeding at discharge, GORD, surgical site dehiscence, episodes of infection (e.g.

Table 2.23 Condition-specific severity factors

Condition	Factors related to condition-specific severity	Condition-specific management factors	Condition-specific outcomes that are associated with long-term outcome variation
Congenital diaphragmatic hernia	Prenatal lung-to-head ratio, presence of true defect, thoracic liver herniation, presence of hernia sac, congenital pulmonary hypoplasia, size of diaphragmatic defect, right-sided vs left-sided CDH, grade of stomach displacement in left-sided CDH	GORD therapy, protein intake during PICU admission, requiring prolonged resuscitation prior to CDH repair, need for ECMO, type of repair (thoracotomy vs laparotomy)	-
Oesophageal atresia	Long-gap oesophageal atresia, severe tracheomalacia, number of oesophageal dilatations, severe oesophageal atresia (defined as the presence of at least one of the following: major revisional surgery, another congenital disabling anomaly, delayed anastomosis or oesophageal replacement, or severe tracheomalacia), cyanotic/dying spells, acute life-threatening event, anastomotic tension	Repair type (primary or patch), gastrostomy insertion, anti-reflux surgery	Anastomotic stricture, stricture length ≥10mm, history of leak, major anastomotic re-operation, respiratory infections
Gastroschisis	Complex gastroschisis vs. simple gastroschisis, volvulus, abnormal vascular supply to the small intestine	Age at commencing enteral feeds	-
Surgical necrotising enterocolitis	Region/extent of bowel affected, presence of free air	-	-
Hirschsprung's disease	Total colonic aganglionosis, length of aganglionic section, pre-operative HAEC	Type of procedure (e.g. Duhamel vs. Soave procedure), ostomy takedowns during pull-through procedure vs. pull-through without a levelling ostomy, bowel preparation time, diet control,	Damaged anal canal vs. intact anal canal, recurrent postoperative HAEC
Posterior urethral valves	Symptomatic presentation, bilateral pre-operative vesicoureteral reflux	Deflux injection	Recurrent UTIs, bilateral loss of corticomedullary differentiation

CDH = congenital diaphragmatic hernia, GORD = gastro-oesophageal reflux disease; PICU = paediatric intensive care unit; ECMO = extracorporeal membrane oxygenation; HAEC = Hirschsprung-associated enterocolitis; UTI = urinary tract infection

2.12 Discussion

2.12.1 Outcome reporting

Out of the six outcome domains (survival, quality of life, developmental outcomes, re-operation, episodes of infection, readmission), only survival was consistently reported across the six study conditions. Reporting for quality of life outcomes was notably sparse, with only oesophageal atresia and Hirschsprung's disease yielding studies that reported on long-term quality of life outcomes. As illustrated by the meta-analyses, it was difficult to produce any meaningful summary estimates of outcomes due to significant heterogeneity, even for the outcome of one-year survival, the most reported outcome. Only for the condition of gastroschisis was any meaningful summary estimate for one-year survival able to be produced (estimated predictive interval 0.95-0.97, $I^2 = 0.00\%$, p=0.86, **Figure 2.2**), where the one-year survival was relatively high.

The inability to aggregate data or existing literature to produce any meaningful summary estimate for long-term outcomes is problematic, particularly in terms of providing accurate prognostication and counselling for parents. Thus, it is perhaps no surprise that parents of children born with surgical conditions often receive conflicting information regarding their child's conditions, as found in a study by Hinton et al.[22] The reason for this inability to aggregate data is manifold, with reasons including small case incidences and significant variations in the outcome reporting. These highlight some of the greatest challenges and barriers in paediatric surgical research.

2.12.2 Heterogeneity and variation in outcome reporting

2.12.2.1 Heterogeneity in study population

One cause of heterogeneity is the variation in study population, even within conditions, particularly as studies may have varying inclusion and exclusion criteria. For instance, the one-year survival data from DeBie 2020 et al. appear to be higher than those reported by other studies on congenital diaphragmatic hernia.[188] Part of this can perhaps be attributed to its study participants, which consisted only of neonates with isolated, left-sided, Bochdalek type hernias. Neonates who received ECMO or were treated prenatally were excluded. Many of these characteristics are known to be associated with lower condition severity, thus differing study population characteristics may undermine meaningful comparison between studies. This search was not restricted based on country, however one of the factors found to be associated with outcome variation was country of residence.[139] It is likely that country, setting, available resource, cultural factors, and management practices in differing hospitals or regions are all factors that result in a divergence of outcome measurement and reporting, thus contributing to the heterogeneity found in the meta-analyses.

Part of the difficulty in aggregating data was also due to differences in outcome measures reported. This was most pronounced in the domain of developmental outcomes, where there was a range of outcomes and measures used. Although the Bayley Scale of Infant Development was commonly used, there was a wide variety of measures used to report developmental outcomes, such as need for special school help, need for services such as occupational therapy, physiotherapy, and speech and language therapy, referral for developmental therapy, autism spectrum disorder, neurodevelopmental delay across cognitive, language and motor outcomes, and the Vineland Adaptive Behaviour Scale.

Finally, there was a wide range of time-points at which outcomes were measured. Even if the same outcome was reported using the same outcome measurement amongst comparable study populations, meaningful comparisons cannot be drawn if the outcomes are measured at differing time-points, as the likelihood of an outcome occurring increases as time passes. Although some studies did measure outcomes at given time-points, mainly at one year, the majority of studies reported outcomes simply during the follow-up time that they had available. This is likely due to convenience for the study investigators, however it nonetheless makes it more challenging to compare and aggregate outcome data that is of differing timepoints.

Although the reporting of outcomes during available follow-up may be of interest, it has little applicability or external validity beyond the study population, as it is challenging to compare studies of differing and often arbitrary follow-up time. Thus, studies should not only strive to report consistent outcomes from standardised core outcome sets, but also outcomes at specific time-points.

2.12.3 Scarcity of data

As previously mentioned, one of the challenges in paediatric surgical research is the low incidence of many of these conditions. Prior studies have shown that there is a higher volume of smaller case series and studies with fewer participants in paediatric surgery, meaning there is often less reliable data.[4] To address this issue, we only included studies with greater than 100 cases of the study condition. However, as this systematic review has demonstrated, there are few such studies, particularly in certain outcome domains. This highlights the potential use and advantage of using "big data" from routinely collected

nationwide databases, which have been utilised and well-reported in certain areas, such as neonatal medicine.

2.12.4 The need for quality of life data

As this systematic review has demonstrated, there is a scarcity of outcome data in the domain of quality of life, and even developmental outcomes. Quality of life is not often captured in routinely collected databases and the recognition of the utility of parent-reported outcomes is a relatively new phenomenon. The difficulty of capturing long-term quality of life means that researchers may preferentially report outcomes that are more readily available, such as mortality, re-operation, and readmission. However, when asked what is most important for parents and clinicians, it is actually quality of life that is deemed as being most important, even over survival.[239] It is time that our research reflects these priorities – to overlook crucial outcomes such as quality of life would be a disservice to the academic community, clinicians, and most importantly, parents and their children. Researchers should strive to report what matters, not what is merely convenient.

2.12.5 Factors associated with long-term outcomes

This systematic review identified numerous factors that were reported to be associated with long-term outcomes amongst children with one of the six study conditions. Furthermore, there were several factors that were common across a number of outcomes and conditions, particularly gestational age, birthweight, sex and major congenital anomaly (including chromosomal anomalies and major cardiac anomalies). Several important condition-specific factors were found, particularly those relating to condition severity, such as thoracic liver herniation in congenital diaphragmatic hernia, long-gap oesophageal

atresia, complex gastroschisis, and total colonic aganglionosis in Hirschsprung's disease, along with condition-specific management factors and outcomes (**Table 2.23**).

Notably, some short-term outcomes were often associated with other outcomes, for instance, chronic lung disease and long-term survival in congenital diaphragmatic hernia, intraventricular haemorrhage and long-term readmission in oesophageal atresia, and recurrent UTIs and re-operation in posterior urethral valves. Certain risk factors (e.g. gestational age) were associated with poorer outcomes across domains – for instance, gestational age was associated with variations in long-term survival, quality of life, developmental outcomes, re-operation, and readmission.

"Management factors" or resulting management decisions are often closely linked with condition severity, which in turn is closely related to outcomes, both general outcomes and condition-specific, such as faecal incontinence in Hirschsprung's disease or recurrent UTIs in posterior urethral valves. These complex relationships between exposures, variables and outcome are depicted and mapped out in the directed acyclic graph (**Figure 2.6**).

This systematic review found both general factors that are common across several outcomes and conditions, as well as condition-specific factors regarding disease severity. However, in this systematic review, we could only identify factors that were measurable and documented to be associated with long-term outcomes, which is heavily dependent on the interest and aims of individual study authors. This in turn is often dependent on variables that are accessible or available. The absence of "latent variables" that are not measured is therefore an important consideration in the process of developing a directed acyclic graph, which is why the application of knowledge is always critical.

Particularly with the advent of big data resulting from routinely collected data, one cannot always choose the variables. Rather, researchers often have to make use of available and measurable variables. However, there are often variables that are important, yet difficult to accurately measure, for instance socio-economic status and other social determinants of health that we know have a significant impact on health outcomes.[240] For these variables, we may rely on proxy markers (e.g. private health insurance), which may only measure or account for a proportion of that variable.

2.12.6 Limitations

2.12.6.1 Short vs. long-term outcomes

As the focus of this systematic review was on long-term outcomes, factors associated with short-term outcomes were not explored. However, it must be acknowledged that factors that influence short-term outcomes, are likely to consequently affect long-term outcomes. It is possible that some factors that influence long-term outcome variation may have been missed, simply because it has not been documented in the literature specifically pertaining to long-term outcomes, even if it has been documented in the literature pertaining to short-term outcomes. Consequently, factors associated with both short-term and long-term outcomes were examined for the purposes of this thesis. Similarly, as previously mentioned, it was not possible to capture unmeasured or latent variables. For instance, factors that may affect outcomes for which were not able to extract any evidence in this systematic review include surgeon experience, nadir creatine in children with posterior urethral valves, and the impact of being managed in a low- and middle-income setting compared to a high-income setting.

Another limitation is that this systematic review is bound by the quality of included studies. It is perhaps no surprise that most of the included studies were retrospective cohort studies, given the study question and follow-up time required. However, it also demonstrated how few randomised controlled trials have long-term follow-up in this field of research, for instance one-year or two-year follow-up. Although likely to be costly, even logistically difficult, this would nonetheless be valuable information and build upon our knowledge of long-term outcomes.

2.12.7 Conclusion

To my knowledge, this is the largest systematic review to date that examines long-term outcomes across six different outcome domains and six paediatric surgery conditions. I have mapped out the outcome domains reported and identified both general and condition-specific factors associated with outcome variation, which has been used to construct a directed acyclic graph.

Chapter 3

A population-based cohort study investigating the short-term outcomes of surgical infants admitted to neonatal care in England and Wales from 2012-2020

3.1 Background

In order to examine the long-term outcomes of children requiring early surgery, it is important to first elucidate their short-term outcomes, as factors associated with short-term outcome variation are likely to consequently affect long-term outcomes, as noted in the previous chapter. Big data generated from routinely collected databases could provide novel insights into outcomes of paediatric surgical conditions. Due to the advent of electronic healthcare record systems and the widespread use of the BadgerNet service (Clevermed: Edinburgh, UK) both nationally amongst UK neonatal units and internationally, new opportunities have arisen for the utilisation of routinely collected health records to conduct whole-population research and audits for infants admitted to neonatal care.[241] Databases holding neonatal care data include the National Neonatal Research Database (NNRD) in the UK, the Pediatrix BabySteps Clinical Data Warehouse in the US, the Australia and New Zealand Neonatal Network, and the National Perinatal Registry of the Netherlands.[242-244]

The NNRD was established in 2007 to streamline the use of routinely collected neonatal data for quality improvement and research across the UK. The database was developed by and is held at the Neonatal Data Analysis Unit (NDAU) at Imperial College London, who oversee the maintenance, cleaning, extraction, and transfer of data from the database. All NHS neonatal units in England have been contributing data to the NNRD since 2012 and each of these units have their own UK Neonatal Collaborative Lead.[245] Previous studies have found that it is feasible to utilise the NNRD to investigate the characteristics and outcomes of conditions affecting the neonate, including hypoxic-ischaemic encephalopathy, retinopathy of prematurity and bloodstream infections.[246-248] A validation study conducted by Battersby et al. found that the NNRD had high data completeness and

quality.[249] In comparison to its global counterparts, one of the strengths of the NNRD is its near population-wide coverage in the UK. It includes neonatal units from Scotland, England, Isle of Man and Wales.[245]

Several rigorous prospective cohort studies have been undertaken by the British Association of Paediatric Surgeons Congenital Anomalies Surveillance System (BAPS CASS) in each of the six study conditions.[3 38 39] These studies incorporated all paediatric surgical units in the UK in a single reporting system to investigate rare paediatric surgical conditions. As prospective cohort studies are often time-consuming and costly to conduct, the use of routinely collected data could provide opportunities for continued exploration of contemporary outcomes, population-wide condition surveillance and benchmarking between health services. Nonetheless, the use of routinely collected data may present additional challenges, from inadequate data quality to the absence of clinically meaningful exposures and outcomes. Although the NNRD has been used to investigate neonatal necrotising enterocolitis, it has not yet been utilised to specifically explore HD, gastroschisis, OA, CDH or PUV.[250]

3.2 Chapter aims and objectives

The overall aim of this chapter was to explore whether it would be feasible to utilise data held within the NNRD in order to investigate short-term outcomes of surgical neonates diagnosed with one or more of the six study conditions: Hirschsprung's disease, gastroschisis, oesophageal atresia, congenital diaphragmatic hernia, posterior urethral valves and surgical necrotising enterocolitis.

From this overarching aim, there were three objectives:

1. To describe the incidences of the six study conditions using NNRD data.
2. To describe characteristics of this population using NNRD data.
3. To describe the neonatal outcomes of this population using NNRD data.

3.3 Methods

3.3.1 Study design

A secondary analysis of previously prospectively collected data was undertaken utilising the National Neonatal Research Database (NNRD).

3.3.2 Data management

Routine medical and healthcare data are entered into the BadgerNet platform by healthcare professionals, such as the treating doctor or nurse, throughout the patient's admission. Over 400 data items that comprise the Neonatal Set are then extracted quarterly from these electronic healthcare records to construct the NNRD, which is held on a secure NHS server in a 256bit encrypted MA SQL 2012 file. This adheres to the Data Security and Protection Toolkit standards.[251] The data undergo a number of quality assurance checks, such as the

identification of duplicates or potentially erroneous data (such as outliers), which are then reviewed by the clinical team, who are able to make corrections. Finally, the data are anonymised and entered into the NNRD.[241]

Specific identifiers (namely date of birth, postcode and NHS number) are held in a separate file on a secure NHS server, only to be used for approved uses such as data linkage to the Office of National Statistics (ONS) mortality data and Hospital Episodes Statistics (HES) data. Approval for this is given by the UK Health Research Authority Confidentiality Advisory Group (reference number ECC 8-05[f] 2010). Parents also have the opportunity to opt-out of having their neonate's data included in the NNRD. Units are able to access their own local data to carry out audits and quality improvement projects. There are no non-NHS neonatal intensive care units in England and Wales, thus the NNRD has nearly whole-population coverage of infants requiring neonatal intensive care in these nations.[251 252]

3.3.3 Study participants

All neonates diagnosed with one of six predetermined conditions (surgical necrotising enterocolitis, Hirschsprung's disease, gastroschisis, oesophageal atresia, congenital diaphragmatic hernia and posterior urethral valves) and admitted to neonatal care in England and Wales during the study period (01 January 2012 – 31 December 2020) of any gestational age were eligible and identified through the NNRD.

3.3.4 Exposures

Neonates were coded as having one of the study conditions if they met the following criteria outlined in **Table 3.1**. Within the NNRD, there are multiple locations in which

diagnoses are entered and stored. The majority of diagnoses are stored in the diagnosis table, along with the relevant diagnostic code. However, in some cases, a diagnosis may not appear in the diagnosis table, rather it will appear in a different location. Thus, in order to find all corresponding diagnoses with a particular study condition (for instance, Hirschsprung's disease), the diagnosis table was searched along with the diagnosis columns in the episodic and daily summary tables. This process was undertaken by a NNRD data analyst (J. Lanoue), who then extracted this as an anonymised dataset and stored the data on a secure server at the Neonatal Data Analysis Unit.

3.3.4.1 Hierarchy of conditions for primary diagnosis

Where the neonate met the definition for more than one of the study conditions, the primary diagnosis was classified according to the most severe condition based on the condition-specific mortality rate from **Chapter 2**, except for where the condition could be regarded as a sequela of another condition of interest. For instance, neonates with gastroschisis may subsequently develop necrotising enterocolitis requiring surgery, in which case the primary diagnosis for the neonate was gastroschisis, and surgical necrotising enterocolitis was the secondary diagnosis. The hierarchy of conditions from least to most severity, with the exception of NEC, which may develop as a complication of the primary condition, was therefore: NEC, HD, gastroschisis, PUV, OA and CDH.

Table 3.1 Coding and definitions of surgical conditions in the NNRD

Coding and definitions of conditions in the National Neonatal Research Database
A. Necrotising Enterocolitis
The following terms in PrincipalDiagnosisAtDischarge, GastrointestinalDiagnoses or PrincipleProceduresDuringStay: • NECROTISING ENTEROCOLITIS: 15809 • NECROTISING ENTEROCOLITIS – PERFORATED: 10708 • NECROTISING ENTEROCOLITIS - PROVEN (ON XRAY OR AT SURGERY) • NECROTISING ENTEROCOLITIS – CONFIRMED • LAPAROTOMY • LAPAROTOMY APPROACH NEC • COLECTOMY AND ILEOSTOMY NEC AND The following in the daily table: NECTreatment = 2 (surgical) OR The following in the abdominal x-ray table: LaparotomyPerformed = 'y' and HistologyConfirmationNEC = 'Yes' THEN surgical NEC = 1
B. Hirschsprung's disease
The following terms in PrincipalDiagnosisAtDischarge, GastrointestinalDiagnoses, PrincipleProceduresDuringStay or diagnosis table: • HIRSCHSPRUNG'S DISEASE LONG-SEGMENT: 16227, 10501 • HIRSCHSPRUNG'S DISEASE SHORT-SEGMENT: 16228, 10502 • HIRSCHSPRUNG'S ENTEROCOLITIS: 10503 • PULL THROUGH FOR HIRSCHSPRUNGS DISEASE (ANY TECHNIQUE): 100039 • DEFINITIVE HIRSCHSPRUNGS SURGERY DUHAMEL: 11270 • DEFINITIVE HIRSCHSPRUNGS SURGERY LESTER MARTIN: 11271 • DEFINITIVE HIRSCHSPRUNGS SURGERY TRANSANAL PULL THROUGH: 11272 • DEFINITIVE HIRSCHSPRUNGS SURGERY REHBEIN: 11273 • DEFINITIVE HIRSCHSPRUNGS SURGERY SOAVE-BOLEY: 11274 • DEFINITIVE HIRSCHSPRUNGS SURGERY SWENSON: 11275 • LAPAROSCOPIC ASSISTED DEFINITIVE HIRSCHSPRUNGS SURGERY: 11499 • HIRSCHSPRUNGS DISEASE: 16226, 16227 • HIRSCHSPRUNGS DISEASE SHORT-SEGMENT: 16228 • TOTAL INTESTINAL AGANGLIONOSIS: 11058 • PULL THROUGH FOR HIRSCHSPRUNGS DISEASE (ANY TECHNIQUE): 100039

Table 3.1 (continued)

Coding and definitions of conditions in the National Neonatal Research Database
C. Gastroschisis
The following terms in PrincipalDiagnosisAtDischarge, GastrointestinalDiagnoses, PrincipleProceduresDuringStay or diagnosis table: • DELAYED CLOSURE GASTROSCHISIS: 11277 • PRIMARY REPAIR OF GASTROSCHISIS: 11654 • REPAIR GASTROSCHISIS USING PROSTHESIS: 11708 • SILO INSERTION FOR REDUCTION OF GASTROSCHISIS: 11784 • CLOSURE OF GASTROSCHISIS INCLUDES CLOSURE OF EXOMPHALOS: 1006730 • GASTROSCHISIS: 16499 • GASTROSCHISIS REPAIR (PRIMARY OR STAGED): 100035 • GASTROSCHISIS: 200310 • GASTROSCHISIS: 10464
D. Oesophageal Atresia
The following terms PrincipalDiagnosisAtDischarge, GastrointestinalDiagnoses, PrincipleProceduresDuringStay or diagnosis table: • ESOPHAGEAL ATRESIA: 200303 • OESOPHAGEAL ATRESIA WITH DISTAL TRACHEA-OESOPHAGEAL FISTULA: 10740 • OESOPHAGEAL ATRESIA WITHOUT DISTAL FISTULA: 10741 • PRIMARY REPAIR OF OESOPHAGEAL ATRESIA: 11658 • OESOPHAGEAL ATRESIA WITHOUT TRACHEOESOPHAGEAL FISTULA: 10741, 1010245 • OESOPHAGEAL ATRESIA WITH TRACHEOESOPHAGEAL FISTULA: 10740, 1010246 • ATRESIA OF OESOPHAGUS WITHOUT FISTULA: 16195 • ATRESIA OF OESOPHAGUS WITH TRACHEA-OESOPHAGEAL FISTULA: 16196 • TRACHEOESOPHAGEAL ATRESIA AND/OR/FISTULA REPAIR: 100010 • OESOPHAGEAL ATRESIA WITHOUT TRACHEOESOPHAGEAL FISTULA: 1010245, 10741 • ESOPHAGEAL ATRESIA: 200303

Table 3.1 (continued)

Coding and definitions of conditions in the National Neonatal Research Database
E. Congenital Diaphragmatic Hernia
The following terms in PrincipalDiagnosisAtDischarge, GastrointestinalDiagnoses, PrincipleProceduresDuringStay or diagnosis table: • CONGENITAL DIAPHRAGMATIC HERNIA: 10246 • MORGAGNI DIAPHRAGMATIC HERNIA: 10694 • RECURRENT CONGENITAL DIAPHRAGMATIC HERNIA: 10905 • OTHER REPAIR OF DIAPHRAGMATIC HERNIA (SPECIFY): 11597 • CONGENITAL DIAPHRAGMATIC HERNIA: 10246 • PRIMARY REPAIR OF CONGENITAL DIAPHRAGMATIC HERNIA: 11657 • PROSTHETIC REPAIR OF CONGENITAL DIAPHRAGMATIC HERNIA: 11660 • FETOSCOPIC INSERTION OF TRACHEAL PLUG FOR CONGENITAL DIAPHRAGMATIC HERNIA: 1006132 • PERCUTANEOUS INSERTION OF TRACHEAL PLUG FOR CONGENITAL DIAPHRAGMATIC HERNIA: 1006148 • REPAIR OF CONGENITAL DIAPHRAGMATIC HERNIA: 1006671 • REPAIR OF DIAPHRAGMATIC HERNIA: 100044 • CONGENITAL DIAPHRAGMATIC HERNIA: 200602 • OTHER SPECIFIC REPAIR OF DIAPHRAGMATIC HERNIA: 1001924 • REPAIR OF DIAPHRAGMATIC HERNIA USING ABDOMINAL APPROACH: 1001923 • REPAIR OF DIAPHRAGMATIC HERNIA USING THORACIC APPROACH: 1001921 • UNSPECIFIED REPAIR OF DIAPHRAGMATIC HERNIA: 1001925
F. Posterior Urethral Valves
The following terms in PrincipalDiagnosisAtDischarge, GastrointestinalDiagnoses, PrincipleProceduresDuringStay or diagnosis table: • POSTERIOR URETHRAL VALVES: 10854 • ENDOSCOPIC DESTRUCTION OF URETHRAL VALVES: 1004687 • HOOK ABLATION OF POSTERIOR URETHRAL VALVE: 11444 • CONGENITAL POSTERIOR URETHRAL VALVES: 10854, 16357 • RESECTION OF POSTERIOR URETHRAL VALVES: 100058 • ENDOSCOPIC RESECTION OF POSTERIOR URETHRAL VALVE: 11338

3.3.5 Outcomes

Outcomes were selected *a priori* based on outcomes from previously developed core outcome sets (such as the COIN and NETS1HD core outcome sets)[18 82] and those that were feasible to derive from the NNRD.

Therefore, the outcomes of interest included the following:

1) Number of operations (split into major and minor as per NICE criteria)[253]
2) Number of times infants were treated in hospital for an infection
3) Survival
4) Outcomes identified from the Core Outcomes in Neonatology (COIN) set, NETS1HD core outcomes for children with Hirschsprung's disease and the NETS1G core outcomes for children with gastroschisis[18 82 254]

However, not all of these outcomes of interest were available in the NNRD dataset. This is outlined in **Table 3.2**.

Table 3.2 Outcomes from the Core Outcomes in Neonatology (COIN) outcome set and other relevant core outcome sets that can and cannot be analysed using NNRD data

Short-term outcomes during neonatal care	**Outcomes at two-year assessment**	**Outcomes that cannot be analysed using NNRD data**
• Age they survived to • Survival • Late onset sepsis • Severe NEC • Brain injury on imaging • Retinopathy of prematurity (preterm only) • Chronic lung disease/ bronchopulmonary dysplasia (preterm only)	• General gross motor ability • General cognitive ability • Visual impairment or blindness • Hearing impairment or deafness	• Number of operations • Number of times patients were treated in hospital for an infection • Quality of life • Adverse events

3.3.6 Definition of outcomes

In this chapter, survival was defined as survival to discharge from neonatal care. Late-onset sepsis was defined as a pure pathogenic growth on blood culture after the first 72 hours of life. The definition of severe necrotising enterocolitis is outlined in **Table 3.3** below. As surgical necrotising enterocolitis was one of the study conditions, the outcome of severe necrotising enterocolitis was only reported for neonates with one of the other five study conditions. In keeping with the NNRD definition, brain injury on imaging was defined as the presence of left or right intraventricular haemorrhage (IVH) grade 3 or above, or the presence of periventricular leukomalacia (PVL). Term infants were defined as having severe brain injury if they had any of the following diagnoses: hypoxic ischaemic encephalopathy (HIE) (Grade 2 or 3), intracranial haemorrhage (Grade 3 or 4), perinatal stroke, central nervous system infection, kernicterus or seizures. Preterm infants were defined as having severe brain injury if they had any of the following diagnoses: seizures, HIE (Grade 2 or 3), cranial haemorrhage (Grade 3 or 4), preterm white matter injury, perinatal stroke, central nervous system infection or kernicterus.

Treated retinopathy of prematurity (ROP) was only reported for neonates who were less than 32 weeks gestational age at birth and was defined as having Avastin (bevacizumab) therapy or surgery for ROP, including cryotherapy, laser therapy, anti-VEGF treatment or other treatment for one or both eyes. Similarly, bronchopulmonary dysplasia was only reported for neonates born less than 32 weeks gestational age and was defined as infants who required respiratory support at 36 weeks corrected gestational age. Where there was an absence of data at 36 weeks corrected gestational age, the data were utilised from the final or penultimate day in neonatal care. Further details regarding the coding of these outcomes in the NNRD are outlined in **Table 3.4**.

Table 3.3 Coding definition of severe necrotising enterocolitis, as defined in the NNRD

Severe necrotising enterocolitis definition
Neonates who meet any of the following 8 criteria were flagged as having severe necrotising enterocolitis. 1. NEC is listed as 'Cause of Death' 2. 'Postmortem confirmation' is true. 3. Any of the following in 'Gastrointestinal Diagnoses', 'Principle Procedures during stay' or 'Principal Diagnosis at discharge': • LAPAROTOMY • LAPAROTOMY APPROACH NEC • COLECTOMY AND ILEOSTOMY NEC AND Any of the following in 'Gastrointestinal Diagnoses' or 'Principal Diagnosis at discharge': • NECROTISING ENTEROCOLITIS • NECROTIZING ENTEROCOLITIS • NECROTIZING ENTEROCOLITIS – CONFIRMED • NECROTISING ENTEROCOLITIS – CONFIRMED • NECROTISING ENTEROCOLITIS – PERFORATED • NECROTIZING ENTEROCOLITIS – PERFORATED • NECROTISING ENTEROCOLITIS - PROVEN (ON XRAY OR AT SURGERY) • NECROTIZING ENTEROCOLITIS - PROVEN (ON XRAY OR AT SURGERY) 4. Any of the following in 'Gastrointestinal Diagnoses' or 'Principal Diagnosis at discharge': • NECROTISING ENTEROCOLITIS* • NECROTIZING ENTEROCOLITIS* • NECROTIZING ENTEROCOLITIS – CONFIRMED • NECROTISING ENTEROCOLITIS – CONFIRMED • NECROTISING ENTEROCOLITIS – PERFORATED • NECROTIZING ENTEROCOLITIS – PERFORATED • NECROTISING ENTEROCOLITIS - PROVEN (ON XRAY OR AT SURGERY) • NECROTIZING ENTEROCOLITIS - PROVEN (ON XRAY OR AT SURGERY) AND 'Discharge Destination' listed as Death. 5. Any of the following in 'Gastrointestinal Diagnoses' or 'Principal Diagnosis at discharge': NECROTISING ENTEROCOLITIS – PERFORATED NECROTIZING ENTEROCOLITIS – PERFORATED Within the Daily summary table 6. Surgery is listed on any day in 'NEC Treatment'. AND Any of the following in 'Gastrointestinal Diagnoses' or 'Principal Diagnosis at discharge': • NECROTISING ENTEROCOLITIS • NECROTIZING ENTEROCOLITIS • NECROTIZING ENTEROCOLITIS – CONFIRMED

Note. Adapted from *Data dictionary for the National Neonatal Research Database*. Neonatal Data Analysis Unit. 2022. United Kingdom: Imperial College London.

Table 3.3 (continued)

Severe necrotising enterocolitis definition
• NECROTISING ENTEROCOLITIS – CONFIRMED • NECROTISING ENTEROCOLITIS – PERFORATED • NECROTIZING ENTEROCOLITIS – PERFORATED • NECROTISING ENTEROCOLITIS - PROVEN (ON XRAY OR AT SURGERY) • NECROTIZING ENTEROCOLITIS - PROVEN (ON XRAY OR AT SURGERY Within the Abdoxray table 7. 'Yes' is listed under 'Laparotomy Performed' and 'Yes' listed in 'Histology Confirmation NEC' 'Yes' listed in 'Visual Inspection Confirmation NEC'

Note. Adapted from *Data dictionary for the National Neonatal Research Database*. Neonatal Data Analysis Unit. 2022. United Kingdom: Imperial College London.

Table 3.4 Outcomes as coded in the NNRD

Legend: Grey shading = not available in NNRD; white shading = short-term neonatal outcomes; green shading = two-year outcomes

Outcome	**NNRD**
Number of operations	Not available in the NNRD
Number of times patients were treated in hospital for an infection	Not available in the NNRD
Age they survived to	DateofDeath – pseudo-anonymised time of event from birth in minutes There is also a "Age at death" variable (DateDeathAnon) given in minutes from birth in the "Static Items: Two-Year outcomes)
Survival	NNRD has "survival to discharge without comorbidity" Where DischargeDestination != 3 AND TreatedROP = 0 AND BPD = 0 AND NEC = 0 AND Brain Injury = 0 THEN (0) Coding: 0 – Did not survive or comorbidities present 1 – Survived with no comorbidities Blank – At least one comorbidity missing OR: Final NNU outcome 1 – Home 2 – Ward 3 – Died 4 - Unknown
Sepsis	LateOnsetSepsis WHERE SampleType = BLD AND PathogensForDBSYNC = pure_pathogen THEN (1) Coding 0 – No late onset sepsis detected 1 – Late onset sepsis detected (pure pathogen growth)
Necrotising enterocolitis	There is a "SevereNEC" and "NEC_NNAP" item.

Note. Adapted from *Data dictionary for the National Neonatal Research Database*. Neonatal Data Analysis Unit. 2022. United Kingdom: Imperial College London.

Table 3.4 (continued)

Outcome	**NNRD**
Brain injury on imaging	BrainInjuryImaging WHERE 'LeftIVH' >= 3 OR 'RightIVH' >= 3 OR PVL = 'Y' THEN (1) Coding: 0 = No brain injury on imaging 1 = Brain injury on imaging
Retinopathy of prematurity [preterm only]	NNRD has the following outcomes: retinopathy of prematurity (any grade), retinopathy of prematurity stage 3+, treated retinopathy of prematurity (surgery or Avastin) ROPAbove3 WHERE 'LeftEyeStage' > 2 OR 'RightEyeStage' > 2 THEN (1) Coding 0 – No 1 – ROP stage 3 or above present
General gross motor ability	NNRD has the following 2-year outcomes: neuromotor abnormal mobility, neuromotor difficulty using both hands, neuromotor difficulty using one hand, neuromotor difficulty walking, neuromotor neurological diagnosis, neuromotor supported sitting, neuromotor unable sitting, neuromotor unable use hands feet, neuromotor unable walk without assistance Coding: 0 No 1 Yes 9 Unknown

Note. Adapted from *Data dictionary for the National Neonatal Research Database*. Neonatal Data Analysis Unit. 2022. United Kingdom: Imperial College London.

Table 3.4 (continued)

General cognitive ability	NNRD has the following 2-year outcomes: comprehension difficulty communicating, comprehension difficulty speech, comprehension familiar, comprehension less than 5 words, comprehension words, referred for detailed developmental assessment, had detailed developmental assessment, mild delay, moderate delay, normal less than 3-month delay, severe delay, difficult test
Quality of life	Not available in the NNRD
Adverse events	N/A
Visual impairment or blindness	NNRD has the following items: vision blind, vision defect not correctable, visual problems specify
Hearing impairment or deafness	2-year outcomes: HearingImpairment WHERE auditory_hearing_impairement = 0 THEN (0) auditory_hearing_impairement = 1 THEN (1) auditory_hearing_impairement = 9 THEN (9) Coding 0 – No hearing impairment at two-year follow-up 1 – Hearing impairment at two-year follow-up 9 – Unknown There is also: hearing impairment not corrected by aids, and hearing impairment corrected by aids
Chronic lung disease/ bronchopulmonary dysplasia [preterm only]	BPD WHERE 'RespiratorySupport' ^= 0 OR 'AddedO2' ^= 10 AT WEEK 36 CGA THEN (1) Coding 0 – Died before week 36 1 – No respiratory support given at 36 weeks 2 – Respiratory support at 36 weeks Blank – Unknown

Note. Adapted from *Data dictionary for the National Neonatal Research Database*. Neonatal Data Analysis Unit. 2022. United Kingdom: Imperial College London.

3.3.7 Exposures

3.3.7.1 Weight-for-age z-scores

To calculate weigh-for-age z-scores, the UK-WHO Preterm Growth Reference and the UK-WHO Term Growth Reference was used according to the neonate's gestational age at birth. These references were used rather than the Intergrowth-21st reference charts to maintain consistency, as the Neonatal Data Analysis Unit at Imperial College London uses the UK-WHO Growth Reference for NNRD analysis. Weight-for-age z-scores were calculated using a package in Stata (Stata/SE Version 17.0 [Statacorp LLC]), which was entitled "*Zanthro – Extensions to generate: Standardising anthropometric measures in children and adolescents*" (SJ13-2:dm0004_1). This Stata package was developed by Vidmar et al. in 2013.[255]

3.3.7.2 Additional major congenital anomaly

The "additional major congenital anomaly" field was constructed based on existing code lists developed by the NNRD-AI and Harnden et al.[256] The NNRD-AI is an enhanced version of the NNRD that undergoes additional processing and is optimised for the application of data science techniques.[257] It includes definitions for important neonatal conditions, such as bronchopulmonary dysplasia and major congenital anomalies. The NNRD-AI categorises major congenital anomalies as being either non-cardiac or cardiac. These code lists were chosen to maintain consistency, as they were developed and are utilised at the National Data Analysis Unit. The full code list is outlined in **Appendix 3.1**. In addition, another code list was developed by Harnden et al. The first two categories were classified as follows: Category 1 codes were comprised of antenatal or postnatal diagnoses of conditions that were incompatible with long-term survival, such as anencephaly (diagnostic code 15890) and craniorachischisis (15891). Category 2

conditions were defined as conditions that were associated with a high risk of significant morbidity or mortality, such as absence of bladder (code 10008), Werdig-Hoffman – SMA type 1 (15180), mitochondrial myopathy (15203) and lissencephaly (15911).

Some of the study conditions themselves were part of these code lists (for instance, congenital diaphragmatic hernia [16495]), however as the interest was in any *additional* major congenital anomaly, only infants with additional anomalies apart from the original study condition were flagged as having an "additional major congenital anomaly". Similarly, infants with a diagnostic code of pulmonary hypoplasia did not flag as having an additional anomaly if the infant's condition was CDH, as all infants with CDH are likely to have some degree of pulmonary hypoplasia.

3.3.8 Ethics approval

Access to identifiable data was not needed for this project. This project has received ethics approval (Imperial College London - CAG reference: 21/CAG/0081; REC approval: 21/EM/0130; IRAS project ID: 293603).

3.3.9 Statistical analysis

Statistical analysis was performed using Stata/SE Version 17.0 (StataCorp LLC 2015: Texas, USA). Descriptive statistics were used to describe the study data and key demographics. The summary characteristics of surgical neonates were described (by gestational age and condition of interest) using medians for non-normally distributed continuous variables, and counts and proportions for categorical variables. Pearson's chi-squared test was used to calculate p-values for categorical variables. For non-normally

distributed continuous variables, the Wilcoxon rank-sum test was used to compare two groups.

3.3.10 Handling of missing data

The proportion of missing data for each variable and outcome was reported. Variables with greater than 10% missing data were considered to have a significant amount of missingness. The characteristics of those with and without missing data was reported for variables that had a significant amount of missingness and were part of the adjustment set derived from the DAG in **Chapter 2**.

3.4 Results

3.4.1 Missingness in all variables in the dataset

In the NNRD, the proportion of missing data was acceptable for many of the variables included the adjustment set derived from the DAG in **Chapter 2**. There was no missing data for gestational age at birth (0/8090) and sex (0/8090), and 0.5% and 2.6% of missing data for presence of an additional major congenital anomaly (43/8090) and IMD decile (210/8090) respectively. However, there was a high proportion of missing data for mother's ethnicity (18.31%, 1481/8090). The proportion of missing data for each variable is outlined in **Table 3.5**.

Table 3.5 Proportion of missing data for each variable

Variable	**Missingness**
Additional major congenital anomaly	43/8090 (0.53%)
Apgar at 5 min	796/8090 (9.84%)
Birth weight	0/0 (0%)
Sex	0/0 (0%)
Gestational age (in weeks)	0/0 (0%)
Maternal pyrexia in labour	1505/8090 (18.60%)
Meconium-stained liquor	867/8090 (10.72%)
Mode of delivery	462/8090 (5.71%)
Mother's blood group	938/8090 (11.59%)
Number of previous pregnancies	843/8090 (10.42%)
Onset of labour	536/8090 (6.63%)
Smoking in pregnancy	1064/8090 (13.15%)
Antenatal steroids given	283/8090 (3.50%)
Surfactant given during resuscitation	1086/8090 (13.42%)
IMD decile	210/8090 (2.60%)
Mother's ethnicity	1481/8090 (18.31%)
Mother's age	101/8090 (1.25%)
Reason for admission	153/8090 (1.89%)

3.4.2 Missing data for maternal ethnicity

Of the factors from the directed acyclic graph described in **Chapter 2**, there was a significant proportion of missingness in the maternal ethnicity variable, warranting further investigation into the characteristics of infants with missing and non-missing data for maternal ethnicity (**Table 3.6**). Infants with missing data for mother's ethnicity had a greater median birthweight (2454.0 g vs. 2370 g, Wilcoxon rank-sum test p=0.04) and lower rates of antenatal steroid therapy compared to infants with maternal ethnicity data. The characteristics of those with and without missing data for mother's ethnicity are shown in **Table 3.6**.

Table 3.6 Characteristics of those with and without missing data for mother's ethnicity

	Missing N=1,481	**Not missing** N=6,609	**Total** N=8,090	**p-value**
Birthweight (grams)	2454.0 (1585.0-3080.0)	2370.0 (1370.0-3010.0)	2381.5 (1410.0-3020.0)	0.004
Prematurity				0.057
Extremely preterm (<28 weeks)	229 (15.5%)	1,131 (17.1%)	1,360 (16.8%)	
Very preterm (28 to <32 weeks)	127 (8.6%)	676 (10.2%)	803 (9.9%)	
Moderate to late preterm (32 weeks to <37 weeks)	404 (27.3%)	1,775 (26.9%)	2,179 (26.9%)	
Term (≥37 weeks)	721 (48.7%)	3,027 (45.8%)	3,748 (46.3%)	
Surgical Condition				0.011
Hirschsprung's Disease	144 (9.7%)	503 (7.6%)	647 (8.0%)	
Gastroschisis	348 (23.5%)	1,491 (22.6%)	1,839 (22.7%)	
Oesophageal Atresia	322 (21.7%)	1,373 (20.8%)	1,695 (21.0%)	
Congenital Diaphragmatic Hernia	231 (15.6%)	1,108 (16.8%)	1,339 (16.6%)	
Posterior Urethral Valves	102 (6.9%)	419 (6.3%)	521 (6.4%)	
Surgical Necrotising Enterocolitis	334 (22.6%)	1,715 (25.9%)	2,049 (25.3%)	
Sex				0.94
Indeterminate/intersex	2 (0.1%)	10 (0.2%)	12 (0.1%)	
Male	909 (61.4%)	4,026 (60.9%)	4,935 (61.0%)	
Female	570 (38.5%)	2,573 (38.9%)	3,143 (38.9%)	

Data are presented as median (IQR) for continuous measures, and n (%) for categorical measures. Pearson's chi-squared test was used to calculate p-values for categorical variables. For non-normally distributed continuous variables, the Wilcoxon rank-sum test was used to compare two groups.

Table 3.7 (continued)

	Missing N=1,481	Not missing N=6,609	Total N=8,090	p-value
Additional major congenital anomaly				0.24
No	1,319 (89.6%)	5,821 (88.5%)	7,140 (88.7%)	
Yes	153 (10.4%)	754 (11.5%)	907 (11.3%)	
Major cardiac anomaly				0.24
No major cardiac anomaly	1,388 (94.3%)	6,249 (95.0%)	7,637 (94.9%)	
Major cardiac anomaly	84 (5.7%)	326 (5.0%)	410 (5.1%)	
Birth year				<0.001
2012	60 (4.1%)	942 (14.3%)	1,002 (12.4%)	
2013	98 (6.6%)	825 (12.5%)	923 (11.4%)	
2014	158 (10.7%)	821 (12.4%)	979 (12.1%)	
2015	160 (10.8%)	764 (11.6%)	924 (11.4%)	
2016	175 (11.8%)	716 (10.8%)	891 (11.0%)	
2017	175 (11.8%)	747 (11.3%)	922 (11.4%)	
2018	188 (12.7%)	611 (9.2%)	799 (9.9%)	
2019	232 (15.7%)	640 (9.7%)	872 (10.8%)	
2020	235 (15.9%)	543 (8.2%)	778 (9.6%)	
Multiple birth				0.061
Singleton birth	1,357 (91.7%)	5,955 (90.1%)	7,312 (90.4%)	
Multiple birth	123 (8.3%)	654 (9.9%)	777 (9.6%)	
Mother's age (year)	29.0 (24.0-34.0)	29.0 (24.0-34.0)	29.0 (24.0-34.0)	0.86
Mother's ethnicity				<0.001
Non-white ethnicity	0 (0.0%)	1,510 (22.8%)	1,510 (18.7%)	
White ethnicity	0 (0.0%)	5,099 (77.2%)	5,099 (63.0%)	
Missing	1,481 (100.0%)	0 (0.0%)	1,481 (18.3%)	
IMD Decile				0.26
IMD Decile 1-5	943 (65.4%)	4,113 (63.9%)	5,056 (64.2%)	
IMD Decile 6-10	498 (34.6%)	2,326 (36.1%)	2,824 (35.8%)	
Smoking during pregnancy				0.27
No smoking during pregnancy	892 (79.1%)	4,749 (80.5%)	5,641 (80.3%)	
Smoking during pregnancy	236 (20.9%)	1,149 (19.5%)	1,385 (19.7%)	
Antenatal steroids given				0.009
No	808 (57.6%)	3,442 (53.7%)	4,250 (54.4%)	
Yes	595 (42.4%)	2,962 (46.3%)	3,557 (45.6%)	
Caesarean				0.94
No caesarean	733 (54.5%)	3,434 (54.6%)	4,167 (54.6%)	
Caesarean	611 (45.5%)	2,850 (45.4%)	3,461 (45.4%)	
1-minute Apgar score				0.78
Apgar score 0-6	533 (42.2%)	2,596 (42.6%)	3,129 (42.6%)	
Apgar score 7-10	730 (57.8%)	3,493 (57.4%)	4,223 (57.4%)	
5-minute Apgar score				0.69
Apgar score 0-6	221 (17.7%)	1,101 (18.2%)	1,322 (18.1%)	
Apgar score 7-10	1,026 (82.3%)	4,946 (81.8%)	5,972 (81.9%)	

Data are presented as median (IQR) for continuous measures, and n (%) for categorical measures. Pearson's chi-squared test was used to calculate p-values for categorical variables. For non-normally distributed continuous variables, the Wilcoxon rank-sum test was used to compare two group

3.4.3 Incidence per 100,000 live births

Since Welsh units only contributed data to the NNRD from 2015 onwards, a subset of the cohort from 2015-2020 was used for the purposes of calculating incidence data. During this period, there were 405 infants admitted to neonatal care with Hirschsprung's disease, 1081 infants with gastroschisis, 1102 infants with oesophageal atresia, 881 infants with congenital diaphragmatic hernia, 376 infants with posterior urethral valves and 1341 infants with surgical necrotising enterocolitis in England and Wales. In the same period, there were 3,986,544 liveborn infants in England and Wales, based on data from the Office of National Statistics (ONS).[258] The incidence of admission to neonatal care with each surgical condition is outlined in **Table 3.7**.

Table 3.7 Incidence of babies admitted to neonatal care with specific surgical conditions in England and Wales per 100,000 live births

Surgical condition	**Incidence (95% CI) per 100,000 live births**
Hirschsprung's disease	10.2 (9.2-11.2)
Gastroschisis	27.1 (25.5-28.8)
Oesophageal atresia	27.6 (26.0-29.3)
Congenital diaphragmatic hernia	22.1 (20.7-23.6)
Posterior urethral valves	9.4 (8.5-10.4)
Surgical necrotising enterocolitis	33.6 (31.9-35.5)

3.4.4 Cohort characteristics

A total of 8,090 infants were included in this study, of which 647 neonates were diagnosed with Hirschsprung's disease, 1,839 diagnosed with gastroschisis, 1,695 with oesophageal atresia, 1,339 with congenital diaphragmatic hernia, 521 with posterior urethral valves and 2,049 with surgical necrotising enterocolitis (**Figure 3.1**). Hirschsprung's disease had the highest proportion of term infants (77.4%, n=501), followed by congenital diaphragmatic hernia (74.7%, n=1,000), posterior urethral valves (72.0%, n=521), oesophageal atresia (58.1%, n=984), gastroschisis (44.0%, n=809) and surgical necrotising enterocolitis (3.9%, n=79). There was a greater proportion of infants with surgical necrotising enterocolitis who were born extremely preterm (<28 weeks) compared to infants with Hirschsprung's disease (61.4% vs. 1.9%) (**Table 3.8**). Similarly, infants born with PUV and Hirschsprung's disease had a higher birthweight than infants born with surgical necrotising enterocolitis. Greater than 10% of data was missing for mother's ethnicity. **Figure 3.2**, **Figure 3.3** and **Figure 3.4** depict the birthweight and weight-for-age z-scores (by surgical condition and for the whole population).

Figure 3.1 Flow diagram of cohort

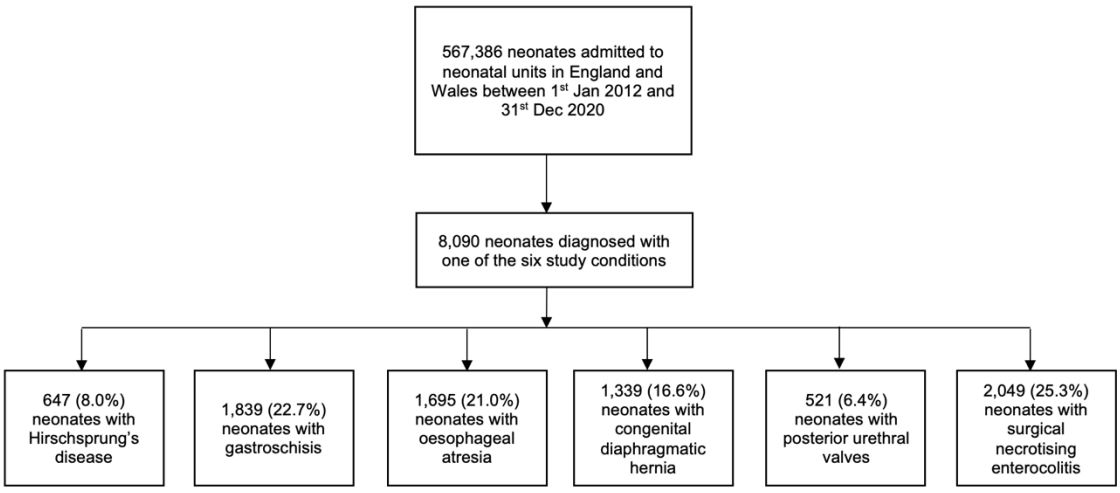


Table 3.8 Characteristics of surgical neonates in England 2012-2020

	Hirschsprung's Disease N=647	Gastroschisis N=1,839	Oesophageal Atresia N=1,695	Congenital Diaphragmatic Hernia N=1,339	Posterior Urethral Valves N=521	Surgical Necrotising Enterocolitis N=2,049	Total N=8,090
Birthweight (grams)	3204.0 (2660.0-3580.0)	2401.0 (2064.0-2740.0)	2538.0 (1935.0-3060.0)	2960.0 (2450.0-3335.0)	3180.0 (2800.0-3560.0)	860.0 (684.0-1190.0)	2381.5 (1410.0-3020.0)
Prematurity							
Extremely preterm (<28 weeks)	12 (1.9%)	6 (0.3%)	51 (3.0%)	11 (0.8%)	9 (1.7%)	1,271 (62.0%)	1,360 (16.8%)
Very preterm (28 to <32 weeks)	24 (3.7%)	49 (2.7%)	149 (8.8%)	62 (4.6%)	17 (3.3%)	502 (24.5%)	803 (9.9%)
Moderate to late preterm (32 weeks to <37 weeks)	110 (17.0%)	975 (53.0%)	511 (30.1%)	266 (19.9%)	120 (23.0%)	197 (9.6%)	2,179 (26.9%)
Term (≥37 weeks)	501 (77.4%)	809 (44.0%)	984 (58.1%)	1,000 (74.7%)	375 (72.0%)	79 (3.9%)	3,748 (46.3%)
Sex							
Indeterminate/intersex	0 (0.0%)	1 (0.1%)	5 (0.3%)	3 (0.2%)	0 (0.0%)	3 (0.1%)	12 (0.1%)
Male	468 (72.3%)	964 (52.4%)	976 (57.6%)	790 (59.0%)	521 (100.0%)	1,216 (59.3%)	4,935 (61.0%)
Female	179 (27.7%)	874 (47.5%)	714 (42.1%)	546 (40.8%)	0 (0.0%)	830 (40.5%)	3,143 (38.9%)
Weight-for-age z-score	-0.2 (-0.9-0.4)	-1.0 (-1.7--0.4)	-0.9 (-1.5--0.2)	-0.6 (-1.3-0.2)	-0.1 (-0.8-0.6)	-0.3 (-1.0-0.2)	-0.6 (-1.4-0.1)
Additional major congenital anomaly							
No additional major congenital anomaly	581 (89.8%)	1,638 (89.1%)	1,349 (79.6%)	1,170 (87.4%)	499 (95.8%)	1,903 (92.9%)	7,140 (88.3%)
Additional major congenital anomaly	63 (9.7%)	182 (9.9%)	342 (20.2%)	160 (11.9%)	22 (4.2%)	138 (6.7%)	907 (11.2%)
Missing	3 (0.5%)	19 (1.0%)	4 (0.2%)	9 (0.7%)	0 (0.0%)	8 (0.4%)	43 (0.5%)

Data are presented as median (IQR) for continuous measures, and n (%) for categorical measures.

Table 3.8 (continued)

	Hirschsprung's Disease N=647	Gastroschisis N=1,839	Oesophageal Atresia N=1,695	Congenital Diaphragmatic Hernia N=1,339	Posterior Urethral Valves N=521	Surgical Necrotising Enterocolitis N=2,049	Total N=8,090
Major cardiac anomaly							
No major cardiac anomaly	617 (95.4%)	1,799 (97.8%)	1,500 (88.5%)	1,243 (92.8%)	516 (99.0%)	1,962 (95.8%)	7,637 (94.4%)
Major cardiac anomaly	27 (4.2%)	21 (1.1%)	191 (11.3%)	87 (6.5%)	5 (1.0%)	79 (3.9%)	410 (5.1%)
Missing	3 (0.5%)	19 (1.0%)	4 (0.2%)	9 (0.7%)	0 (0.0%)	8 (0.4%)	43 (0.5%)
Multiple birth							
Singleton birth	617 (95.4%)	1,806 (98.2%)	1,562 (92.2%)	1,276 (95.3%)	503 (96.5%)	1,548 (75.5%)	7,312 (90.4%)
Multiple birth	30 (4.6%)	32 (1.7%)	133 (7.8%)	63 (4.7%)	18 (3.5%)	501 (24.5%)	777 (9.6%)
Missing	0 (0.0%)	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.0%)
Mother's age (year)	31.0 (26.0-36.0)	24.0 (21.0-28.0)	31.0 (27.0-35.0)	30.0 (26.0-35.0)	31.0 (26.0-34.0)	30.0 (26.0-35.0)	29.0 (24.0-34.0)
Mother's ethnicity							
Non-white ethnicity	138 (21.3%)	110 (6.0%)	274 (16.2%)	287 (21.4%)	156 (29.9%)	545 (26.6%)	1,510 (18.7%)
White ethnicity	365 (56.4%)	1,381 (75.1%)	1,099 (64.8%)	821 (61.3%)	263 (50.5%)	1,170 (57.1%)	5,099 (63.0%)
Missing	144 (22.3%)	348 (18.9%)	322 (19.0%)	231 (17.3%)	102 (19.6%)	334 (16.3%)	1,481 (18.3%)
IMD Decile							
IMD Decile 1-5	395 (61.1%)	1,189 (64.7%)	974 (57.5%)	802 (59.9%)	342 (65.6%)	1,354 (66.1%)	5,056 (62.5%)
IMD Decile 6-10	237 (36.6%)	584 (31.8%)	667 (39.4%)	513 (38.3%)	171 (32.8%)	652 (31.8%)	2,824 (34.9%)
Missing	15 (2.3%)	66 (3.6%)	54 (3.2%)	24 (1.8%)	8 (1.5%)	43 (2.1%)	210 (2.6%)

Data are presented as median (IQR) for continuous measures, and n (%) for categorical measures.

Table 3.8 (continued)

	Hirschsprung's Disease N=647	Gastroschisis N=1,839	Oesophageal Atresia N=1,695	Congenital Diaphragmatic Hernia N=1,339	Posterior Urethral Valves N=521	Surgical Necrotising Enterocolitis N=2,049	Total N=8,090
Smoking							
No smoking during pregnancy	462 (71.4%)	1,096 (59.6%)	1,299 (76.6%)	999 (74.6%)	392 (75.2%)	1,393 (68.0%)	5,641 (69.7%)
Smoking during pregnancy	72 (11.1%)	462 (25.1%)	194 (11.4%)	171 (12.8%)	53 (10.2%)	433 (21.1%)	1,385 (17.1%)
Missing	113 (17.5%)	281 (15.3%)	202 (11.9%)	169 (12.6%)	76 (14.6%)	223 (10.9%)	1,064 (13.2%)
Antenatal steroids given							
No	506 (78.2%)	1,083 (58.9%)	1,055 (62.2%)	931 (69.5%)	379 (72.7%)	296 (14.4%)	4,250 (52.5%)
Yes	112 (17.3%)	633 (34.4%)	591 (34.9%)	357 (26.7%)	121 (23.2%)	1,743 (85.1%)	3,557 (44.0%)
Missing	29 (4.5%)	123 (6.7%)	49 (2.9%)	51 (3.8%)	21 (4.0%)	10 (0.5%)	283 (3.5%)
Caesarean							
No caesarean	321 (49.6%)	960 (52.2%)	817 (48.2%)	773 (57.7%)	274 (52.6%)	1,022 (49.9%)	4,167 (51.5%)
Caesarean	258 (39.9%)	767 (41.7%)	774 (45.7%)	489 (36.5%)	203 (39.0%)	970 (47.3%)	3,461 (42.8%)
Missing	68 (10.5%)	112 (6.1%)	104 (6.1%)	77 (5.8%)	44 (8.4%)	57 (2.8%)	462 (5.7%)
1-minute Apgar score							
Apgar score 0-6	101 (15.6%)	446 (24.3%)	549 (32.4%)	688 (51.4%)	110 (21.1%)	1,235 (60.3%)	3,129 (38.7%)
Apgar score 7-10	469 (72.5%)	1,255 (68.2%)	1,016 (59.9%)	486 (36.3%)	363 (69.7%)	634 (30.9%)	4,223 (52.2%)
Missing	77 (11.9%)	138 (7.5%)	130 (7.7%)	165 (12.3%)	48 (9.2%)	180 (8.8%)	738 (9.1%)
5-minute Apgar score							
Apgar score 0-6	30 (4.6%)	161 (8.8%)	204 (12.0%)	364 (27.2%)	52 (10.0%)	511 (24.9%)	1,322 (16.3%)
Apgar score 7-10	540 (83.5%)	1,537 (83.6%)	1,352 (79.8%)	774 (57.8%)	418 (80.2%)	1,351 (65.9%)	5,972 (73.8%)
Missing	77 (11.9%)	141 (7.7%)	139 (8.2%)	201 (15.0%)	51 (9.8%)	187 (9.1%)	796 (9.8%)

Data are presented as median (IQR) for continuous measures, and n (%) for categorical measures.

Figure 3.2 Distribution of birthweight by surgical condition

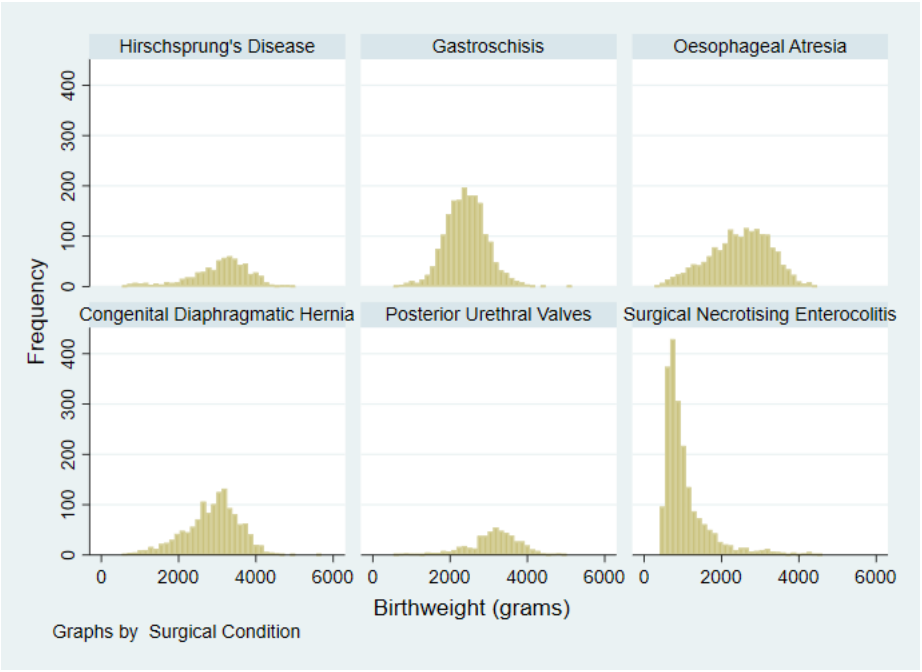


Figure 3.3 Weight-for-age z-scores for whole population

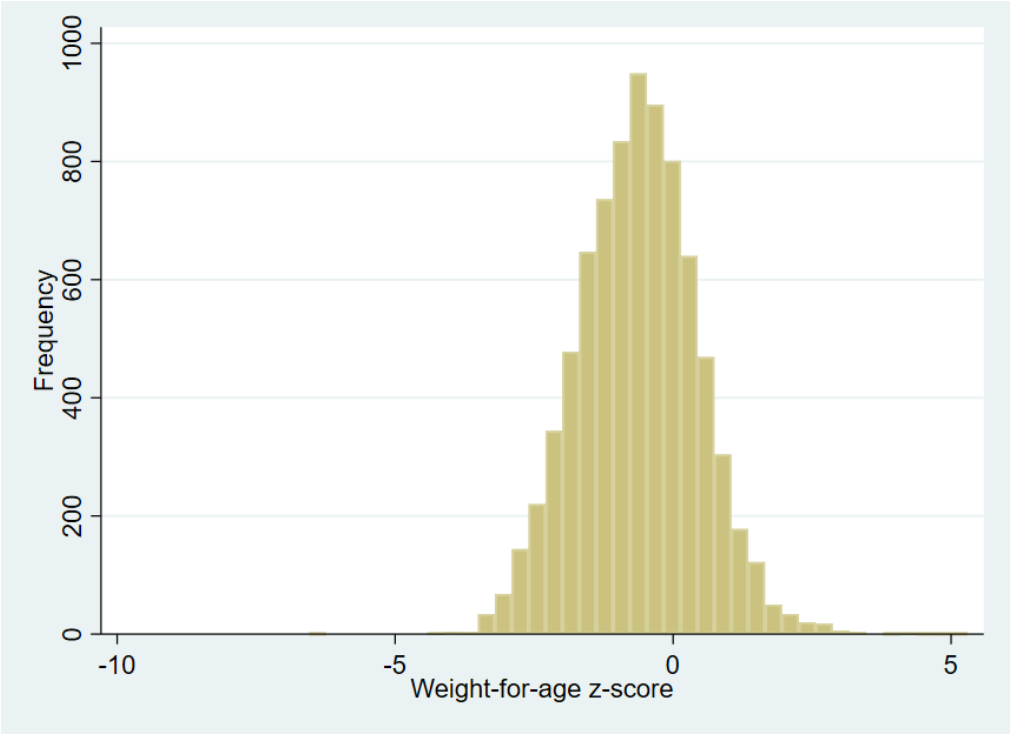
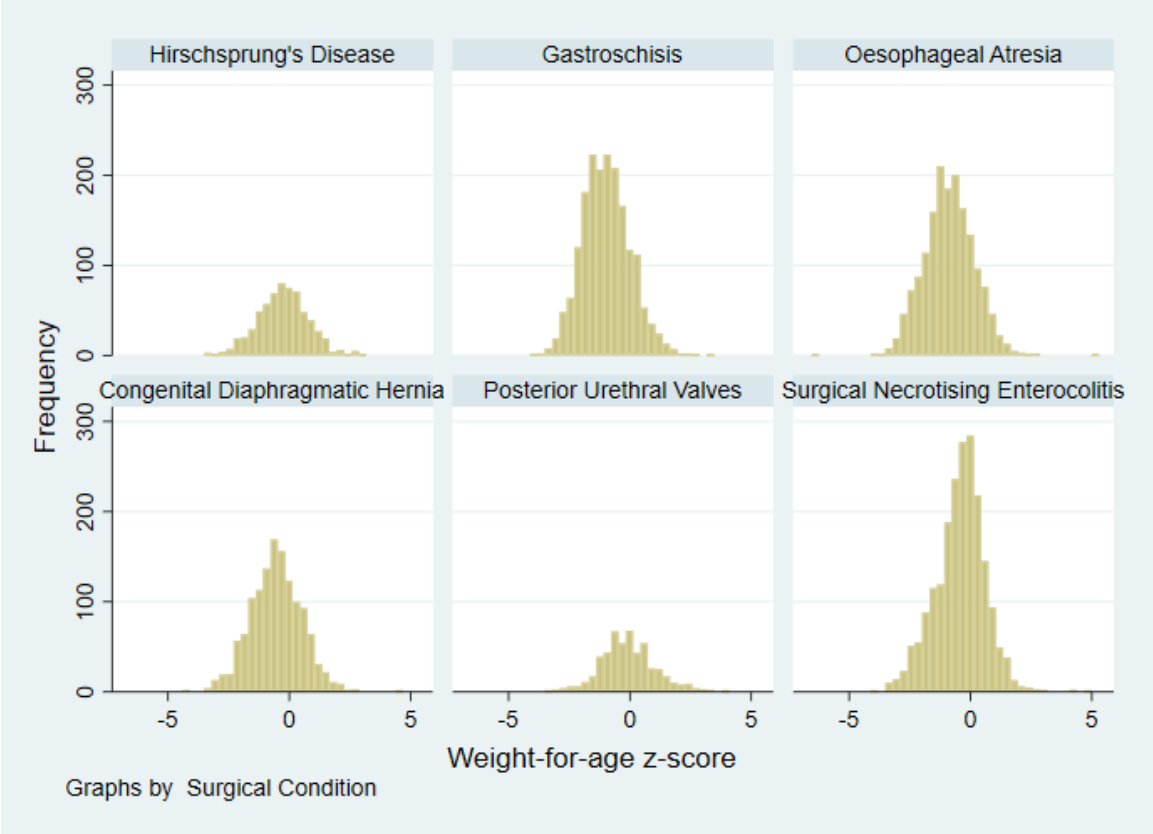


Figure 3.4 Weight-for-age z-scores by condition

Weight-for-ace z-scores calculated using the zanthro package (using the UK WHO preterm and term growth charts)



3.4.5 Neonatal outcomes by surgical condition

Infants with surgical NEC had the lowest crude survival to discharge rate (n=1523, 74.3%), followed by congenital diaphragmatic hernia (n=1014, 75.7%), then oesophageal atresia (n=1589, 93.7%), posterior urethral valves (n=493, 94.6%), gastroschisis (n=1814, 98.6%) and Hirschsprung's disease (n=647, 99.4%) (**Table 3.9**). Nearly 1 in 5 infants with surgical NEC had late-onset sepsis (19.2%, n=394), whereas the proportion of infants who had late-onset sepsis was lower for neonates with OA (1.1%, n=18), PUV (1.2%, n=6) and HD (1.2%, n=8). Similarly, infants with surgical NEC had the highest crude rate of severe brain injury (30.1%, n=617), followed by OA (5.3%, n=90) and CDH (4.9%, n=66). Of infants with gastroschisis, 1.0% (n=18) developed severe NEC.

3.4.6 Neonatal outcomes: Preterm infants <32 weeks

Infants with surgical NEC had the highest crude rate of treated retinopathy of prematurity (15.8%, n=280), as well as the outcome of respiratory support at 36 weeks (55.4%, n=982) (**Table 3.10**). Preterm infants with OA and gastroschisis also had a high proportion of infants requiring respiratory support at 36 weeks corrected gestational age, 55.0% (n=55.0%) and 50.9% (n=28) respectively.

Table 3.9 Neonatal outcomes of surgical neonates

	Hirschsprung's Disease N=647	Gastroschisis N=1,839	Oesophageal Atresia N=1,695	Congenital Diaphragmatic Hernia N=1,339	Posterior Urethral Valves N=521	Surgical Necrotising Enterocolitis N=2,049	Total N=8,090
Survival to discharge							
Survived	643 (99.4%)	1,814 (98.6%)	1,589 (93.7%)	1,014 (75.7%)	493 (94.6%)	1,523 (74.3%)	7,076 (87.5%)
Died	4 (0.6%)	24 (1.3%)	104 (6.1%)	325 (24.3%)	28 (5.4%)	526 (25.7%)	1,011 (12.5%)
Missing	0 (0.0%)	1 (0.1%)	2 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (0.0%)
Late-onset sepsis							
No	639 (98.8%)	1,783 (97.0%)	1,677 (98.9%)	1,320 (98.6%)	515 (98.8%)	1,655 (80.8%)	7,589 (93.8%)
Yes	8 (1.2%)	56 (3.0%)	18 (1.1%)	19 (1.4%)	6 (1.2%)	394 (19.2%)	501 (6.2%)
Severe brain injury							
No	629 (97.2%)	1,787 (97.2%)	1,605 (94.7%)	1,273 (95.1%)	509 (97.7%)	1,432 (69.9%)	7,235 (89.4%)
Yes	18 (2.8%)	52 (2.8%)	90 (5.3%)	66 (4.9%)	12 (2.3%)	617 (30.1%)	855 (10.6%)
Severe NEC							
No	644 (99.5%)	1,821 (99.0%)	1,685 (99.4%)	1,336 (99.8%)	520 (99.8%)	N/A	N/A
Yes	3 (0.5%)	18 (1.0%)	10 (0.6%)	3 (0.2%)	1 (0.2%)	N/A	N/A

Data are presented as n (%).

Table 3.10 Neonatal outcomes of all surgical infants <32 weeks

	Hirschsprung's Disease N=36	Gastroschisis N=55	Oesophageal Atresia N=200	Congenital Diaphragmatic Hernia N=73	Posterior Urethral Valves N=26	Surgical Necrotising Enterocolitis N=1,773	Total N=2,163
Treated retinopathy of prematurity*							
No	36 (100.0%)	54 (98.2%)	194 (97.0%)	73 (100.0%)	25 (96.2%)	1,493 (84.2%)	1,875 (86.7%)
Yes	0 (0.0%)	1 (1.8%)	6 (3.0%)	0 (0.0%)	1 (3.8%)	280 (15.8%)	288 (13.3%)
Respiratory support at 36 weeks							
Died before week 36	0 (0.0%)	2 (3.6%)	39 (19.5%)	33 (45.2%)	3 (11.5%)	380 (21.4%)	457 (21.1%)
No respiratory support given at 36 weeks	20 (55.6%)	24 (43.6%)	49 (24.5%)	11 (15.1%)	11 (42.3%)	398 (22.4%)	513 (23.7%)
Respiratory support at 36 weeks	12 (33.3%)	28 (50.9%)	110 (55.0%)	29 (39.7%)	12 (46.2%)	982 (55.4%)	1,173 (54.2%)
Missing	4 (11.1%)	1 (1.8%)	2 (1.0%)	0 (0.0%)	0 (0.0%)	13 (0.7%)	20 (0.9%)

Data are presented as n (%). *Data includes all surgical infants <32 weeks, including infants that may have died without a diagnosis of retinopathy of prematurity

3.5 Discussion

To date, this is the largest population-based cohort study to specifically examine the outcomes of surgical neonates using the National Neonatal Research Database (NNRD). Whilst this study demonstrates that it is not feasible to utilise routinely collected data held in the NNRD to investigate all short-term outcomes of interest, it is possible to investigate some short-term outcomes of neonates diagnosed with one of the study conditions. Nonetheless, the epidemiology and outcomes of surgical neonates in England and Wales during this study period have never been described before, which highlights that routinely collected databases, such as the NNRD, can provide novel insights into the characteristics and short-term prognosis of surgical neonates for certain outcomes.

3.5.1 Incidence

In this study population, surgical necrotising enterocolitis had the highest incidence (34.2 per 100,000 live births), followed by oesophageal atresia (27.6 per 100,000), gastroschisis (27.1 per 100,000), congenital diaphragmatic hernia (22.0 per 100,000), Hirschsprung's disease (10.1 per 100,000) and posterior urethral valves (9.5 per 100,000). The incidence of gastroschisis is similar to data reported in previous national population studies by BAPS-CASS, whilst the incidence of congenital diaphragmatic hernia was slightly higher than expected.[3 39] Only Hirschsprung's disease presenting in the neonatal period was included in this study, thus the incidence of Hirschsprung's disease was considerably lower than what has been previously reported in the literature.[259] This is one of the disadvantages of using NNRD data, as only patients who are admitted to neonatal care are captured in the database. Thus, conclusions can only be drawn about a specific population

of neonates with Hirschsprung's disease, rather than all patients with Hirschsprung's disease, who may present at varying stages of childhood, and indeed, even in adulthood.

3.5.2 Neonatal outcomes

Of 8090 neonates, 87.5% (7076/8090) neonates survived to discharge from neonatal care, 6.2% neonates (7589/8090) had late-onset sepsis, and 10.6% (7235/8090) had severe brain injury. Of 2163 neonates with a gestational age of less than 32 weeks at birth, 13.3% (288/2163) received treatment for retinopathy of prematurity and 54.2% (1173/2163) had bronchopulmonary dysplasia (defined as infants requiring respiratory support at 36 weeks corrected gestational age). The proportion of infants with surgical NEC who survived to discharge or had late-onset sepsis is within the range of what has been previously reported in the literature, which suggests that NNRD is a reliable data source to explore these outcomes for the six specific conditions investigated.[233 260]

3.5.3 Missing data

Missing data is often an issue that arises when handling databases of routinely collected data, particularly as data that is missing not at random can lead to bias. Although there was a high proportion of missing data for certain variables in the NNRD, missingness was acceptable for many of the variables of interest (i.e. less than 10%), including for most of the adjustment set derived from the directed acyclic graph and systematic review presented in **Chapter 2**: gestational age at birth (0/8090, 0.0% missingness), sex (0/8090, 0.0% missing), IMD decile (210/8090, 2.6%) and presence of an additional major congenital anomaly (43/8090, 0.53%). The exception was mother's ethnicity, for which the proportion of missing data was 18.31% (1481/8090). However, previous studies that have

shown that the characteristics of those with missing ethnicity data are similar to the characteristics of those with Caucasian ethnicity.[261 262]

3.5.4 Implications for further research and rationale for data linkage

Another limitation of this study and the NNRD is that outcomes may be lost for neonates who are transferred out of neonatal care and never return, for instance, surgical neonates who are transferred out to one of the following paediatric surgical centres: Great Ormond Street, Alder Hey, Sheffield and Birmingham. Thus, for this cohort of neonates, their actual neonatal outcomes may be unknown, despite them being coded as surviving to discharge from the neonatal unit. For instance, a surgical neonate who is transferred to one of the four paediatric surgical centres on day 2 or 3 of life, will be coded as surviving to discharge from the neonatal unit, even if they subsequently die on day 4 of life. Thus, the use of other datasets, such as the HES database, would provide valuable outcome information for this cohort of infants.

The NNRD does contain two-year neurodevelopmental outcomes for a subset of infants and a recent study suggests that the recording of two-year neurodevelopmental outcomes for preterm infants born less than 30 weeks' gestation has improved in the database over time, but a substantial proportion are still missing.[263] Though guidelines from the National Institute for Health and Care Excellent recommend follow-up assessment at two-years for all infants born less than 30 weeks' gestation, protocols for follow-up may vary between centres.[264] Furthermore, children with a surgical condition may not meet the gestational age criteria for neurodevelopmental follow-up. For instance, most infants with Hirschsprung's disease are term infants. Thus, it was not feasible to utilise the NNRD to examine long-term neurodevelopmental outcomes following childhood surgery.

Finally, although the analysis from this chapter suggests that NNRD is a robust dataset, particularly for neonatal outcomes, there were several outcomes of interest that were not available, such as number of operations and number of times patients were treated in hospital for an infection. Furthermore, granular condition-specific severity data were not available for all of the study conditions in the NNRD. For instance, the database did not include variables to delineate between simple and complex gastroschisis, nor was there data on the length of bowel affected in Hirschsprung's disease. The lack of these clinically meaningful exposures and outcomes highlights one of the limitations of utilising routinely collected data to investigate outcomes following paediatric surgery. Record linkage could provide opportunities to access a wider array of important outcomes and provide novel insights into the outcomes of surgical neonates.

Chapter 4

Assessing whether National Neonatal Research Database data can be used to develop models to predict short-term outcomes of surgical neonates admitted to neonatal care in in England and Wales from 2012-2020

4.1 Background

Broadly speaking, there are three main approaches to statistical modelling depending on the purpose of the model. These are often categorised as descriptive, explanatory or predictive, though they are not necessarily mutually exclusive. As described by Shmueli, a model may have both explanatory and predictive properties, though the two should not be assumed to be the same.[265] Whereas explanatory modelling seeks to elucidate biological mechanisms, prediction modelling aims to forecast outcomes based on patterns in existing data. Prediction models may be developed using statistical methods, such as linear and logistic regression, or more complex algorithmic modelling and machine learning techniques, such as neural networks and other "black-box" approaches.[266]

Unlike explanatory modelling, prediction modelling may sacrifice interpretability for more accurate prediction. However, in cases where both causal interpretation and prediction is desired, compromises may be required. For instance, if prediction is the primary purpose of the model, a more interpretable model may be developed, at the cost of some predictive power. If explanation is the primary purpose, the predictive ability of the model can still be assessed and modified if necessary. Importantly, the best prediction model may not be the same as the best explanatory model.[267]

There are two main uses for a prediction model: diagnostic, in which the model predicts or distinguishes whether a case has a condition of interest based on known characteristics, and prognostic, in which the model predicts the development of certain outcome at some point in time. Although prediction models are being increasingly used in healthcare, they remain relatively sparse in the field of paediatric surgery. One study by Cooper et al. developed models to predict surgical morbidity within 30 days of surgery, however

excluded neonates. Other studies have explored prediction modelling following paediatric cardiac surgery and for the prognostication of children with gastroschisis.[268 269] The NNRD has been previously used to externally validate prediction models for bronchopulmonary dysplasia and develop models to predict mortality amongst neonates with a birthweight less than 2000 grams.[270 271] The feasibility of utilising the NNRD to develop prediction models for the six study conditions has not yet been investigated.

4.1.1 Assessing the performance of the prediction models and internal validation

In multivariable logistic regression prediction models, there are two properties that should be evaluated: discrimination (the ability of the model to distinguish between patients at low or high risk of developing the outcome) and calibration (the agreement between observed and predicted risk of the outcome). The c-statistic—the area under the receiver operating characteristic (ROC) curve—is used to evaluate the former, whilst the calibration belt plot can be used to evaluate the latter.[272] The predictive performance of a model tends to be inflated or over-optimistic when the assessment is based on the same data from which the model was developed. Therefore, it is crucial for prediction models to undergo internal validation to address the issues of optimism (i.e. overestimating the performance of a model) and overfitting.[273] For the same reason, external validation in a separate database is desirable, though this may not always be feasible. Internal validation of prediction models, which is also referred to as resampling techniques, may be undertaken using several methods, including cross-validation, split-sample and bootstrapping techniques. Bootstrapping techniques are preferred as they result in accurate and stable estimates.[274]

4.2 Chapter aims and objectives

As stated in **Chapter 1**, the overarching aim of this thesis was to explore whether it was feasible to utilise big data to develop a better understanding of the following: (1) the outcomes following childhood surgery, and (2) the factors that influence these outcomes. Whilst the former is described in **Chapter 3** for short-term outcomes, this chapter addresses the latter. As the point of interest is factors that influence or predict outcome variation, prediction modelling is more appropriate than explanatory modelling.

The results presented in **Chapter 3** demonstrated that it was feasible to utilise the NNRD to describe some short-term outcomes for the six study conditions, namely survival, late-onset sepsis and severe brain injury. Thus, the primary aim of this chapter was to explore the feasibility and utility of NNRD data in developing prediction models for these short-term outcomes. The secondary aim was to develop models with high predictive power but which could also be easily interpreted by clinicians and researchers.

From the overarching aim, there were three objectives:

4. To develop multivariable prediction models which allow for case-mix adjustment of patient factors influencing short-term survival,
5. To develop multivariable prediction models which allow for case-mix adjustment of patient factors influencing late-onset sepsis, and;
6. To develop multivariable prediction models which allow for case-mix adjustment of patient factors influencing severe brain injury.

4.3 Statistical modelling

One of the aims of this chapter was to produce predictive models – that is, to be able to model and predict the occurrence of the outcome (one of survival, late-onset sepsis and severe brain injury) based on the infant's characteristics. However, interpretability of the model was also a secondary aim, in order to elucidate potential associations and relationships, as well as communicate this with healthcare professionals. There are a number of acceptable model building techniques and processes, of which two variable selection processes are common—one driven predominantly by subject matter knowledge and another driven by more traditional prediction modelling methods, sometimes referred to as "data-driven". As both predictive performance and interpretability of the model was desired, a variable selection process driven by subject matter knowledge was preferred. Where this variable selection process resulted in a model with suboptimal performance based on model discrimination and calibration, a second model was developed using a more traditional data-driven approach to variable selection, to see if this approach would result in a superior prediction model.

More complex machine learning techniques, such as neural networks and other "black-box" approaches, are beyond the scope of this thesis and not suitable for this project. This is because the efficacy of these methods is often proportional to the amount of input data available, thus large amounts of training data are required, which was not available from the NNRD.[266] Furthermore, using "black-box" approaches, one is unable to ascertain how the program generates its outputs, which is unhelpful if explanation for biological mechanisms is desired. This study followed the "Transparent reporting of multivariable prediction model for individual prognosis or diagnosis" (TRIPOD) guidelines.[273]

4.3.1 Model 1: Variable selection strategy

To identify potential confounders to be included in the model, a directed acyclic graph (DAG) was developed based on factors identified from the systematic review (**Chapter 2**).

From the DAG based on the systematic review, the following were identified as potential predictive factors: gestational age at birth, sex, ethnicity, socio-economic status and presence of an additional major congenital anomaly. This was used to inform the multivariable regression model. As the outcomes of interest were binary (for instance, survival or death), a multivariable logistic regression model was used.

Guided by subject-matter knowledge, all five potential predictors from the DAG were entered into the model. To determine if there were additional variables that should be included in the model, univariable logistic regression was conducted to characterise the association between candidate predictors and the outcome of interest (one of survival, late-onset sepsis and severe brain injury). Additional plausible candidate predictors were entered into the model one at a time and were retained if they improved the model fit. Details of assessment of model goodness of fit are described in **Section 4.3.8: Assessing the performance of the prediction models**.

4.3.2 Model 2: Variable selection strategy

For Model 2, a more traditional approach to variable selection was used. A base model was created with the outcome of survival and the one exposure variable indicating surgical condition. All plausible variables with less than 20% of missing data were then added to the model individually and the Akaike information criterion (AIC) of the resulting model was recorded (i.e. the model would consist of the outcome “survival” and the exposure

"surgical condition", along with one additional exposure variable, such as "maternal age"). All variables that resulted in improved fit (which was defined as a difference of ≥5 in the AIC) compared to the base model of only the outcome of survival and the exposure "surgical condition" were then entered into the final model. Both Model 1 and Model 2 underwent the same process for choosing the functional form of continuous variables and internal validation, as outlined below.

4.3.3 Variable selection for both models

Variables that were highly correlated (for instance, Apgar score at 1 minute and 5 minutes) were not entered into the model simultaneously. Similarly, gestational age at birth and birthweight were not included simultaneously in the models. However, weight-for-age z-scores was used to account for those who were born smaller than expected for their gestational age.

4.3.4 Choosing the functional form of continuous variables

Although it is common practice to categorise continuous variables prior to entering them into a model, there are some disadvantages in doing so, including the loss of information and creating an artificial "step function" where patients of varying risks are pooled together based on an arbitrary cut-off.[275] Thus, despite common practices, it is important that categorisation of continuous variables is not done as an automatic process without any justification or consideration of the implications of doing so. Furthermore, the effect of continuous variables on the outcome is often assumed to be linear, without further exploration or inquiry into the most optimal functional form of the variable.[276] To address this, the appropriateness of categorising certain continuous variables was considered and

other techniques were explored, such as the use of simple transformations (e.g. quadratic and cubic) and flexible modelling techniques—in particular, restricted cubic splines.

4.3.5 Interaction terms and other methods to optimise the model

The following interaction terms were explored in the model based on biological plausibility: condition and sex, and condition and gestational age at birth. A probit regression model and penalised regression model was explored in an attempt to optimise the model for survival.

4.3.6 Handling of missing data

A missing indicator (where missingness was a category within the variable) was utilised where the characteristics of those missing could be reasonably known. For instance, previous studies have demonstrated that the characteristics of those with missing ethnicity data are similar to those with Caucasian ethnicity.[261] Complete-case analysis was undertaken. Variables with greater than 10% missing data were considered to have a significant amount of missingness.

4.3.7 Assessing the performance of the prediction models

Both the area-under-ROC-curve (AUROC) and the calibration belt were calculated. To generate the calibration belt plot, the "calibrationbelt" package was used in Stata (package name: SJ17-4:gr0071), which was developed by Nattino et al.[272] Model calibration was also assessed using calibration plot, calibration-in-the-large (CITL) and the calibration slope. Measures of model goodness-of-fit were reported, including the AIC, BIC, and log-likelihood value. Measures of overall model performance were reported, including the Brier score and Cragg & Uhler's R^2 (also known as Nagelkerke's R^2).

4.3.8 Internal validation of prediction models

Internal validation was assessed using a bootstrapping approach to determine the apparent and optimism adjusted (i.e. bootstrap) performance of the prediction models. A total of 100 bootstrap samples were used. Overall performance was reported using the Brier scaled score, discrimination was reported using the c-statistic, and calibration was reported using the ratio of expected and observed events (E:O), CITL and calibration slope, along with a calibration graph. The "Bootstrap internal validation of logistic models" method in Stata (package name: SJ21-2:st0644), which was developed by Fernandez-Felix et al. was used for model validation.[277]

4.3.9 Interpretation of model performance

Model discrimination was considered acceptable where the area under the ROC curve (AUROC) was 0.7-0.8, excellent where the AUROC was 0.8-0.9 and outstanding for an AUROC of greater then 0.9. For assessing model calibration using the calibration method developed by Nattino et al., calibration was deemed good (i.e. the null hypothesis of good calibration not rejected) if the p-value of the test statistic was greater than 0.05.[272] In terms of the calibration slope, a slope close to 1 suggests good model calibration. A slope less than 1 suggests that the model overestimates risk whereas a slope greater than 1 suggests that the model underestimates risk. A calibration intercept, which assesses calibration-in-the-large, close to the value of zero suggests good calibration, whereas values less than zero suggest that the model overestimates risk and values greater than zero suggests underestimation of risk.[278]

The AIC, BIC and log-likelihood value can aid model selection as they can be used as a tool to compare models. A lower AIC and BIC value is preferrable. Conversely, a high log-likelihood value suggests a better model. The Cragg & Uhler's R^2 (Nagelkerke's R^2) is a modified version of the Cox & Snell's R^2 where the value of the statistic can lie between 0 and 1. The higher the value, the more variability the model explains. The Brier score evaluates the accuracy of a model's probabilistic predictions. Scores lie between 0 and 1, with a lower score indicating superior accuracy.

4.3.10 Sensitivity analysis

There was an increase in the proportion of neonates coded as having late-onset sepsis during the period from 2012 to 2020, particularly after 2016. To explore whether this would affect the prediction model for late-onset sepsis, a sensitivity analysis was performed by examining whether running the model on the three different cohorts (i.e. the whole cohort, the cohort for those born from 2012 to 2016, and the cohort for those born from 2017 to 2020), would result in changes to the association between the predictors and the outcome of late-onset sepsis (**Appendix 4.1**).

4.4 Results

4.4.1 Multivariable prediction model for survival until discharge

4.4.1.1 Restricted cubic splines: Gestational age at birth

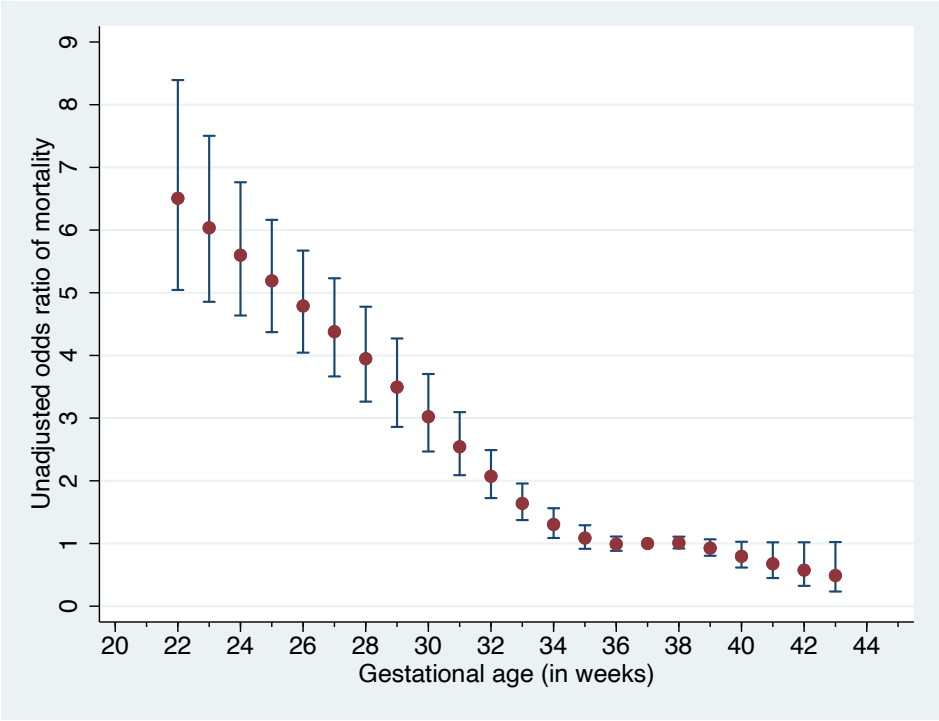
As gestational age had a non-linear association with the outcome of survival to discharge, the use of restricted cubic splines was explored. First, the following restricted cubic spline variations were generated and compared:

1. Restricted cubic spline with five system-generated knots at 24, 32, 36, 38 and 40 weeks (system-generated knots refers to where knots were not specified, so the knots were then determined by Harrell's default percentiles)[279] (**Figure 4.1**),
2. Restricted cubic spline with four system-generated knots (at 24, 34, 37 and 40 weeks) (**Figure 4.2**),
3. Restricted cubic spline with three system-generated knots (at 26, 36 and 40 weeks),
4. Restricted cubic spline with clinically relevant specified knots (at 28 weeks, 32 weeks, and 37 weeks).

By comparing Akaike information criteria (AICs) between models and favouring simpler models (i.e. those estimating fewer parameters), the restricted cubic spline with four system-generated knots at 24, 34, 37 and 40 weeks was chosen. The restricted cubic spline with five knots performed similarly to the restricted cubic spline with four knots, thus the latter was chosen on the grounds of parsimony (i.e. fewer knots).

Figure 4.1 Modelling using restricted cubic spline with five knots

Legend: Unadjusted odds ratios with 95%CI for the association between gestational age (in weeks) and mortality. Gestational age was modelled by restricted cubic splines with five knots (at 24, 32, 36, 38 and 40 weeks). The reference value is 37 weeks.



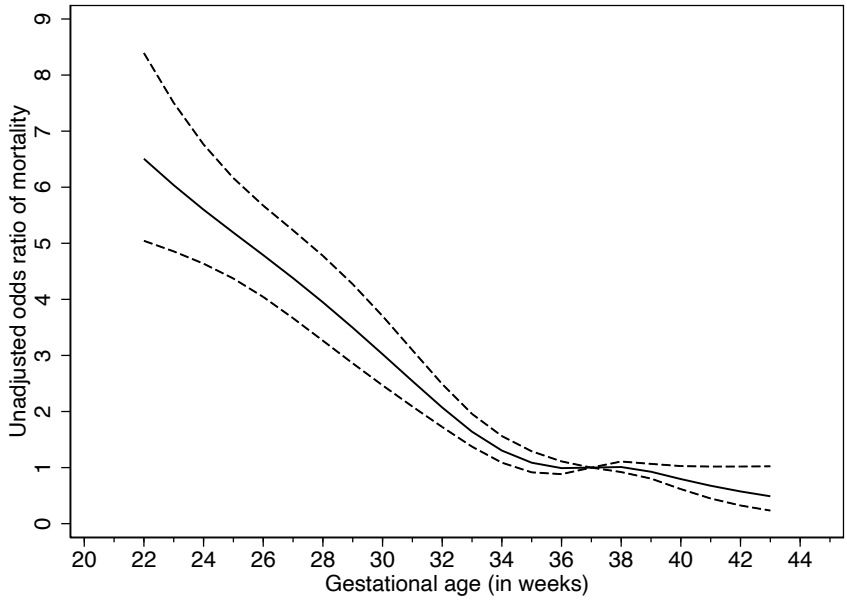
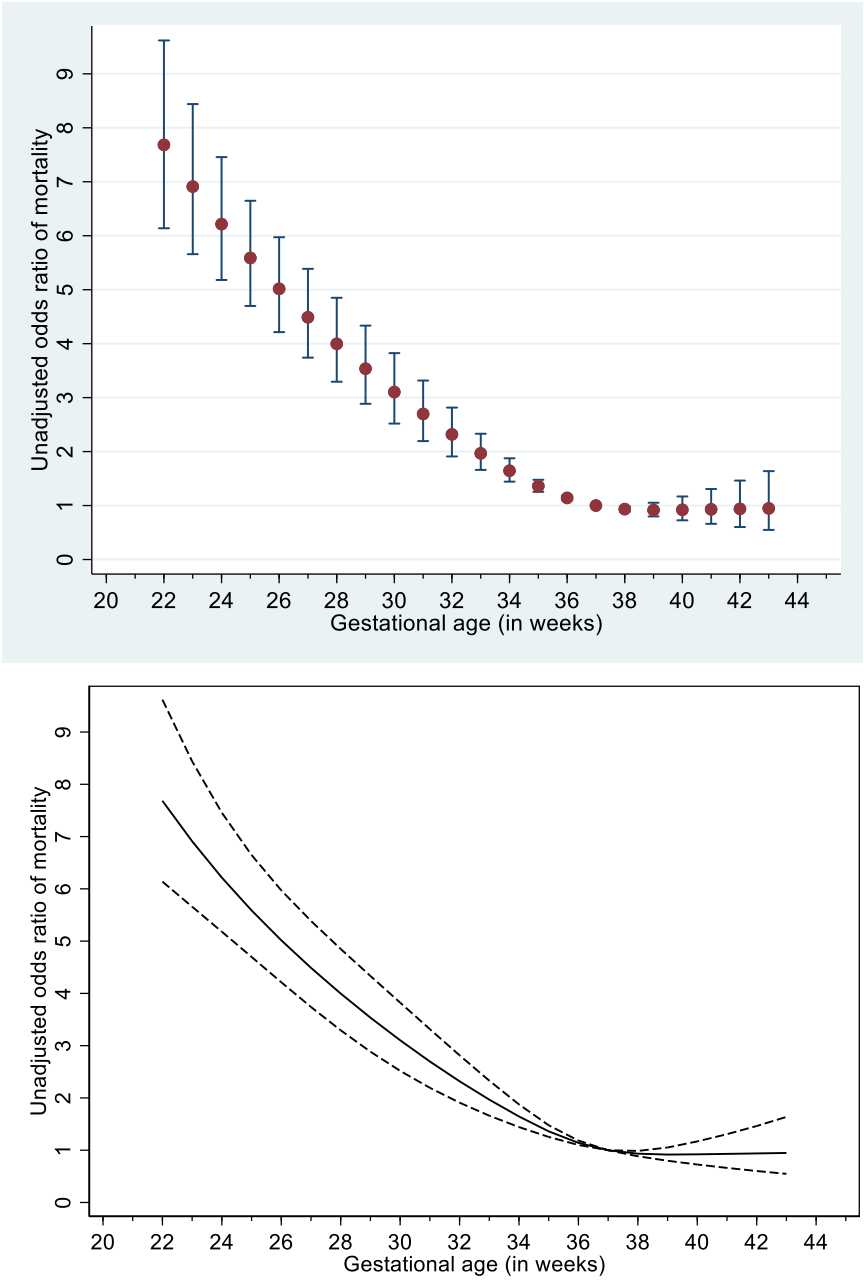


Figure 4.2 Modelling using restricted cubic spline with four knots

Legend: Unadjusted odds ratios with 95%CI for the association between gestational age (in weeks) and mortality. Gestational age was modelled by restricted cubic splines with fours knots (at 24, 34, 37, and 40 weeks). The reference value is 37 weeks.



4.4.2 Model 1

Model 1 for survival until discharge included the following variables: gestational age at birth in weeks (restricted cubic spline with four knots), mother's ethnicity (with the following categories: White, mixed, Asian or Asian British, Black or Black British, other ethnic groups and a missing category), IMD decile (continuous), presence of an additional major congenital anomaly (binary variable), sex (male or female), surgical condition (categorical variable), Apgar score at 5 minutes (two categories: score 0-6 or 7-10), weight-for-age z-score (continuous variable) and smoking during pregnancy (binary variable) (**Table 4.1**).

The area under the ROC curve for Model 1 was 0.8251, suggesting excellent discrimination (**Figure 4.3**).[280 281] However, the output of the calibration belt plot showed strong evidence that the predictions of the model deviated from the observed risk in the sample and therefore the model's internal calibration was poor (**Figure 4.4**). Conversely, the calibration plot, shown in **Figure 4.5**, suggests good calibration (calibration-in-the-large -0.000, calibration slope 1.000). The AIC, BIC and the loglikelihood value is reported in **Table 4.2**, along with measures of overall performance (i.e. the Brier score and Nagelkerke's R^2). The number of observations used in Model 1 was 6,265 (out of 8,090 infants).

In an attempt to improve the model, a probit regression model and penalised regression model were explored. As both approaches did not substantially improve the model, they were not subsequently used. The outputs of these models are displayed in **Appendix 4.2**.

Table 4.1 Multivariable prediction model for survival: Model 1 based on the literature

Predictors	Adjusted OR	SE	95% CI	p-value
Gestational age at births (in weeks)*				<0.001
24-34 weeks	1.03	0.03	0.98-1.09	
34-37 weeks	1.11	0.05	1.01-1.22	
37-40 weeks	0.74	0.55	0.17-3.21	
Maternal ethnicity				0.037
White (Reference)	-	-	-	
Mixed	1.48	0.63	0.64-3.40	
Asian or Asian British	0.72	0.09	0.56-0.92	
Black or Black British	0.72	0.11	0.53-0.98	
Other Ethnic Groups	0.72	0.19	0.42-1.21	
Unknown	1.02	0.13	0.79-1.30	
IMD Decile	1.02	0.02	0.99-1.05	0.204
Additional major congenital anomaly				<0.001
No additional major congenital anomaly (Reference)	-	-	-	
Additional major congenital anomaly	0.51	0.06	0.40-0.66	
Sex				0.502
Female (Reference)	-	-	-	
Male	1.06	0.09	0.89-1.26	
Surgical Condition				<0.001
Hirschsprung's Disease (Reference)	-	-	-	
Gastroschisis	0.26	0.27	0.03-1.95	
Oesophageal Atresia	0.05	0.06	0.01-0.40	
Congenital Diaphragmatic Hernia	0.01	0.01	0.00-0.06	
Posterior Urethral Valves	0.03	0.04	0.00-0.26	
Surgical Necrotising Enterocolitis	0.02	0.02	0.00-0.17	
Apgar score at 5 minutes				<0.001
Apgar score 0-6 (Reference)	-	-	-	
Apgar score 7-10	2.15	0.20	1.79-2.58	
Weight-for-age z-score	1.26	0.05	1.16-1.37	<0.001
Smoking during pregnancy				0.100
No smoking during pregnancy (Reference)	-	-	-	
Smoking during pregnancy	0.83	0.09	0.67-1.04	
_cons	34.57	44.26	2.81-425.07	0.006

OR = odds ratio; SE = standard error; CI = confidence interval; _cons = constant. Wald test used to calculate global p-values. *Gestational age modelled using restricted cubic splines, therefore coefficients cannot be interpreted.

Figure 4.3 Receiver operating characteristic curve for the prediction model for survival (Model 1)

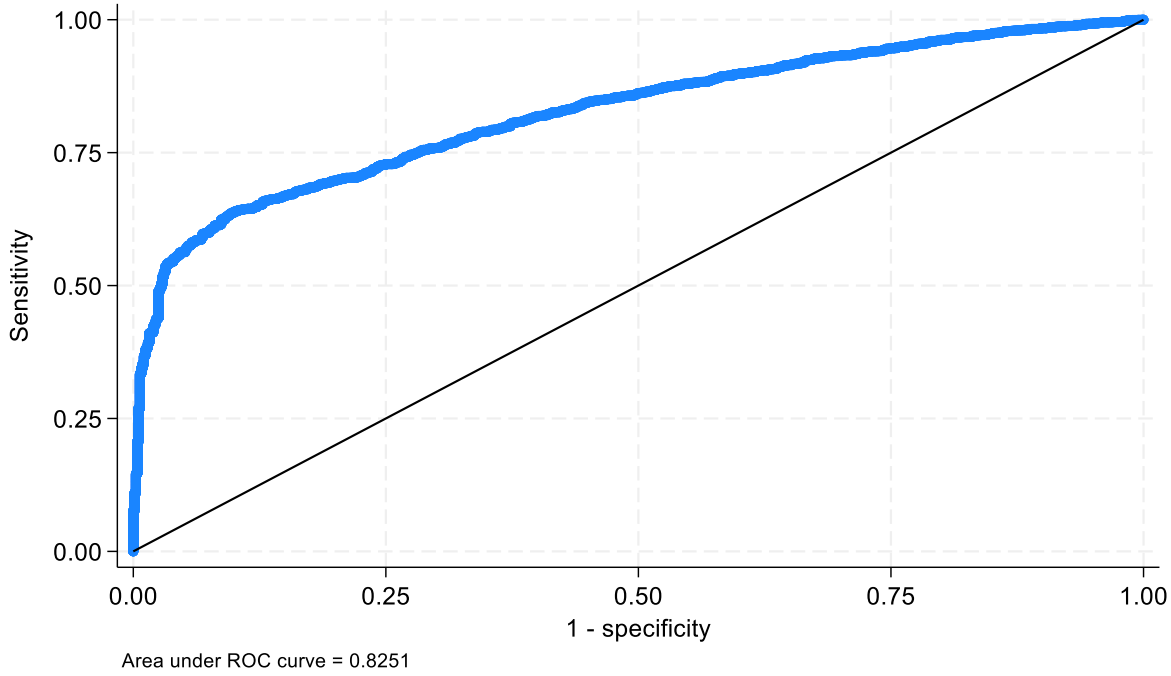


Figure 4.4 Evaluating the calibration of the prediction model for survival (Model 1) using a calibration belt plot

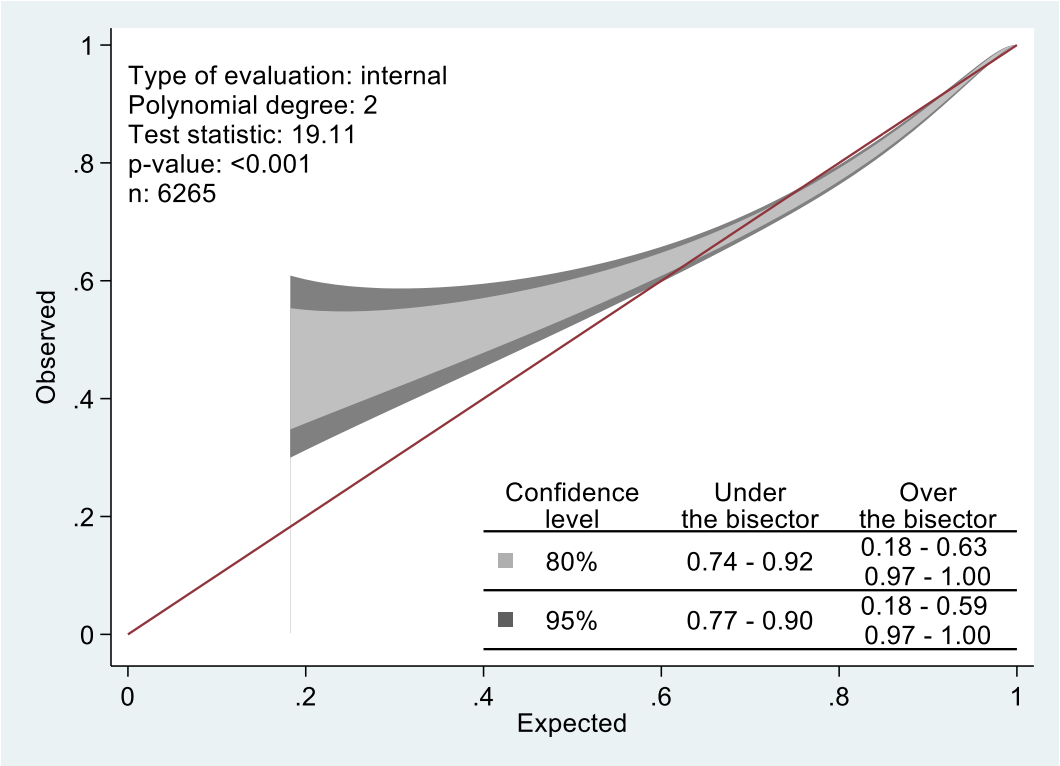
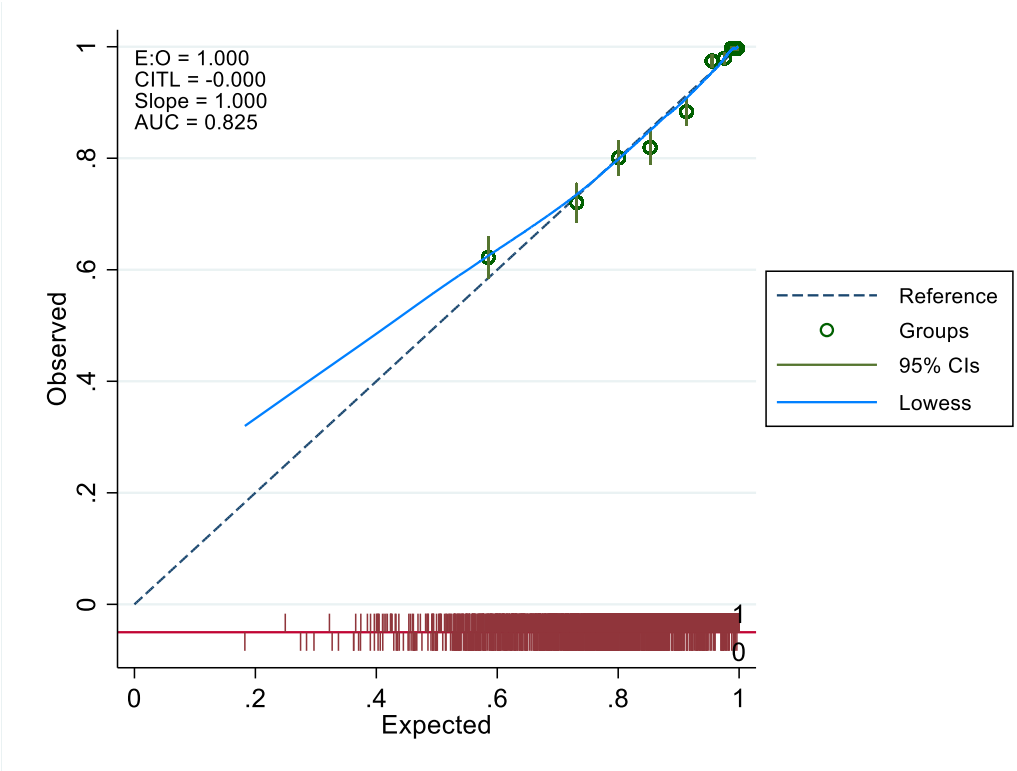


Figure 4.5 Evaluating the calibration of the prediction model for survival (Model 1) using a calibration plot



E:O = Ratio of expected and observed events for model calibration; CITL = calibration-in-the-large for model calibration; Slope = calibration slope for model calibration; AUC = area under the receiver operating characteristic (ROC) curve

Table 4.2 Measures of model assessment for the multivariable prediction model for survival (Model 1) using logistic regression

Model assessment	**Value**
Akaike Information Criterion (AIC)	3668.411
Bayesian Information Criterion (BIC)	-50929.505
Log-likelihood value (Full Model)	-1808.206
Cragg & Uhler's R^2 (Nagelkerke's R^2)	0.148
Brier score	0.0904

Internal validation: Survival prediction model (Model 1)

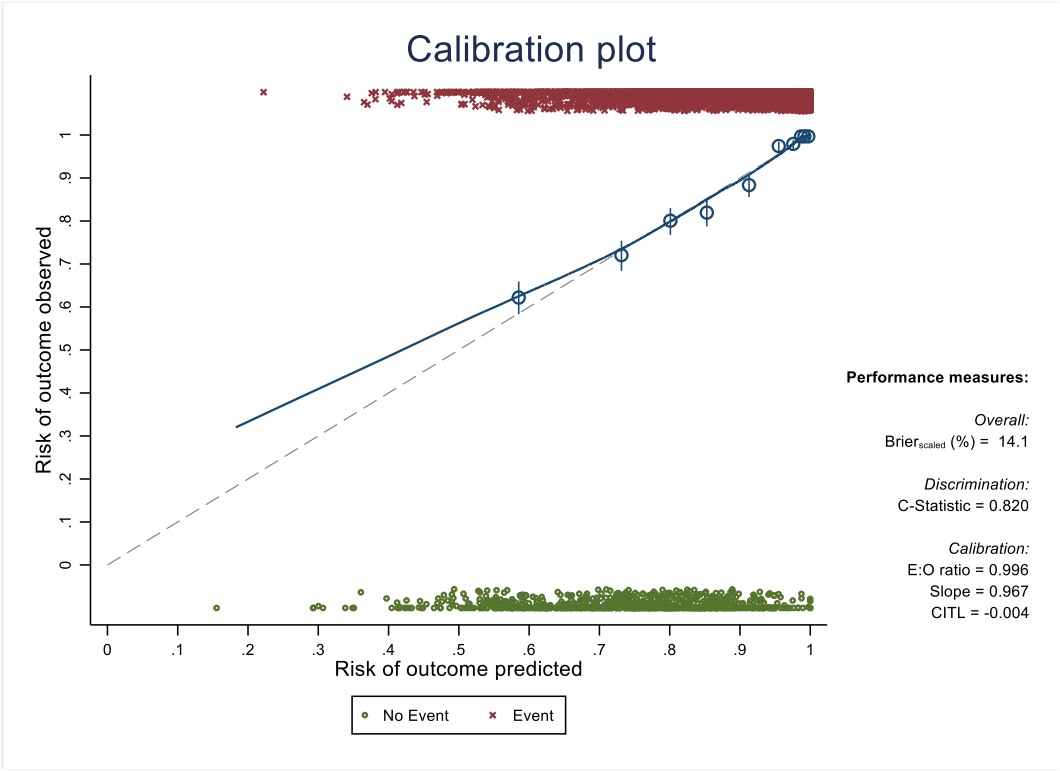
The optimism-adjusted C-statistic was 0.820, which was calculated from 100 bootstrap samples. The bootstrap performance for calibration was similar to the apparent performance (CITL -0.000, slope 1.000). The results of internal validation using a bootstrap validation approach, including the apparent performance, bootstrap performance and shrinkage factors, are presented in **Table 4.3**. The calibration plot is presented in **Figure 4.6**.

Table 4.3 Internal validation using a bootstrap validation approach for the prediction model for survival (Model 1): Apparent performance, bootstrap performance and shrinkage factors

Apparent performance			**Bootstrap performance (Optimism adjusted)**		
	Value	**95% CI**		**Value**	**Bootstrap 95% CI**
Overall:			**Overall:**		
Brier scaled (%)	15.0		Brier scaled (%)	14.1	
Discrimination:			**Discrimination:**		
C-Statistic	0.825	0.813-0.838	C-Statistic	0.820	0.808-0.838
Calibration:			**Calibration:**		
E:O ratio	1.000		E:O ratio	0.996	0.983-1.007
CITL	-0.000	-0.083-0.083	CITL	-0.004	-0.084-0.073
Slope	1.000	0.918-1.082	Slope	0.967	0.893-1.069
Shrinkage factors					
Heuristic shrinkage	0.981				
Bootstrap shrinkage	0.967				

E:O = Ratio of expected and observed events for model calibration; CITL = calibration-in-the-large for model calibration; Slope = calibration slope for model calibration

Figure 4.6 Internal validation using a bootstrap validation approach: calibration plot for prediction model for survival (Model 1)



4.4.3 Multivariable prediction model for survival: Model 2

In an attempt to improve the performance for the prediction model for survival, a more traditional approach to variable selection was employed to see if this result in a higher performing model.

This model (Model 2) for survival until discharge included the following variables: gestational age at birth in weeks (restricted cubic spline), surgical condition (categorical variable), presence of an additional major congenital anomaly (binary variable), Apgar score at 5 minutes (two categories: score 0-6 or 7-10), maternal pyrexia in labour (binary), presence of meconium stained liquor (binary), mode of delivery (categorical), mother's blood group (categorical), number of previous pregnancies (continuous), onset of labour (categorical), IMD decile (binary: deciles 1-5 or deciles 6-10), mother' ethnicity (with the following categories: White, mixed, Asian or Asian British, Black or Black British, other ethnic groups and a missing category), mother's age (continuous), reason for admission (categorical), weight-for-age z-score (continuous variable) and smoking during pregnancy (binary variable) (**Table 4.4**).

The area under the ROC curve for Model 2 was 0.8228, which was similar to that of Model 1 and suggests excellent discrimination (where 0.7-0.8 is acceptable, 0.8-0.9 is excellent and >0.9 is outstanding) (**Figure 4.7**). The output of the calibration belt plot showed strong evidence that the predictions of the model deviated from the observed risk in the sample and therefore the model's internal calibration was poor (**Figure 4.8**). The calibration plot is shown in **Figure 4.9** (calibration-in-the-large 0.006, calibration slope 1.016). The AIC, BIC and the loglikelihood value is reported in **Table 4.5**, along with measures of overall performance (i.e. the Brier score and Nagelkerke's R^2).

Model 2 was unable to generate outcome predictions for the condition of Hirschsprung's disease due to too few events (i.e. deaths) in this group. The number of observations used in Model 2 was 4,312 (out of 8,090 infants).

Table 4.4 Multivariable prediction model for survival: Model 2 (based on a more traditional approach to variable selection)

Predictors	Adjusted OR	SE	95% CI	p-value
Gestational age at births (in weeks)*				<0.001
24-34 weeks	0.96	0.04	0.89-1.04	
34-37 weeks	1.22	0.08	1.08-1.39	
37-40 weeks	0.25	0.24	0.04-1.61	
Surgical Condition				<0.001
Gastroschisis (Reference)	-	-	-	
Oesophageal Atresia	0.20	0.07	0.10-0.40	
Congenital Diaphragmatic Hernia	0.03	0.01	0.01-0.06	
Posterior Urethral Valves	0.11	0.05	0.05-0.26	
Surgical Necrotising Enterocolitis	0.08	0.03	0.04-0.16	
Additional major congenital anomaly				<0.001
No additional major congenital anomaly (Reference)	-	-	-	
Additional major congenital anomaly	0.48	0.07	0.36-0.64	
Apgar score at 5 minutes				<0.001
Apgar score 0-6 (Reference)	-	-	-	
Apgar score 7-10	2.50	0.28	2.00-3.12	
Maternal pyrexia during labour				0.880
No (Reference)	-	-	-	
Yes	0.97	0.22	0.62-1.51	
Meconium-stained liquor				0.971
No (Reference)	-	-	-	
Yes	0.99	0.19	0.68-1.45	
Mode of delivery				0.282
Emergency caesarean section - not in labour (Reference)	-	-	-	
Emergency caesarean - in labour	1.06	0.27	0.65-1.74	
Elective section – not in labour	0.66	0.14	0.43-1.02	
Elective section – in labour	0.92	0.50	0.32-2.69	
Vaginal – forceps assisted	1.27	0.44	0.64-2.51	
Vaginal – spontaneous	0.92	0.22	0.57-1.47	
Vaginal – ventouse assisted	1.59	0.70	0.67-3.79	

OR = odds ratio; SE = standard error; CI = confidence interval; _cons = constant. Wald test used to calculate global p-values. *Gestational age modelled using restricted cubic splines, therefore coefficients cannot be interpreted.

Table 4.4 (continued)

Predictors	Adjusted OR	SE	95% CI	p-value
Mother's blood group				0.643
A+ (Reference)	-	-	-	
A-	1.31	0.33	0.80-2.15	
B+	1.00	0.17	0.72-1.39	
B-	0.84	0.31	0.41-1.74	
AB+	0.71	0.19	0.42-1.20	
AB-	0.45	0.30	0.12-1.65	
O+	1.05	0.13	0.82-1.34	
O-	0.93	0.22	0.59-1.47	
Number of previous pregnancies	0.96	0.03	0.90-1.01	0.115
Onset of labour				0.675
Not in labour (Reference)	-	-	-	
Spontaneous	0.80	0.20	0.49-1.31	
Induced	0.85	0.22	0.51-1.41	
IMD Decile	1.00	0.02	0.96-1.04	0.896
Maternal ethnicity				0.036
White (Reference)	-	-	-	
Mixed	1.52	0.85	0.51-4.53	
Asian or Asian British	0.64	0.10	0.47-0.87	
Black or Black British	0.64	0.13	0.43-0.94	
Other Ethnic Groups	0.71	0.24	0.37-1.37	
Unknown	0.88	0.14	0.64-1.19	
Maternal age	1.02	0.01	1.00-1.04	0.036
Reason for admission				0.346
Medical intensive care (Reference)	-	-	-	
Medical high dependency care	1.72	0.42	1.06-2.79	
Medical special care	1.13	0.35	0.61-2.07	
Surgical care	1.28	0.33	0.77-2.14	
Cardiac care	0.41	0.36	0.07-2.25	
Transitional care	1.26	1.33	0.16-9.98	
Other	1.08	0.81	0.25-4.67	
Weight-for-age z-score	1.36	0.08	1.23-1.52	<0.001
Smoking during pregnancy				0.205
No smoking during pregnancy (Reference)	-	-	-	
Smoking during pregnancy	0.84	0.12	0.63-1.10	
_cons	57.49	69.17	5.44-607.70	0.001

OR = odds ratio; SE = standard error; CI = confidence interval; _cons = constant. Wald test used to calculate global p-values. *Gestational age modelled using restricted cubic splines, therefore coefficients cannot be interpreted.

Figure 4.7 Receiver operating characteristic curve for the prediction model for survival (Model 2)

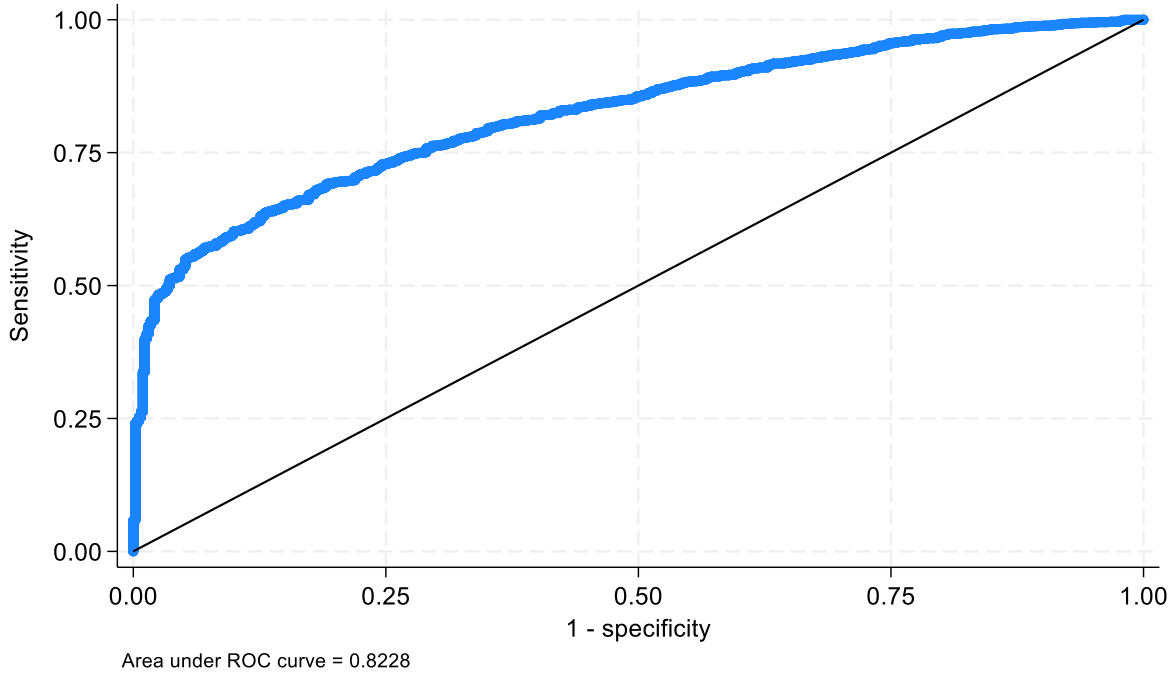


Figure 4.8 Evaluating the calibration of the prediction model for survival (Model 2) using a calibration belt plot

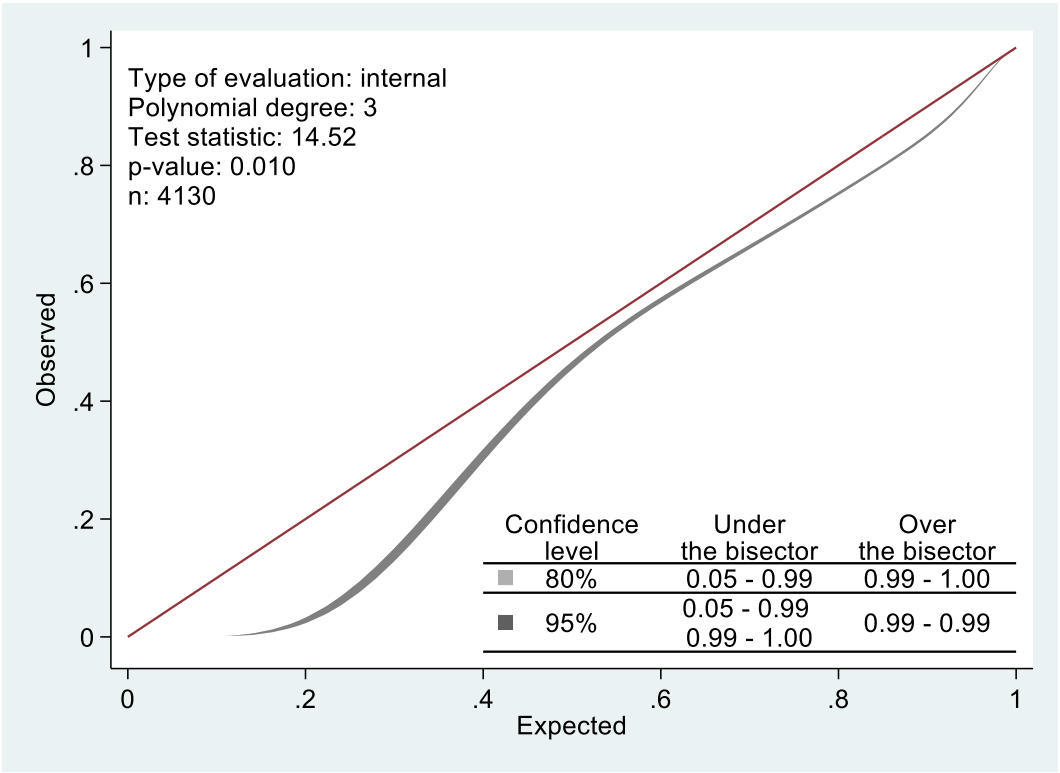
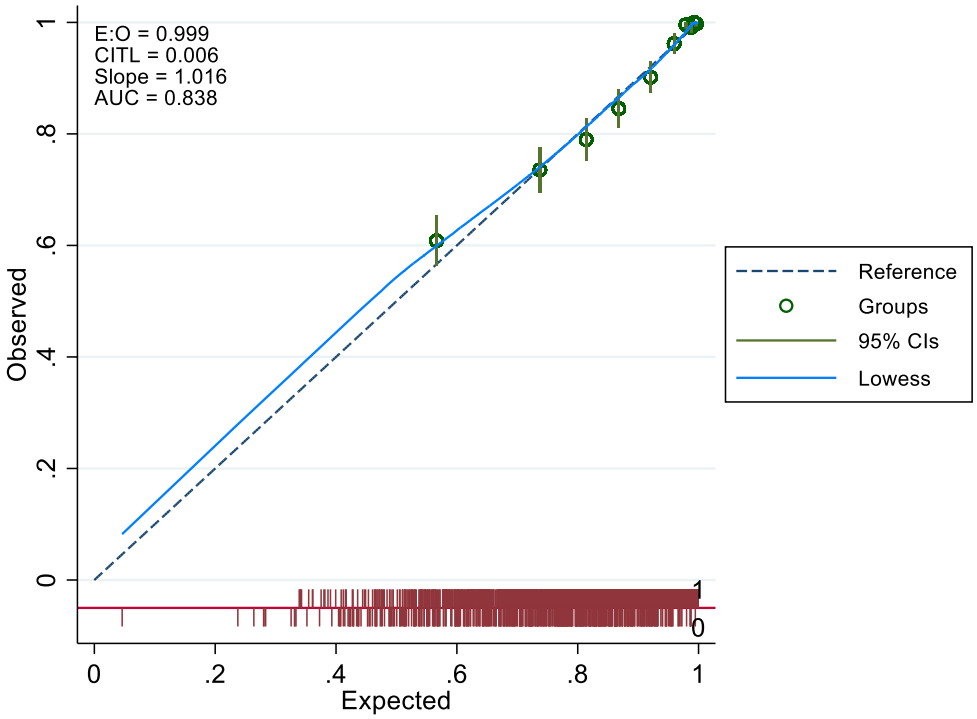


Figure 4.9 Evaluating the calibration of the prediction model for survival (Model 2) using a calibration plot



E:O = Ratio of expected and observed events for model calibration; CITL = calibration-in-the-large for model calibration; Slope = calibration slope for model calibration; AUC = area under the receiver operating characteristic (ROC) curve

Table 4.5 Measures of model assessment for the multivariable prediction model for survival (Model 2) using logistic regression

Model assessment	**Value**
Akaike Information Criterion (AIC)	2572.187
Bayesian Information Criterion (BIC)	-31472.722
Log-likelihood value (Full Model)	-1232.094
Cragg & Uhler's R^2 (Nagelkerke's R^2)	0.151
Brier score	0.0861

4.4.4 Multivariable prediction model for late-onset sepsis

The prediction model for late-onset sepsis included the following variables: gestational age at birth (in weeks), mother' ethnicity (with the following categories: White, mixed, Asian or Asian British, Black or Black British, other ethnic groups and a missing category), IMD decile (continuous), presence of an additional major congenital anomaly (binary variable), sex (male or female), and surgical condition (categorical variable) (**Table 4.6**).

For this model, the area under the ROC curve was 0.8443, suggesting excellent discrimination (**Figure 4.10**). The output of the calibration belt plot suggested good calibration (**Figure 4.11**). The calibration plot is shown in **Figure 4.12** (calibration-in-the-large -0.000, calibration slope 1.000). As this model performed well on both discrimination and calibration, a more traditional approach to variable selection was not explored. The AIC, BIC and the loglikelihood value is reported in **Table 4.7**, along with measures of overall performance (i.e. the Brier score and Nagelkerke's R^2). The number of observations used in the model was 7,828 (out of 8,090 infants).

Table 4.6 Prediction model for late-onset sepsis

Predictors	**Adjusted OR**	**SE**	**95% CI**	**p-value**
Gestational age at births (in weeks)	0.87	0.01	0.84-0.90	<0.001
Maternal ethnicity				0.125
White (Reference)	-	-	-	
Mixed	1.65	0.57	0.84-3.26	
Asian or Asian British	1.31	0.20	0.97-1.78	
Black or Black British	0.74	0.15	0.50-1.09	
Other Ethnic Groups	1.00	0.36	0.50-2.01	
Unknown	1.00	0.14	0.77-1.31	
IMD Decile	0.99	0.02	0.95-1.02	
Additional major congenital anomaly				0.010
No additional major congenital anomaly (Reference)	-	-	-	
Additional major congenital anomaly	1.56	0.27	1.11-2.18	
Sex				0.090
Female (Reference)	-	-	-	
Male	1.19	0.12	0.97-1.46	
Surgical Condition				<0.001
Hirschsprung's Disease (Reference)	-	-	-	
Gastroschisis	2.14	0.82	1.01-4.55	
Oesophageal Atresia	0.62	0.27	0.26-1.45	
Congenital Diaphragmatic Hernia	1.03	0.44	0.45-2.40	
Posterior Urethral Valves	0.67	0.38	0.22-2.06	
Surgical Necrotising Enterocolitis	4.84	1.91	2.24-10.49	
_cons	1.91	1.34	0.48-7.57	0.358

OR = odds ratio; SE = standard error; CI = confidence interval; _cons = constant. Wald test used to calculate global p-values.

Figure 4.10 Receiver operating characteristic curve for the prediction model for late-onset sepsis

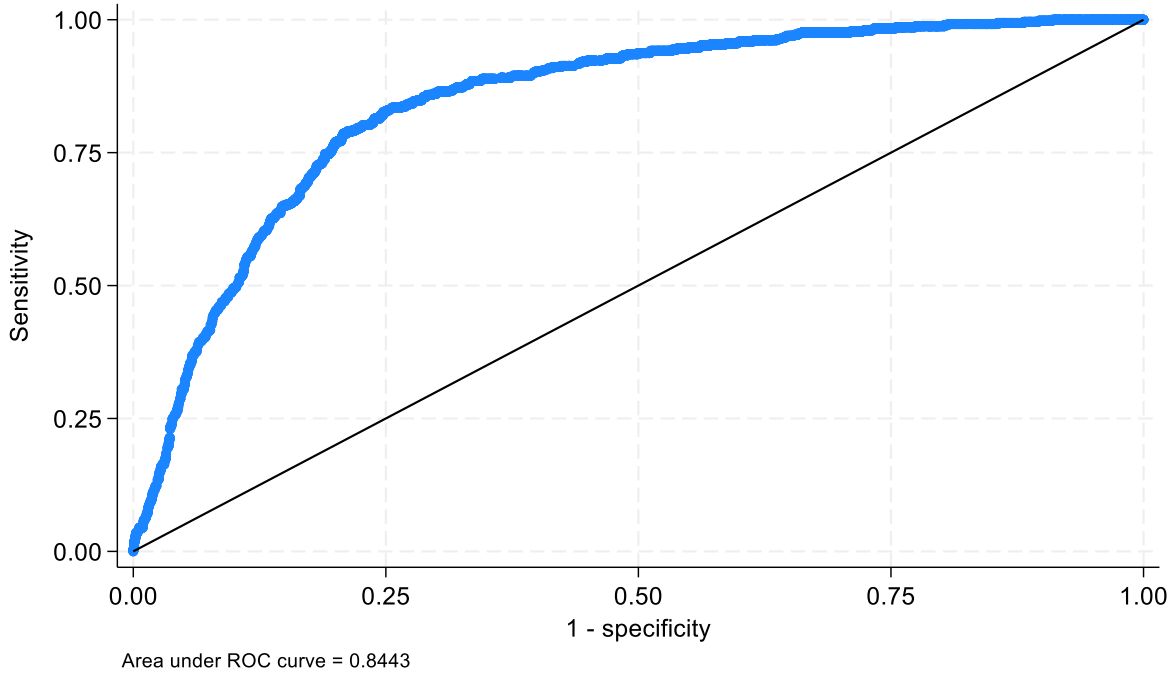


Figure 4.11 Evaluating the calibration of the prediction model for late-onset sepsis using a calibration belt plot

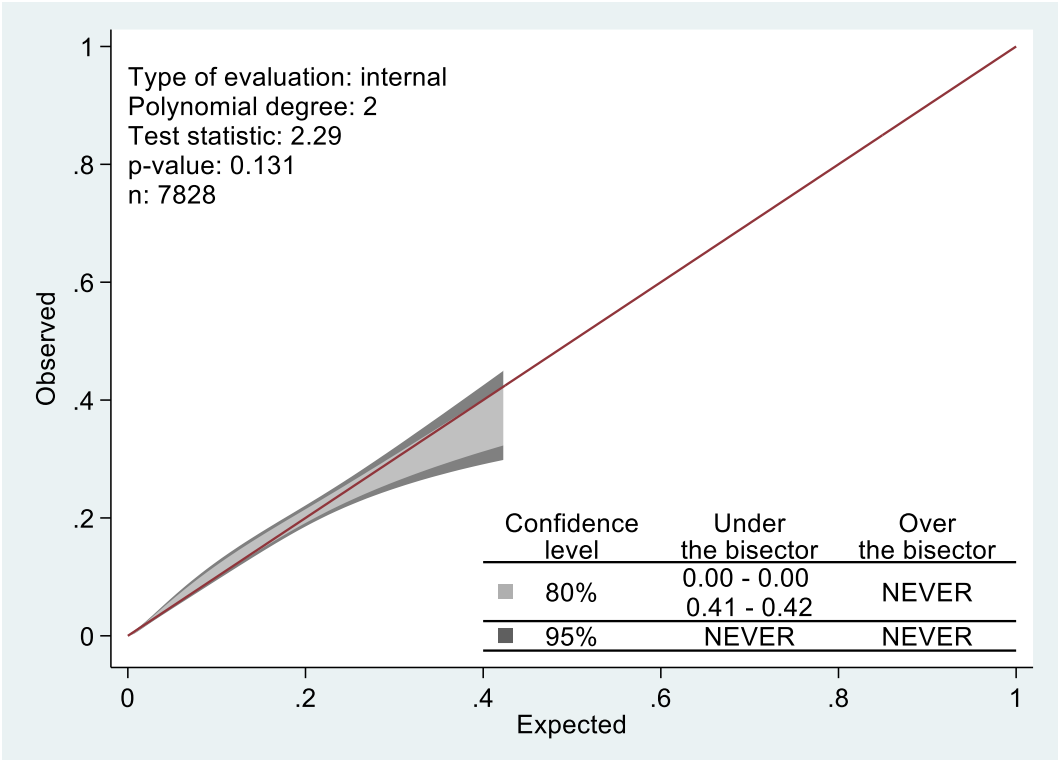
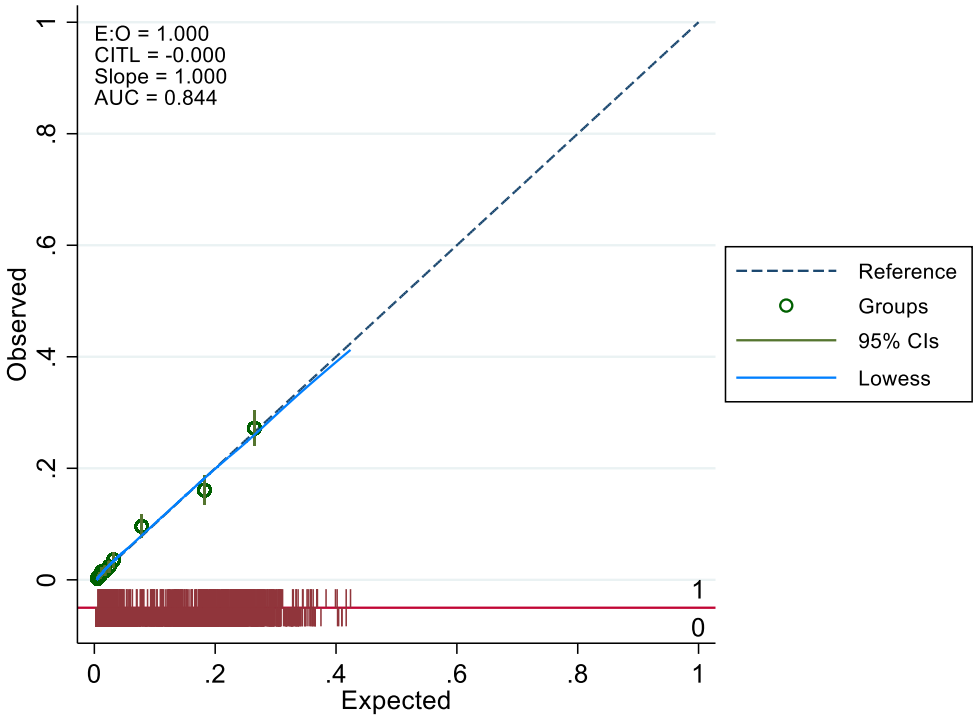


Figure 4.12 Evaluating the calibration of the prediction model for late-onset sepsis using a calibration plot



E:O = Ratio of expected and observed events for model calibration; CITL = calibration-in-the-large for model calibration; Slope = calibration slope for model calibration; AUC = area under the receiver operating characteristic (ROC) curve

Table 4.7 Measures of model assessment for the multivariable prediction model for late-onset sepsis using logistic regression

Model assessment	**Value**
Akaike Information Criterion (AIC)	2934.164
Bayesian Information Criterion (BIC)	-67115.132
Log-likelihood value (Full Model)	-1448.082
Cragg & Uhler's R^2 (Nagelkerke's R^2)	0.097
Brier score	0.0520

Internal validation: late-onset sepsis prediction model

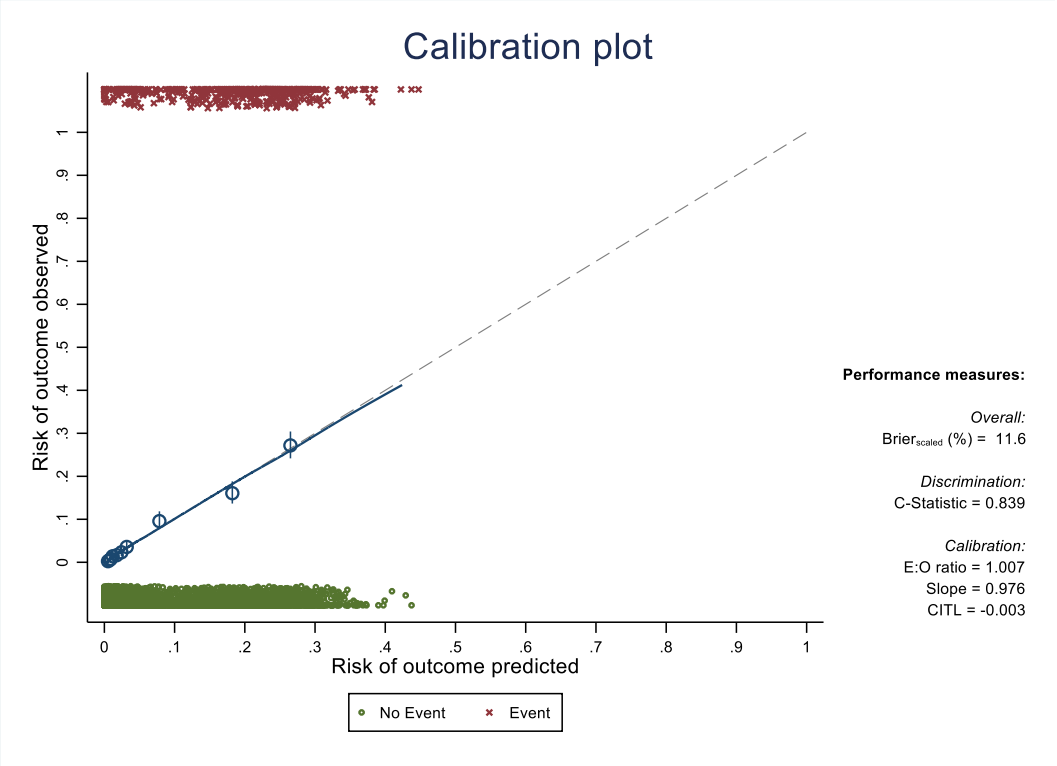
The optimism-adjusted C-statistic was 0.839, which was calculated from 100 bootstrap samples. The bootstrap performance for calibration was similar to the apparent performance (CITL 0.000, slope 1.000). The results of internal validation using a bootstrap validation approach, including the apparent performance, bootstrap performance and shrinkage factors, are presented in **Table 4.8**. The calibration plot is presented in **Figure 4.13**.

Table 4.8 Internal validation using a bootstrap validation approach for the prediction model for late-onset sepsis: Apparent performance, bootstrap performance and shrinkage factors

Apparent performance			**Bootstrap performance (Optimism adjusted)**		
	Value	**95% CI**		**Value**	**Bootstrap 95% CI**
Overall:			**Overall:**		
Brier scaled (%)	12.3		Brier scaled (%)	11.6	
Discrimination:			**Discrimination:**		
C-Statistic	0.844	0.828-0.860	C-Statistic	0.839	0.823-0.854
Calibration:			**Calibration:**		
E:O ratio	1.000		E:O ratio	1.007	0.929-1.095
CITL	0.000	-0.097-0.097	CITL	-0.003	-0.104-0.092
Slope	1.000	0.917-1.083	Slope	0.976	0.898-1.043
Shrinkage factors					
Heuristic shrinkage	0.982				
Bootstrap shrinkage	0.967				

E:O = Ratio of expected and observed events for model calibration; CITL = calibration-in-the-large for model calibration; Slope = calibration slope for model calibration

Figure 4.13 Internal validation using a bootstrap validation approach: calibration plot for the prediction model for late-onset sepsis



4.4.5 Multivariable prediction model for severe brain injury

The prediction model for severe brain injury included the following variables: gestational age at birth in weeks (restricted cubic spline), mother' ethnicity (with the following categories: White, mixed, Asian or Asian British, Black or Black British, other ethnic groups and a missing category), IMD decile (categorical), presence of an additional major congenital anomaly (binary variable), sex (male or female), surgical condition (categorical variable), surfactant given during resuscitation (binary variable), Apgar score at 5 minutes (two categories: score 0-6 or 7-10), and antenatal steroid therapy (binary, yes/no) (**Table 4.9**).

For this model, the area under the ROC curve was 0.83, suggesting excellent discrimination (**Figure 4.14**). The output of the calibration belt plot suggested good calibration (**Figure 4.15**). The calibration plot is shown in **Figure 4.16** (calibration-in-the-large -0.000, calibration slope 1.000). As the literature-based approach to variable selection resulted in good discrimination and internal calibration, a more traditional AIC-based approach to variable selection was not explored. The AIC, BIC and the loglikelihood value is reported in **Table 4.10**, along with measures of overall performance (i.e. the Brier score and Nagelkerke's R^2). The number of observations used in the model was 6,165 (out of 8,090 infants).

Table 4.9 Prediction model for severe brain injury

Predictors	Adjusted OR	SE	95% CI	p-value
Gestational age at births (in weeks)*				<0.001
24-34 weeks	0.85	0.03	0.80-0.90	
34-37 weeks	0.94	0.05	0.85-1.05	
37-40 weeks	12.92	10.60	2.59-64.47	
Maternal ethnicity				0.523
White (Reference)	-	-	-	
Mixed	1.01	0.36	0.50-2.02	
Asian or Asian British	1.17	0.16	0.89-1.53	
Black or Black British	0.92	0.15	0.67-1.28	
Other Ethnic Groups	1.35	0.38	0.78-2.33	
Unknown	0.88	0.11	0.68-1.13	
IMD Decile	1.00	0.02	0.97-1.03	0.945
Additional major congenital anomaly				0.080
No additional major congenital anomaly (Reference)	-	-	-	
Additional major congenital anomaly	1.30	0.20	0.97-1.75	
Sex				0.167
Female (Reference)	-	-	-	
Male	1.14	0.10	0.95-1.36	
Surgical Condition				<0.001
Hirschsprung's Disease (Reference)	-	-	-	
Gastroschisis	1.40	0.47	0.72-2.71	
Oesophageal Atresia	1.48	0.47	0.80-2.74	
Congenital Diaphragmatic Hernia	1.71	0.55	0.91-3.22	
Posterior Urethral Valves	0.86	0.38	0.36-2.06	
Surgical Necrotising Enterocolitis	3.82	1.22	2.04-7.15	
Surfactant given during resuscitation				0.145
No (Reference)	-	-	-	
Yes	1.23	0.18	0.93-1.63	
Apgar score at 5 minutes				<0.001
Apgar score 0-6 (Reference)	-	-	-	
Apgar score 7-10	0.65	0.07	0.53-0.79	
Antenatal steroid therapy given				0.008
No (Reference)	-	-	-	
Yes	0.68	0.10	0.52-0.90	
_cons	12.43	11.44	2.04-75.54	0.006

OR = odds ratio; SE = standard error; CI = confidence interval; _cons = constant. Wald test used to calculate global p-values. *Gestational age modelled using restricted cubic splines, therefore coefficients cannot be interpreted.

Figure 4.14 Receiver operating characteristic curve for the prediction model for severe brain injury

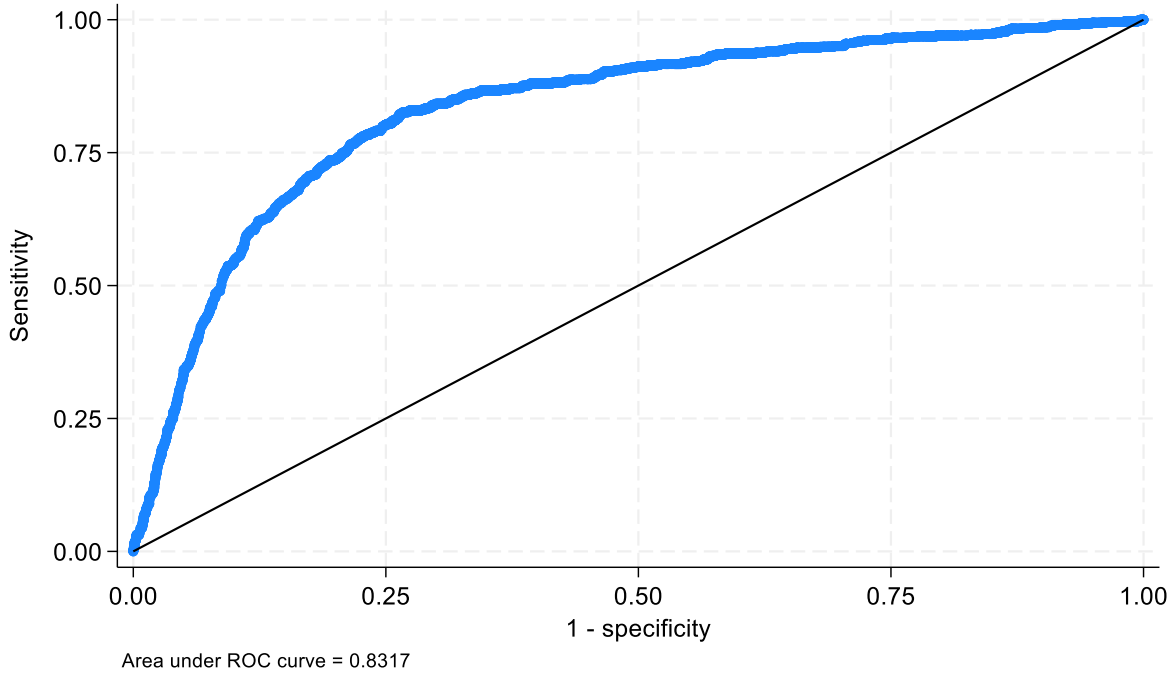


Figure 4.15 Evaluating the calibration of the prediction model for severe brain injury using a calibration belt plot

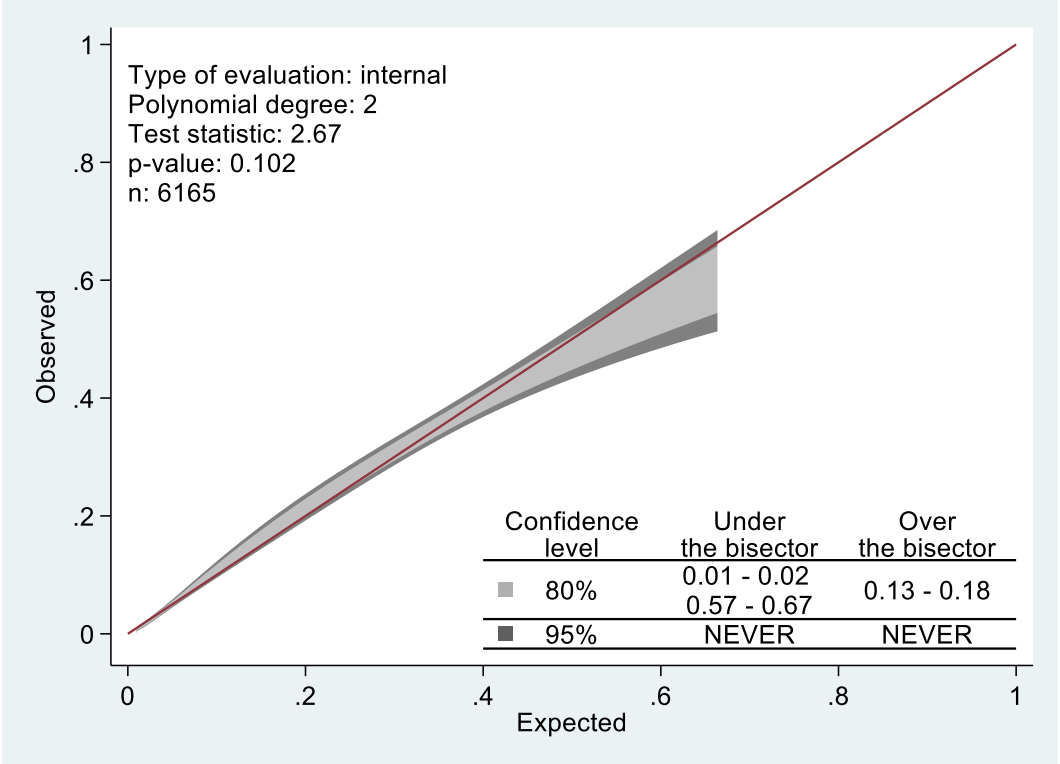
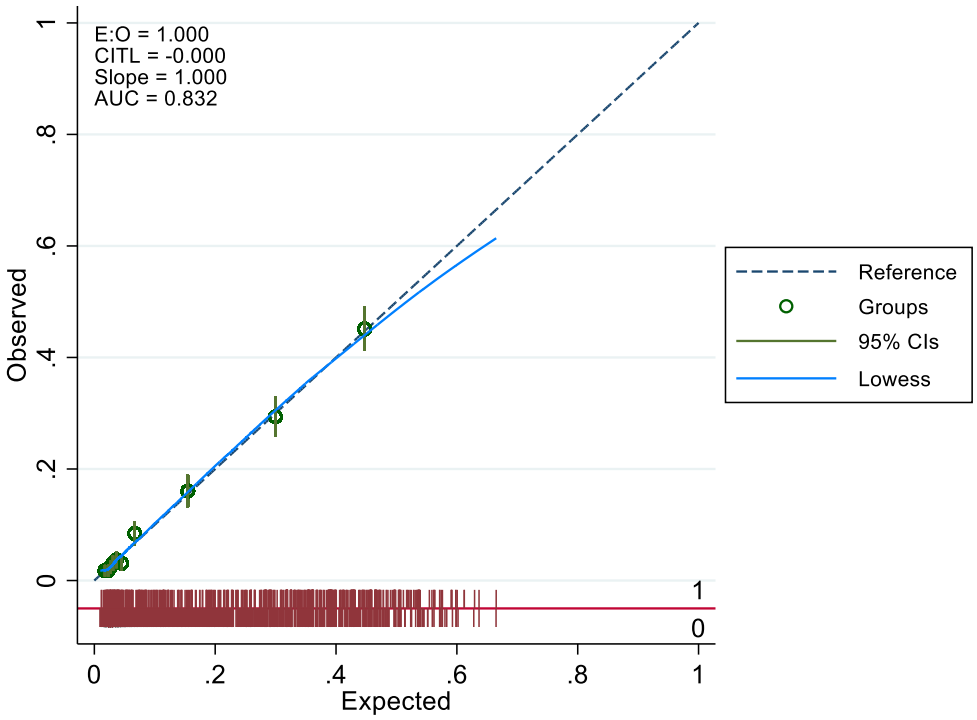


Figure 4.16 Evaluating the calibration of the prediction model for severe brain injury using a calibration belt plot



E:O = Ratio of expected and observed events for model calibration; CITL = calibration-in-the-large for model calibration; Slope = calibration slope for model calibration; AUC = area under the receiver operating characteristic (ROC) curve

Table 4.10 Measures of model assessment for the multivariable prediction model for severe brain injury using logistic regression

Model assessment	**Value**
Akaike Information Criterion (AIC)	3450.067
Bayesian Information Criterion (BIC)	-50168.071
Log-likelihood value (Full Model)	-1698.033
Cragg & Uhler's R^2 (Nagelkerke's R^2)	0.150
Brier score	0.0822

Internal validation: Severe brain injury prediction model

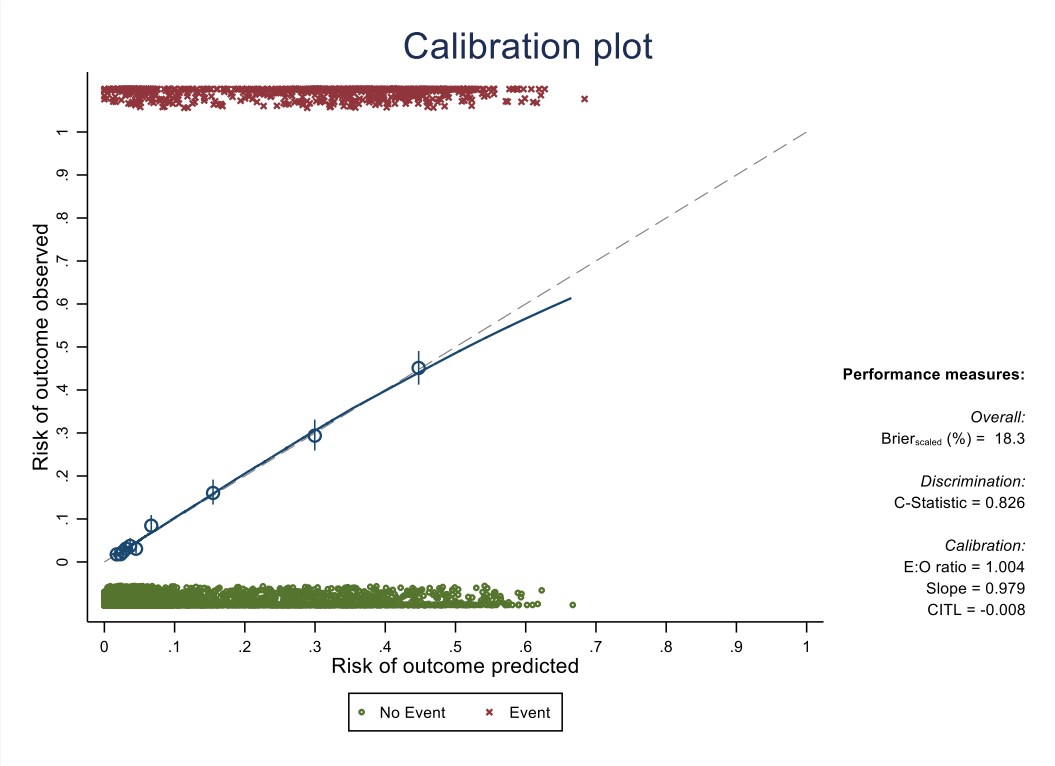
The optimism-adjusted C-statistic was 0.826, which was calculated from 100 bootstrap samples. The bootstrap performance for calibration was similar to the apparent performance (CITL -0.000, slope 1.000). The results of internal validation using a bootstrap validation approach, including the apparent performance, bootstrap performance and shrinkage factors, are presented in **Table 4.11**. The calibration plot is presented in **Figure 4.17**.

Table 4.11 Internal validation using a bootstrap validation approach for prediction model for severe brain injury: Apparent performance, bootstrap performance and shrinkage factors

Apparent performance			**Bootstrap performance (Optimism adjusted)**		
	Value	**95% CI**		**Value**	**Bootstrap 95% CI**
Overall:			**Overall:**		
Brier scaled (%)	19.1		Brier scaled (%)	18.3	
Discrimination:			**Discrimination:**		
C-Statistic	0.832	0.815-0.848	C-Statistic	0.826	0.809-0.843
Calibration:			**Calibration:**		
E:O ratio	1.000		E:O ratio	1.004	0.926-1.056
CITL	-0.000	-0.087-0.087	CITL	-0.079	-0.079-0.103
Slope	1.000	0.930-1.070	Slope	0.979	0.900-1.049
Shrinkage factors					
Heuristic shrinkage	0.981				
Bootstrap shrinkage	0.979				

E:O = Ratio of expected and observed events for model calibration; CITL = calibration-in-the-large for model calibration; Slope = calibration slope for model calibration

Figure 4.17 Internal validation using a bootstrap validation approach: calibration plot of the prediction model for severe brain injury



4.5 Discussion

The aim of a prediction model often falls under two categories: (1) to be used as a clinical prediction tool to inform individual patient care, for instance the CHA_2DS_2-VASc score and the APACHE II classification system, or (2) to be applied to a population to allow for benchmarking and comparison between cohorts, for instance investigating whether a child's predicted outcome score (which is derived from their known characteristics) aligns with their actual observed outcome score, which forms the basis of the CSOR programme.[273] The latter category applies to the prediction models in this study. The results from this chapter demonstrate that it is feasible to utilise routinely collected data to develop models based on known infant and maternal characteristics to predict some short-term neonatal outcomes using NNRD data.

Prediction models were developed for the outcomes of survival to discharge, late-onset sepsis and severe brain injury. For the outcome of survival to discharge, two differing approaches to variable selection were used, one based on literature and another more traditional approach based on AIC. In both models for survival to discharge, discrimination was excellent, but internal calibration was poor. In comparison, the prediction models for late-onset sepsis and severe brain injury performed well both on discrimination and internal calibration. As the literature-based approach resulted in excellent discrimination and internal calibration, a more traditional AIC-based approach to variable selection was not explored. Of the three outcomes, the prediction model for late-onset sepsis performed the best in terms of discrimination (AUROC 0.84), followed by the model for severe brain injury (AUROC 0.83), though the difference in AUROC was small.

Predictors that were common to both the literature-based model and the AIC-based model for survival to discharge included gestational age at birth, mother's ethnicity, Index of Multiple Deprivation (IMD) decile, presence of an additional major congenital anomaly, surgical condition, Apgar score at 5 minutes and maternal smoking during pregnancy. Despite having better internal calibration, the AIC-based model has some disadvantages compared to the literature-based model, such as being more complex with a higher number of predictions in the model. Simpler models are usually preferred due to the principle of parsimony, and too many predictors may increase the risk of overfitting. Furthermore, the model was unable to include neonates with Hirschsprung's disease and included variables that may be more difficult to obtain or may not recorded in other databases, therefore limiting the generalisability and utility of the model beyond the given dataset. Some of the included variables are perhaps less interpretable or explainable, such as mother's blood group, highlighting the tension and difficult balance between the predictive and explanatory power of a model. The literature-based model for survival is advantageous for interpretability, however performs worse on internal calibration, with a calibration belt p-value of <0.002 and thus rejecting the hypothesis of a satisfactory fit. Although it is important to include all data available in the development of the prediction models, it is likely that certain conditions, such as surgical necrotising enterocolitis, may have had greater influence on the model, compared to other conditions with a lower incidence.

Implications for further research

One limitation of utilising the NNRD to develop prediction models was that there was an absence of data pertaining to operative details and condition-specific severity factors, as highlighted in **Chapter 3**. Thus, these could not be included in the prediction models. As these factors are known to influence patient outcomes, the inclusion of these factors would

likely improve the performance of the prediction models. Thus, there is further scope to update the prediction models in future studies should such data be available in a differing database. Similarly, important outcomes, such as total number of operations, were not available in the NNRD, nor was it feasible to investigate long-term outcomes. Therefore, prediction models for these outcomes of interest could not be developed. This warrants further investigation of the utility of other databases of routinely collected data in exploring outcomes following childhood surgery, such as the Hospital Episode Statistics (HES) database. Finally, although robust prediction models have been developed and internally validated using NNRD data, further studies are required to externally validate these models in another database. External validation would more clearly assess the utility and generalisability of the prediction models beyond the database from which they were developed.

Chapter 5

Exploring the utility of Hospital Episode Statistics data to describe the long-term outcomes of children with surgical conditions in England

5.1 Background

In order to improve the management and outcomes of children with a general paediatric surgical condition, there is a need for long-term health outcome data. However, as previously described in **Chapter 2**, it is challenging to both obtain and aggregate long-term outcomes for paediatric surgical conditions due to low population incidences, heterogenous reporting between studies, and variable lengths of follow-up pathways and criteria, particularly for neurodevelopmental follow-up. Long-term health data, by its nature, takes several years to collect prospectively. It requires intensive use of resources and may place an undue burden on patients and their families. Furthermore, recent studies suggest that the COVID-19 pandemic may have contributed to survey and research fatigue, resulting in reduced response rates and greater potential for bias in such studies.[282 283]

As noted previously, routinely collected data could present a potential solution to these issues. Although often collected for a different purpose, the data collection process often requires minimal to no effort on behalf of the patient, parent and clinician, avoiding survey fatigue. Trends in health conditions can be tracked over time across whole populations, as routine clinical care generates large amounts of data. Similar volume analyses were not previously possible and this has launched widespread interest in big data research and machine learning using routinely collected data.[284] This may be particularly advantageous in the investigation of rare conditions, as rigorous research into these conditions may be hampered by inadequate sample sizes and small institutional series, which may be more susceptible to bias and have suboptimal external validity.[285 286]

As demonstrated in **Chapter 3**, it is feasible to utilise existing databases of routinely collected data, specifically the National Neonatal Research Database (NNRD), to

investigate selected short-term outcomes of interest for children with a surgical condition. Conversely, investigating longer-term outcomes across 1, 5 or even 10 years is more challenging, even when using databases of routinely collected data. Whilst data linkage presents new opportunities to combine multiple datasets across a child's lifespan, there are several additional challenges that may present during the data linkage process. It is often costly and time-consuming to access data, there may be technical difficulties in matching records from differing datasets, and bias may be introduced if there are errors during the data linking process.[287 288] Furthermore, identifying information such as name and postcode are often required to link datasets, which may raise concerns regarding privacy and require additional regulatory approvals.[289] The Hospital Episode Statistics (HES) database represents one database of routinely collected data that may allow for long-term health outcomes to be explored without the need for additional record linkage to external databases.

The HES database contains routinely collected clinical and administrative data for all inpatient admissions, outpatient appointments and emergency care attendances occurring within National Health Service (NHS) hospitals across England. It is used for a variety of purposes including service planning, payment of hospitals for the delivery of healthcare, and clinical research.[290 291] Previous studies have validated the HES database for investigating specific conditions and procedures, such as psychiatric conditions, idiopathic inflammatory myopathies and cardiac operations.[35 292 293] However, despite the potential benefits of using the HES database, there are some known limitations. Inaccuracies in diagnostic coding are a cause for concern, as is missing data and clinically important data not being captured.[290] Furthermore, the HES database has been criticised for its lack of clinician input in the early developmental stages of the database.[294] Whilst recent studies

suggest that coding accuracy of the HES database has improved over the years, these aforementioned concerns necessitate further exploration of the utility of the HES database to specifically investigate rare paediatric surgical conditions.[295]

5.2 Chapter aim

The overall aim of this chapter was to explore the utility and feasibility of using the HES database to describe the long-term outcomes for children with one of the six study conditions: Hirschsprung's disease (HD), gastroschisis, oesophageal atresia (OA), congenital diaphragmatic hernia (CDH), posterior urethral valves (PUV) and surgical necrotising enterocolitis (NEC). The utility and feasibility of using HES data to describe long-term outcomes for children with surgical conditions was assessed against the possibility of achieving three specific objectives:

1. To describe the incidence of the six study conditions in England using HES data;
2. To describe the characteristics of the cohort of children with one of the six study conditions in England, and;
3. To report the long-term health outcomes of this cohort at 1-, 5- and 10-year time-points.

5.3 Methods

5.3.1 Study design

A secondary analysis of previously prospectively collected data was undertaken using the HES database.

5.3.2 Data source: HES database

The HES database holds administrative data from all NHS hospitals in England and comes under the Commissioning Data Set. This study uses HES Admitted Patient Care (APC) data, though other HES databases exist and can be linked, such as emergency department attendances, outpatient attendances and adult critical care. Data on deaths, including deaths that occur outside a hospital admission, are available through routine linkage with the death registry held by the Office of National Statistics.[290] The data undergo several data cleaning and quality check processes, such as the application of automated cleaning rules, duplicate identification and removal, advanced person-matching algorithms, feedback to providers where there are missing data, and the publication of data quality reports.[296]

The HES dataset is comprised of "finished consultant episodes" (FCEs), which represent periods of admitted care under a single hospital consultant. If a child is under the care of several consultants during their hospital admission, they may have several FCEs. A "spell" refers to an uninterrupted inpatient admission. In order to allow for analysis of one record per admission, Continuous InPatient Spells (CIPS) are generated from FCEs.[290]

Each CIPS record has a maximum of 20 diagnosis fields and 24 operation fields. In the process of generating CIPS records from FCE records, the first 7 diagnoses of the CIPS record are taken from the last FCE with valid diagnoses, the next 7 diagnoses of the CIPS record are taken from the first 7 diagnoses from the admission episode and the final 6 diagnoses are the 6 most common diagnoses across all FCE records that do not appear in the first 14 diagnoses. For operations, the first 24 operations by date are taken from the FCE records to generate the CIPS record. The HES database uses diagnostic codes from the International Statistical Classification of Diseases and Health Related Problems, 10th

Edition (ICD-10). To record procedures, the Office of Population Censuses and Surveys Classification of Interventions and Procedures Version 4 (OPCS-4) is used.

Data were extracted from the HES database held by the Unit of Health Care Epidemiology (UHCE) and converted into CIPS records by a UHCE data analyst (N Hall). The subsequent data analysis was conducted by the primary author of this thesis (S Sun, DPhil Candidate). All analysis took place on anonymised datasets only. The data were stored on a secure server hosted by the Nuffield Department of Population Health, with security maintained in accordance with Nuffield Department of Population Health operating procedures.

5.3.3 Cohort Development

The initial plan of this study was to identify each study condition based on ICD-10 diagnostic coding alone. For instance, the ICD-10 code *Q43.1: Hirschsprung disease* would be used to identify children with Hirschsprung's disease, and the ICD-10 code *Q79.3: Gastroschisis* would be used to identify children with gastroschisis. However, this resulted in implausible condition incidences and outcomes, such as a significant proportion of CDH and OA children surviving without undergoing an operation when these conditions are largely incompatible with life without surgical correction. Thus, where possible, the identification of children with each study condition was further refined using the presence of a relevant operation code.

Two cohorts were therefore created, Cohort A based on ICD-10 diagnostic coding alone to identify children with a study condition, and Cohort B which was further refined to obtain the most accurate cohort possible to optimise accuracy of including children who truly

have the disease. Most results are presented for Cohort B (i.e. the more accurate of the two based on incidences and outcomes), however the characteristics and the proportion of survivors without an operation are also presented for the cohort based on ICD-10 codes alone (Cohort A) in **Appendix 5.1**. The definition of each cohort is outlined below.

5.3.4 Study participants

5.3.4.1 Cohort A (based on ICD-10 coding):

1. All children who were born and admitted to an NHS hospital in England during the study period (01 January 2005 to 30 November 2022), and;
2. Had a qualifying ICD-10 diagnostic code for one of the six study conditions (i.e. HD, gastroschisis, OA, CDH, PUV or NEC).

The qualifying ICD-10 codes for each surgical condition are outlined in **Table 5.1**.

Table 5.1 Qualifying ICD-10 codes for the study surgical conditions

Surgical condition	**ICD-10 code**
Hirschsprung's disease	Q43.1: Hirschsprung disease
Gastroschisis	Q79.3: Gastroschisis
Oesophageal atresia	Q39.0: Atresia of oesophagus without fistula Q39.1: Atresia of oesophagus with tracheo-oesophageal fistula Q39.2: Congenital tracheo-oesophageal fistula without atresia
Congenital diaphragmatic hernia	Q79.0: Congenital diaphragmatic hernia
Posterior urethral valves	Q64.2: Congenital posterior urethral valves
Necrotising enterocolitis	P77: Necrotizing enterocolitis of newborn P78.0: Perinatal intestinal perforation

5.3.4.2 Cohort B (based on more refined criteria):

A more condition-specific approach was adopted for Cohort B, as outlined below.

Oesophageal atresia and congenital diaphragmatic hernia

Infants with OA and CDH present with clinical complications and are operated on early in life, usually during the neonatal period. It is highly unlikely that a child would survive beyond the first year of life without an operation, as these conditions are often incompatible with life in the absence of further management. However, the sickest infants with the highest condition severity may die before ever receiving an operation.

Therefore, the cohort for OA and CDH was defined as any child who:

1. Was born and admitted to an NHS hospital during the study period (January 2005 to November 2022), and;
2. Had a qualifying ICD diagnosis of the study condition, and;
3. Had a qualifying operation code within the first year of life *or* died during the first year of life.

Hirschsprung's disease and posterior urethral valves

Unlike OA, CDH and surgical NEC, children with HD and PUV may present with clinical complications and be operated on after the first year of life. The inclusion of children who had a qualifying operation code at any time therefore minimises biases which may be caused by exclusion of true cases with a delayed operation.

Children were included in the cohort for HD and PUV if they fulfilled the following criteria:

1. Was born and admitted to an NHS hospital during the study period (January 2005 to November 2022), and;
2. Had a qualifying ICD diagnosis of the study condition, and;
3. Had a qualifying operation code at any time *or* died at any time.

Gastroschisis

Infants with gastroschisis may be treated with a silo on the ward or have a sutureless repair, however this may not always be coded as an operation in the HES dataset and result in a child being erroneously coded as having no operations. In order not to exclude this substantial subset of infants (36% of infants based on the previous BAPS-CASS gastroschisis cohort study)[39] and minimise the possible bias from excluding true cases with a non-operative repair, the gastroschisis cohort is defined as any child who:

1. Was born and admitted to an NHS hospital during the study period (January 2005 to November 2022), and;
2. Had an ICD diagnosis of gastroschisis (ICD-10 code Q79.3), with or without an operation code.

Surgical NEC

Similar to OA and CDH, children with surgical NEC, by definition, will rarely present or have a primary operation after the first year of life.

The cohort for surgical NEC was therefore defined as any child who:

1. Was born and admitted to an NHS hospital during the study period (January 2005 to November 2022), and;
2. Had a qualifying ICD diagnosis of the study condition, and;
3. Had a qualifying operation code within the first year of life

5.3.5 Exclusions

Due to its pathophysiology, PUV is a condition that affects male infants. In the absence of an operation code referring to treatment for posterior urethral valves or a condition relating to differences in sex development, children who were coded as both being female and having posterior urethral valves were excluded on the basis that it could not be ascertained whether the coding of sex or the condition of PUV was erroneous. If a child has a large number of diagnoses in an FCE, some of these diagnoses may be lost during the process of condensing FCEs into CIPS records, as each CIPS record has a maximum of 20 diagnosis fields. Therefore, children were excluded if they did not have a relevant ICD-10 diagnosis of any of the study conditions in the final CIPS database. These exclusions and final cohort numbers are outlined in the results section.

5.3.6 Hierarchy of conditions

Where a child was coded as having two of more of the study conditions, the primary diagnosis was considered to be the most severe condition based on the condition-specific

mortality in **Chapter 3**, with the exception of surgical necrotising enterocolitis, which could develop as a consequence of the presence of another condition, such as gastroschisis. Therefore, the hierarchy of conditions for the primary diagnosis in order from lowest mortality to highest, with the exception of NEC, was:

1. NEC
2. HD
3. Gastroschisis
4. PUV
5. OA
6. CDH (i.e. most severe)

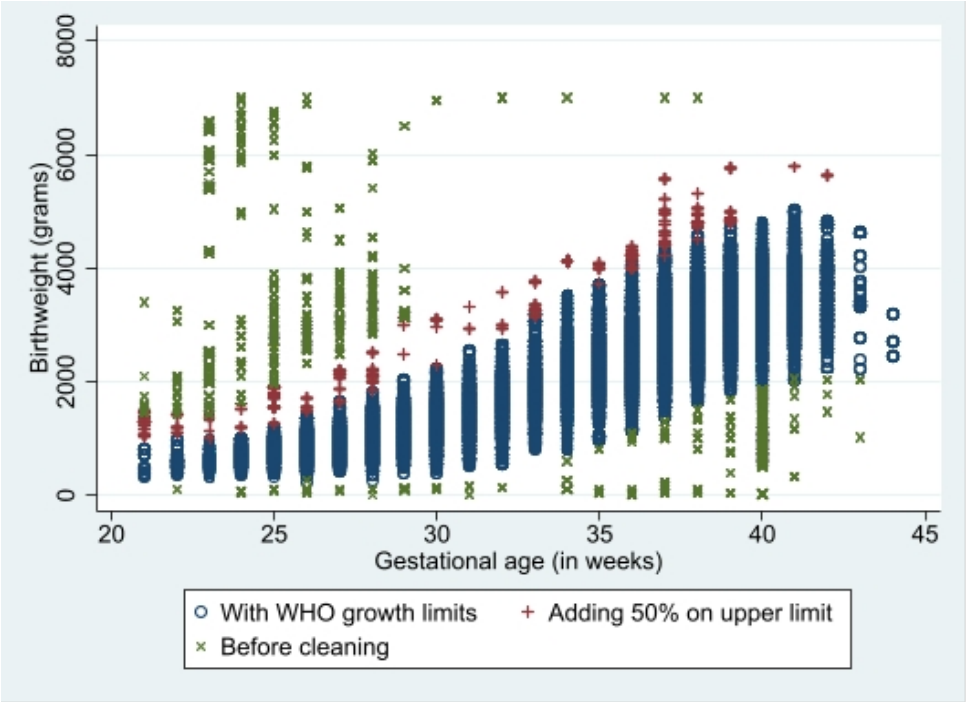
5.3.7 Exposures

5.3.7.1 Gestational age and birthweight

Gestational age at birth was deemed implausible and recorded as missing if the values were less than 21 weeks or greater than 44 weeks. In order to exclude implausible values for birthweight, an upper and lower bound for birthweight was defined based on gestational age and sex using the UK-WHO growth charts (0.4^{th} and 99.6^{th} percentile as the lower and upper bound respectively). However, as these growth parameters were based on 1990 growth reference centiles and the average birthweight of newborns has increased over the years, a 50% increase was added to the value of the upper bound (i.e. the 99.6^{th} percentile) to avoid excluding values that are now plausible due to larger infants.[297 298] The impact of this data cleaning is shown in **Figure 5.1**.

Figure 5.1 The impact of data cleaning on birthweight, before and after the application of UK-WHO growth limits and the addition of 50% on the upper bound

The green crosses represent values deemed to be implausible.



WHO = World Health Organisation

5.3.7.2 Additional major congenital anomaly

The code list for an additional major congenital anomaly was based on the major congenital anomaly definition used in **Chapter 3**, which was developed based on existing code lists by the NNRD-AI (National Neonatal Research Database – Artificial Intelligence) and Harden et al.[256] The NNRD-AI divides major congenital anomalies into two categories: cardiac and non-cardiac. Examples of major cardiac congenital anomalies include tetralogy of Fallot, transposition of the great vessels and hypoplastic left heart syndrome. Examples of major non-cardiac congenital anomalies include spina bifida and chromosomal abnormalities, such as Trisomy 13, 18 and 21. Although there are other definitions of major congenital anomalies, such as the EUROCAT definition, the NNRD-AI definition was used to ensure consistency. As the NNRD uses BadgerNet (Edinburgh, United Kingdom) diagnostic coding and the HES database uses ICD-10 diagnostic coding,

the corresponding ICD codes were mapped onto the Clevermed code list (see **Appendix 5.2**).

Atrial septal defects (including patent foramen ovale) and patent ductus arteriosus were also included to align with previous prospective cohort studies conducted by the British Association of Paediatric Surgeons Congenital Anomalies Surveillance System (BAPS CASS).[299 300] Whilst these conditions may be physiological in preterm infants, they are important anomalies in term infants, which is relevant to a number of the study conditions of interest. As with **Chapter 3**, children were only defined as having an additional major congenital anomaly if they had a relevant diagnosis in addition to the study condition.

5.3.7.3 Condition severity

Condition severity was a binary variable (presence of severe condition vs. non-severe condition), which was based on condition-specific severity markers that were identified in **Chapter 2**. The marker of severity needed to be available in the HES database or identifiable using an ICD-10 diagnostic code. For HD, children were classified as severe if they had pre-operative Hirschsprung-associated enterocolitis (HAEC). Children with gastroschisis were classified as severe if they met the criteria for complex gastroschisis, which was defined as the presence of intestinal atresia, intestinal necrosis, perforation, and/or volvulus. Children with OA were classified as severe if they had Type A OA or a diagnosis of cyanotic spells. Children with CDH were classified as severe if they had a diagnosis of pulmonary hypertension. Children with PUV were classified as severe if they had a diagnosis of acute renal failure.

Infants with surgical necrotising enterocolitis were classified into the following categories, based on first NEC-related operation: (1) resection but no stoma formation, (2) resection and stoma formation, (3) stoma formation but no resection, and (4) other (i.e. suggestive of those infants who were operated on and their abdomen opened but subsequently closed again if nothing could be done due to high condition severity). Infants in the fourth category had the highest mortality and were deemed to have a severe condition.

5.3.8 Outcomes

The outcomes of interest used were the same as those described in **Chapter 3**, which were selected *a priori* and based on outcomes from previously developed core outcome sets that were found to be important to stakeholders, such as parents and clinicians.

The outcomes of interest were:

1. Mortality
2. Number of operations relevant to the surgical condition
3. Number of infections during hospitalisation

As the focus of this chapter was on long-term outcomes, outcomes were reported at 1-, 5- and 10-year timepoints.

5.3.9 Definition of outcomes

5.3.9.1 Mortality

The outcome of mortality and date of death was derived from Office of National Statistics (ONS) death certificates, which are linked to the HES database.

5.3.9.2 Operations

Operations were extracted from fields containing OPCS-4 codes. Operations were classified as either being an emergency or planned operation based on the method of admission. In the HES database, an admission was defined as being elective if there was a time interval between the recorded date of admission and the date of the decision to admit, for instance where the patient was admitted from a waiting list or were booked. Emergency admissions included those admitted from the Accident and Emergency (A&E) department or transfer of a patient from another hospital in an emergency (**Table 5.2**).

Table 5.2 Classification of emergency or planned operation based on the method of admission variable in the HES database

	Method of admission codes from the Hospital Episode Statistics Database
Elective	11 – Waiting list 12 – Booked 13 – Planned 81 – Non-emergency transfer of patient from another hospital
Emergency	21 – A&E 22 – Request by a General Practitioner for immediate admission 23 – Bed Bureau 24 – Consultant Clinic 25 – Admission via the Mental Health Crisis Resolution Team 2A – A&E of another hospital provider 2B – Transfer of a patient from an external hospital 2C – Birth of baby at home, as intended 2D – Other emergency admission 28 – Other, including admission from another A&E, transfer of patient, birth of baby at home 31 – Maternity admission, admitted antepartum 32 – Maternity admission, admitted postpartum 82 – Baby born in hospital 83 – Baby born outside this hospital provider

Operations were further categorised as minor or major, guided by NICE guidelines.[253] Examples of minor procedures included insertion of central venous catheter and colonoscopy. Examples of major procedures included total colectomy, lung transplant and open operations on the mediastinum or abdomen. Operation codes that occurred on the same date were considered to be one operation. For instance, if a child had the OPCS codes *G69.3: Ileectomy and anastomosis of ileum to ileum*, *G73.3: Resection of ileostomy*, and *T41.3: Freeing of adhesions of peritoneum* recorded all on the 1st of January 2010, this was counted as a single operation, rather than three separate operations.

Only relevant operations to the specific surgical condition were flagged as a procedure for each study condition. For instance, the OPCS-4 operation code *M76.5: Endoscopic destruction of urethral valves* was relevant to children with PUV, but not for children with OA; similarly the OPCS operation code *G15.2: Fibreoptic endoscopic balloon dilation of oesophagus* was relevant to children with OA, but not children with HD. Operations were coded into the aforementioned categories by the primary author of this thesis (S Sun, DPhil Candidate) and were discussed with a second study investigator (B Allin, supervisor). Discrepancies were discussed with a third investigator (M Knight, supervisor) and resolved by consensus. The coding of OPCS-4 codes by grade (major vs. minor) and surgical condition is outlined in **Appendix 5.3**. Following coding of operations, the fifty most frequent OPCS-4 codes by surgical condition were checked to ensure there were no additional operation codes that had been missed.

5.3.9.3 Infections

Infections were derived from fields containing ICD-10 diagnostic codes. Codes were categorised as per the ICD-10 classification and included the following infection

categories: central nervous system, eye, ear, circulatory system, respiratory system, gastrointestinal system, skin, musculoskeletal and connective tissue, genitourinary, perinatal, complications of procedures not elsewhere specified, and certain infections and parasitic diseases. To avoid counting duplicate codes (for instance, pneumonia and unspecified acute lower respiratory infection), children could only have one type of infection per spell (i.e. one respiratory system infection per spell). Similarly, to avoid duplicates where the child was coded as both having the causative infectious agent (for instance, Escherichia coli) and the disease manifestation (urinary tract infection), episodes were first screened using disease manifestation codes and then later for infectious agents where no disease manifestation codes were flagged.

5.3.10 Ethics approval

Access to identifiable data was not required for this study. As UHCE only processes pseudonymised data, ethics committee approval was not required.

5.3.11 Statistical analysis

Statistical analysis was conducted using Stata/ MP Version 17.0 (StataCorp LLC 2015: Texas, USA). As whole-population data was used, a power calculation was not performed. Incidence was calculated for each study condition per 100,000 livebirths and 95% confidence intervals were derived from the exact binomial distribution. Descriptive statistics were used to describe key characteristics of the cohort and outcomes. These were described using counts and proportions for categorical variables and medians for non-normally distributed continuous variables. A Kaplan-Meier plot was used to depict cumulative survival by surgical condition.

The outcome of mortality is presented for three cohorts. Children in Cohort 1 had at least 1 year of follow-up and were born between 01 January 2005 and 30 November 2021. Children in Cohort 2 had at least 5-years of follow-up and were born between 01 January 2005 and 30 November 2017. Children in Cohort 3 had at least 10 years of follow-up and were born between 01 January 2005 and 30 November 2012. As the most severe children will die before being able to be operated on several times and some study conditions may present beyond the neonatal period, the outcomes of number of operations and infections were reported amongst survivors and those who had hospital admissions during the age period of interest. For instance, children with HD and PUV may present after the first year of life. Those that presented after the first year of life but before the age of 5 were therefore included in the 5-year and 10-year outcome tables. Total number of operations and infections were reported according to the following categories: 1, 2, 3, and 4 or greater. Long-term outcomes at 1, 5 and 10 years were reported for children born between 2005 and 2012.

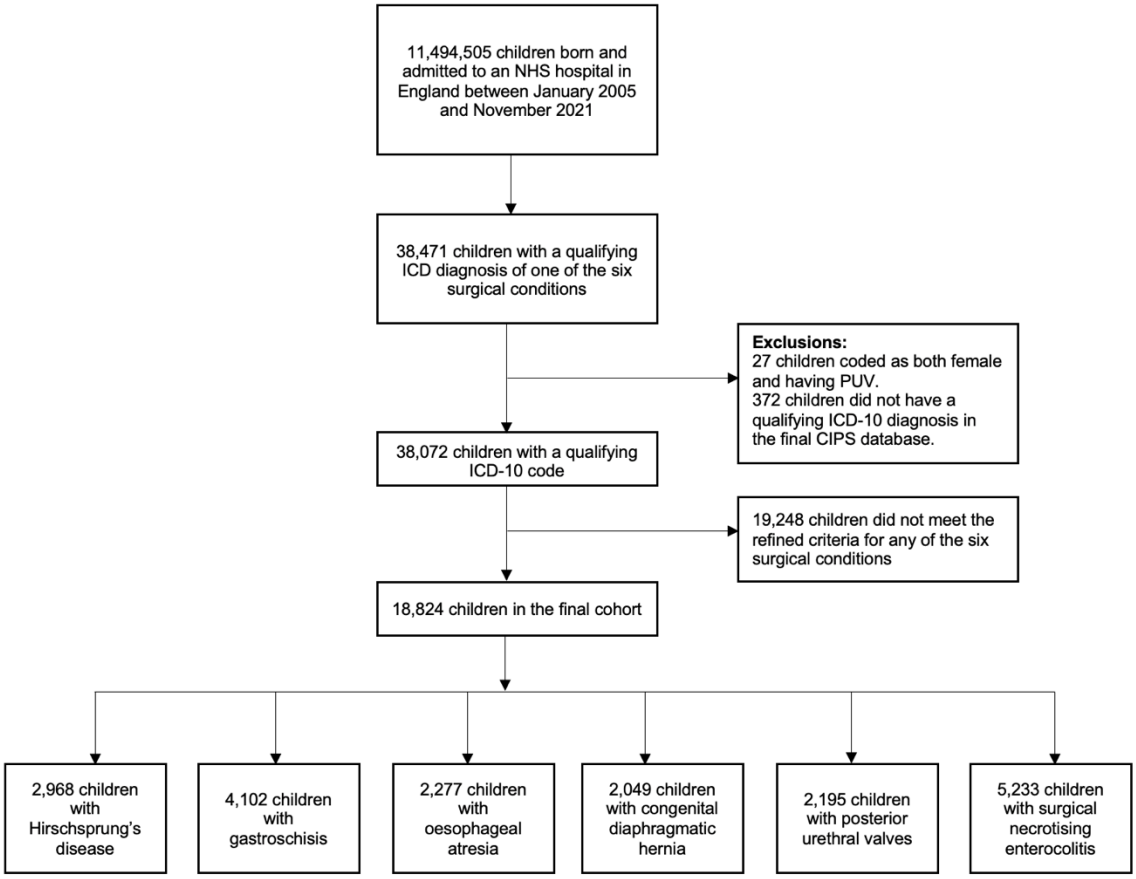
5.4 Results

Selected characteristics of the cohort defined by ICD-10 diagnostic codes alone (*Cohort A*) is outlined in **Appendix 5.1.1**. Based on the presence of a qualifying ICD diagnostic code alone, 32.3% (n=2846) of CDH survivors and 17.2% of OA survivors (n=669) had no operations, which is implausible given the nature of these conditions (**Appendix 5.1.2**). As the cohort based on more refined criteria (*Cohort B*), including the use of OPCS codes, was more accurate based on characteristics and outcomes, the results of this cohort are reported in this section.

5.4.1 Cohort

A total of 18,824 children were included in the cohort, of whom there were 2968 (15.8%) children with HD, 4102 (21.8%) with gastroschisis, 2277 (12.1%) with OA, 2049 (10.9%) with CDH, 2195 (11.7%) with PUV and 5233 (27.8%) with surgical NEC. A flowchart of the cohort is illustrated in **Figure 5.2**.

Figure 5.2 Flow diagram of cohort



5.4.2 Selected characteristics of children admitted to an NHS hospital with a surgical condition

Children with surgical NEC had the lowest median birthweight at 980g (IQR 730-1716), whilst children with HD had the highest median birthweight at 3350g (2940-3700). Children with OA had the highest proportion of children with an additional major congenital anomaly (75.1%, n=1709), followed by children with surgical NEC (62.2%, n=3253), whilst children with PUV had the lowest proportion of children with an additional major congenital anomaly (21.3%, n=468). Children of white ethnicity comprised 73.2% (n=13,778) of the cohort. Nearly 1 in 5 children with surgical NEC

belonged to the most deprived IMD decile (IMD decile 1). The selected characteristics of children with a surgical condition in England are outlined in **Table 5.3**.

Table 5.3 Selected characteristics of children born and admitted to an NHS hospital between January 2005 – November 2022 with one of the six study conditions

	Hirschsprung's Disease N=2,968	Gastroschisis N=4,102	Oesophageal Atresia N=2,277	Congenital Diaphragmatic Hernia N=2,049	Posterior Urethral Valves N=2,195	Surgical Necrotising Enterocolitis N=5,233	Total N=18,824
Birthweight (grams)	3350 (2940-3700)	2370 (2020-2725)	2530 (1910-3070)	2920 (2400-3349)	3310 (2880-3660)	980 (730-1716)	2540 (1620-3220)
Gestational age (in weeks)*	39 (38-40)	36 (35-37)	37 (34-39)	38 (36-39)	38 (37-40)	27 (25-32)	37 (32-39)
Sex							
Male	2,189 (73.8%)	2,116 (51.6%)	1,307 (57.4%)	1,178 (57.5%)	2,194 (100.0%)	3,165 (60.5%)	12,149 (64.5%)
Female	779 (26.2%)	1,979 (48.2%)	968 (42.5%)	865 (42.2%)	0 (0.0%)	2,065 (39.5%)	6,656 (35.4%)
Indeterminate	0 (0.0%)	5 (0.1%)	1 (0.0%)	3 (0.1%)	0 (0.0%)	1 (0.0%)	10 (0.1%)
Missing	0 (0.0%)	2 (0.0%)	1 (0.0%)	3 (0.1%)	1 (0.0%)	2 (0.0%)	9 (0.0%)
Secondary study condition							
Hirschsprung's Disease	-	5 (0.1%)	1 (0.0%)	0 (0.0%)	4 (0.2%)	0 (0.0%)	10 (0.1%)
Gastroschisis	0 (0.0%)	-	2 (0.1%)	7 (0.3%)	2 (0.1%)	0 (0.0%)	11 (0.1%)
Oesophageal Atresia	0 (0.0%)	0 (0.0%)	-	19 (0.9%)	0 (0.0%)	0 (0.0%)	19 (0.1%)
Posterior Urethral Valves	0 (0.0%)	0 (0.0%)	5 (0.2%)	1 (0.0%)	-	0 (0.0%)	6 (0.0%)
Necrotising Enterocolitis	186 (6.3%)	328 (8.0%)	76 (3.3%)	31 (1.5%)	10 (0.5%)	-	631 (3.4%)
No secondary condition	2,782 (93.7%)	3,769 (91.9%)	2,193 (96.3%)	1,991 (97.2%)	2,179 (99.3%)	5,233 (100.0%)	18,147 (96.4%)
Additional MCA							
No	2,189 (73.8%)	3,046 (74.3%)	568 (24.9%)	1,039 (50.7%)	1,727 (78.7%)	1,980 (37.8%)	10,549 (56.0%)
Yes	779 (26.2%)	1,056 (25.7%)	1,709 (75.1%)	1,010 (49.3%)	468 (21.3%)	3,253 (62.2%)	8,275 (44.0%)

Data are presented as median (IQR) for continuous measures, and n (%) for categorical measures. MCA = major congenital anomaly *Missingness: 35.35%

Table 5.3 (continued)

	Hirschsprung's Disease N=2,968	Gastroschisis N=4,102	Oesophageal Atresia N=2,277	Congenital Diaphragmatic Hernia N=2,049	Posterior Urethral Valves N=2,195	Surgical Necrotising Enterocolitis N=5,233	Total N=18,824
Ethnicity							
White	2,197 (74.0%)	3,571 (87.1%)	1,757 (77.2%)	1,395 (68.1%)	1,355 (61.7%)	3,503 (66.9%)	13,778 (73.2%)
Mixed	146 (4.9%)	190 (4.6%)	85 (3.7%)	62 (3.0%)	118 (5.4%)	272 (5.2%)	873 (4.6%)
Asian or Asian British	254 (8.6%)	65 (1.6%)	222 (9.7%)	297 (14.5%)	399 (18.2%)	672 (12.8%)	1,909 (10.1%)
Black or Black British	162 (5.5%)	65 (1.6%)	69 (3.0%)	71 (3.5%)	183 (8.3%)	486 (9.3%)	1,036 (5.5%)
Other	125 (4.2%)	83 (2.0%)	81 (3.6%)	67 (3.3%)	81 (3.7%)	170 (3.2%)	607 (3.2%)
Unknown	84 (2.8%)	128 (3.1%)	63 (2.8%)	157 (7.7%)	59 (2.7%)	130 (2.5%)	621 (3.3%)
IMD rank	12574 (5388-21647)	10259 (4554-18110)	13459 (5846-22342)	11997 (5145-20630)	12743 (6120-22102)	10693 (4483-19592)	11539 (5047-20347)
IMD decile							
1 (Most deprived)	451 (15.2%)	697 (17.0%)	340 (14.9%)	342 (16.7%)	293 (13.3%)	994 (19.0%)	3,117 (16.6%)
2	394 (13.3%)	589 (14.4%)	254 (11.2%)	263 (12.8%)	274 (12.5%)	788 (15.1%)	2,562 (13.6%)
3	336 (11.3%)	536 (13.1%)	253 (11.1%)	246 (12.0%)	276 (12.6%)	641 (12.2%)	2,288 (12.2%)
4	273 (9.2%)	435 (10.6%)	234 (10.3%)	213 (10.4%)	247 (11.3%)	583 (11.1%)	1,985 (10.5%)
5	264 (8.9%)	377 (9.2%)	230 (10.1%)	202 (9.9%)	204 (9.3%)	471 (9.0%)	1,748 (9.3%)
6	273 (9.2%)	332 (8.1%)	185 (8.1%)	170 (8.3%)	181 (8.2%)	386 (7.4%)	1,527 (8.1%)
7	226 (7.6%)	265 (6.5%)	189 (8.3%)	150 (7.3%)	180 (8.2%)	416 (7.9%)	1,426 (7.6%)
8	241 (8.1%)	202 (4.9%)	183 (8.0%)	131 (6.4%)	173 (7.9%)	344 (6.6%)	1,274 (6.8%)
9	201 (6.8%)	193 (4.7%)	191 (8.4%)	133 (6.5%)	153 (7.0%)	268 (5.1%)	1,139 (6.1%)
10 (Least deprived)	163 (5.5%)	135 (3.3%)	141 (6.2%)	124 (6.1%)	147 (6.7%)	242 (4.6%)	952 (5.1%)
Missing	146 (4.9%)	341 (8.3%)	77 (3.4%)	75 (3.7%)	67 (3.1%)	100 (1.9%)	806 (4.3%)

Data are presented as median (IQR) for continuous measures, and n (%) for categorical measures. MCA = major congenital anomaly

5.4.3 Condition incidences

Between 2012 and 2021 (inclusive), there were 7,047,422 live births in the UK, based on data from the Office of National Statistics (ONS).[258] During this period, there were 1661 children admitted to an NHS hospital with HD, 2049 children with gastroschisis, 1285 children with OA, 1159 children with CDH, 1270 children with PUV and 3145 children with surgical NEC.

The incidence of surgical NEC in England was highest amongst the six surgical conditions (44.6 per 100,000 live births), followed by gastroschisis (29.1 per 100,000 live births). Children with CDH and PUV had the lowest incidences (16.5 and 18.0 per 100,000 live births respectively). The incidence of each surgical condition based on HES data is outlined in **Table 5.4**.

Table 5.4 Incidence of children admitted to an NHS hospital with specific surgical conditions in England per 100,000 live births

Condition	**Incidence (95% CI)** *per 100,000 live births*
Hirschsprung's disease	23.6 (22.5-24.7)
Gastroschisis	29.1 (27.8-30.4)
Oesophageal atresia	18.2 (17.3-19.3)
Congenital diaphragmatic hernia	16.5 (15.5-17.4)
Posterior urethral valves	18.0 (17.0-19.0)
Surgical necrotising enterocolitis	44.6 (43.1-46.2)

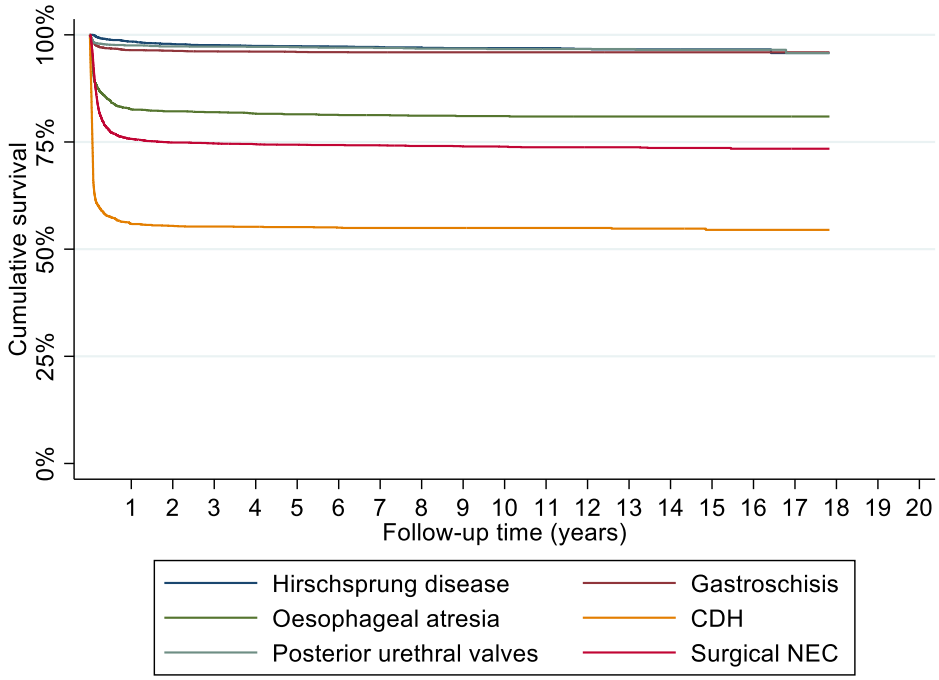
5.4.4 Outcomes

The majority of deaths across the six surgical conditions occurred within the first year of life. The cumulative survival by each surgical condition is depicted in **Figure 5.3**. The outcomes of mortality, total number of operations and total number of infections are reported below for each of the three cohorts.

5.4.5 Outcomes of Cohort 1 (at least one-year follow-up): children with a surgical condition born between 01 January 2005 and 30 November 2021)

Children with CDH had the highest crude mortality within 1 year (44.1%), followed by those with surgical NEC (24.2%), OA (17.5%), gastroschisis (3.6%), PUV (2.5%) and HD (1.6%), as outlined in **Table 5.5**. Amongst survivors, the proportion of infants requiring four or more operations within the first year of life was highest amongst infants with Hirschsprung's disease (37.7%, n=1,025) and lowest amongst infants with gastroschisis (8.4%, n=319) and congenital diaphragmatic hernia (9.5%, n=104) (**Table 5.6**). Whilst 43.9% of infants (n=6,678) did not have any infections within the first year of life,15.9% of infants (n=284) with OA and 14.9% of infants (n=3,812) with surgical NEC had four or more infections within the first year of life (**Table 5.7**).

Figure 5.3 Cumulative survival by surgical condition



CDH = congenital diaphragmatic hernia; NEC = necrotising enterocolitis

Table 5.5 Mortality within 1-year of age amongst children with a surgical condition born between 01 January 2005 and 30 November 2021

	Hirschsprung's Disease N=2,877	Gastroschisis N=3,971	Oesophageal Atresia N=2,167	Congenital Diaphragmatic Hernia N=1,962	Posterior Urethral Valves N=2,131	Surgical Necrotising Enterocolitis N=5,029	Total N=18,137
Survived	2,832 (98.4%)	3,827 (96.4%)	1,787 (82.5%)	1,097 (55.9%)	2,077 (97.5%)	3,812 (75.8%)	15,432 (85.1%)
Died	45 (1.6%)	144 (3.6%)	380 (17.5%)	865 (44.1%)	54 (2.5%)	1,217 (24.2%)	2,705 (14.9%)

Data are presented as n (%).

Table 5.6 Total number of operations within 1-year amongst survivors born between 01 January 2005 and 30 November 2021 and admitted to a hospital in England before the age of 1

	Hirschsprung's Disease N=2,719	Gastroschisis N=3,807	Oesophageal Atresia N=1,787	Congenital Diaphragmatic Hernia N=1,097	Posterior Urethral Valves N=1,973	Surgical Necrotising Enterocolitis N=3,812	Total N=15,195
0	279 (10.3%)	1,596 (41.9%)	0 (0.0%)	0 (0.0%)	420 (21.3%)	0 (0.0%)	2,295 (15.1%)
1	393 (14.5%)	1,030 (27.1%)	544 (30.4%)	618 (56.3%)	460 (23.3%)	826 (21.7%)	3,871 (25.5%)
2	558 (20.5%)	560 (14.7%)	334 (18.7%)	273 (24.9%)	571 (28.9%)	1,020 (26.8%)	3,316 (21.8%)
3	464 (17.1%)	302 (7.9%)	243 (13.6%)	102 (9.3%)	282 (14.3%)	804 (21.1%)	2,197 (14.5%)
4+	1,025 (37.7%)	319 (8.4%)	666 (37.3%)	104 (9.5%)	240 (12.2%)	1,162 (30.5%)	3,516 (23.1%)

Data are presented as n (%).

Table 5.7 Total number of infections within 1-year amongst survivors born between 01 January 2005 and 30 November 2021 and admitted to a hospital in England before the age of 1

	Hirschsprung's Disease N=2,719	**Gastroschisis N=3,807**	**Oesophageal Atresia N=1,787**	**Congenital Diaphragmatic Hernia N=1,097**	**Posterior Urethral Valves N=1,973**	**Surgical Necrotising Enterocolitis N=3,812**	**Total N=15,195**
0	1,433 (52.7%)	1,989 (52.2%)	657 (36.8%)	536 (48.9%)	864 (43.8%)	1,199 (31.5%)	6,678 (43.9%)
1	620 (22.8%)	1,027 (27.0%)	415 (23.2%)	266 (24.2%)	416 (21.1%)	1,036 (27.2%)	3,780 (24.9%)
2	293 (10.8%)	417 (11.0%)	256 (14.3%)	116 (10.6%)	285 (14.4%)	636 (16.7%)	2,003 (13.2%)
3	148 (5.4%)	205 (5.4%)	175 (9.8%)	73 (6.7%)	145 (7.3%)	374 (9.8%)	1,120 (7.4%)
4+	225 (8.3%)	169 (4.4%)	284 (15.9%)	106 (9.7%)	263 (13.3%)	567 (14.9%)	1,614 (10.6%)

Data are presented as n (%).

5.4.6 Outcomes of Cohort 2 (at least 5 years of follow-up): children with a surgical condition born between 01 January 2005 and 30 November 2017)

Of children with a study condition born between 2005 and 2017, the mortality was 14.8% (n=2,131) within the first year of life and 15.8% (n=2,270) within the first five years of life (**Table 5.8 and Table 5.9**). The number of operations amongst survivors within 1 and 5 years of life are reported in **Table 5.10** and

Table 5.11. Amongst survivors, 55.1% of children (n=6,548) had at least one admission with infection within the first year of life and 69.6% of children (n=8,370) had at least one admission with infection with the first five years of life (**Table 5.12** and **Table 5.13**).

Table 5.8 Mortality within 1-year of age amongst children with a surgical condition born between 01 January 2005 and 30 November 2017

	Hirschsprung's Disease N=2,282	Gastroschisis N=3,294	Oesophageal Atresia N=1,706	Congenital Diaphragmatic Hernia N=1,537	Posterior Urethral Valves N=1,672	Surgical Necrotising Enterocolitis N=3,873	Total N=14,364
Survived	2,241 (98.2%)	3,173 (96.3%)	1,405 (82.4%)	857 (55.8%)	1,629 (97.4%)	2,928 (75.6%)	12,233 (85.2%)
Died	41 (1.8%)	121 (3.7%)	301 (17.6%)	680 (44.2%)	43 (2.6%)	945 (24.4%)	2,131 (14.8%)

Data are presented as n (%).

Table 5.9 Mortality within 5-years of age amongst children with a surgical condition born between 01 January 2005 and 30 November 2017

	Hirschsprung's Disease N=2,282	Gastroschisis N=3,294	Oesophageal Atresia N=1,706	Congenital Diaphragmatic Hernia N=1,537	Posterior Urethral Valves N=1,672	Surgical Necrotising Enterocolitis N=3,873	Total N=14,364
Survived	2,213 (97.0%)	3,158 (95.9%)	1,384 (81.1%)	846 (55.0%)	1,621 (96.9%)	2,872 (74.2%)	12,094 (84.2%)
Died	69 (3.0%)	136 (4.1%)	322 (18.9%)	691 (45.0%)	51 (3.1%)	1,001 (25.8%)	2,270 (15.8%)

Data are presented as n (%).

Table 5.10 Total number of operations within 1-year amongst survivors born between 01 January 2005 and 30 November 2017 and admitted to a hospital in England before the age of 1

	Hirschsprung's Disease N=2,111	Gastroschisis N=3,140	Oesophageal Atresia N=1,384	Congenital Diaphragmatic Hernia N=846	Posterior Urethral Valves N=1,523	Surgical Necrotising Enterocolitis N=2,872	Total N=11,876
0	238 (11.3%)	1,339 (42.6%)	0 (0.0%)	0 (0.0%)	374 (24.6%)	0 (0.0%)	1,951 (16.4%)
1	318 (15.1%)	861 (27.4%)	453 (32.7%)	487 (57.6%)	365 (24.0%)	674 (23.5%)	3,158 (26.6%)
2	466 (22.1%)	447 (14.2%)	263 (19.0%)	193 (22.8%)	435 (28.6%)	807 (28.1%)	2,611 (22.0%)
3	361 (17.1%)	236 (7.5%)	190 (13.7%)	81 (9.6%)	189 (12.4%)	577 (20.1%)	1,634 (13.8%)
4+	728 (34.5%)	257 (8.2%)	478 (34.5%)	85 (10.0%)	160 (10.5%)	814 (28.3%)	2,522 (21.2%)

Table 5.11 Total number of operations within 5 years amongst survivors born between 01 January 2005 and 30 November 2017 and admitted to a hospital in England before the age of 5

	Hirschsprung's Disease N=2,190	Gastroschisis N=3,152	Oesophageal Atresia N=1,384	Congenital Diaphragmatic Hernia N=846	Posterior Urethral Valves N=1,578	Surgical Necrotising Enterocolitis N=2,872	Total N=12,022
0	73 (3.3%)	1,136 (36.0%)	0 (0.0%)	0 (0.0%)	188 (11.9%)	0 (0.0%)	1,397 (11.6%)
1	277 (12.6%)	853 (27.1%)	224 (16.2%)	428 (50.6%)	254 (16.1%)	578 (20.1%)	2,614 (21.7%)
2	379 (17.3%)	504 (16.0%)	179 (12.9%)	192 (22.7%)	430 (27.2%)	732 (25.5%)	2,416 (20.1%)
3	318 (14.5%)	278 (8.8%)	191 (13.8%)	96 (11.3%)	219 (13.9%)	541 (18.8%)	1,643 (13.7%)
4+	1143 (52.2%)	381 (12.1%)	790 (57.1%)	130 (15.4%)	487 (30.9%)	1,021 (35.6%)	3,952 (32.9%)

Note: Includes children who were admitted to a hospital in England after the first year of age.

Table 5.12 Total number of admissions with infection within 1-year amongst survivors born between 01 January 2005 and 30 November 2017 and admitted to a hospital in England before the age of 1

	Hirschsprung's Disease	Gastroschisis	Oesophageal Atresia	Congenital Diaphragmatic Hernia	Posterior Urethral Valves	Surgical Necrotising Enterocolitis	Total
	N=2,111	N=3,140	N=1,384	N=846	N=1,523	N=2,872	N=11,876
0	1,152 (54.6%)	1,656 (52.7%)	522 (37.7%)	410 (48.5%)	685 (45.0%)	903 (31.4%)	5,328 (44.9%)
1	460 (21.8%)	827 (26.3%)	322 (23.3%)	201 (23.8%)	307 (20.2%)	777 (27.1%)	2,894 (24.4%)
2	224 (10.6%)	352 (11.2%)	197 (14.2%)	94 (11.1%)	225 (14.8%)	472 (16.4%)	1,564 (13.2%)
3	106 (5.0%)	165 (5.3%)	127 (9.2%)	56 (6.6%)	119 (7.8%)	289 (10.1%)	862 (7.3%)
4+	169 (8.0%)	140 (4.5%)	216 (15.6%)	85 (10.0%)	187 (12.3%)	431 (15.0%)	1,228 (10.3%)

Table 5.13 Total number of admissions with infection within 5 years amongst survivors born between 01 January 2005 and 30 November 2017 and admitted to a hospital in England before the age of 5

	Hirschsprung's Disease	Gastroschisis	Oesophageal Atresia	Congenital Diaphragmatic Hernia	Posterior Urethral Valves	Surgical Necrotising Enterocolitis	Total
	N=2,190	N=3,152	N=1,384	N=846	N=1,578	N=2,872	N=12,022
0	748 (34.2%)	1,310 (41.6%)	269 (19.4%)	279 (33.0%)	451 (28.6%)	595 (20.7%)	3,652 (30.4%)
1	453 (20.7%)	795 (25.2%)	245 (17.7%)	195 (23.0%)	301 (19.1%)	555 (19.3%)	2,544 (21.2%)
2	295 (13.5%)	446 (14.1%)	172 (12.4%)	102 (12.1%)	208 (13.2%)	423 (14.7%)	1,646 (13.7%)
3	181 (8.3%)	204 (6.5%)	143 (10.3%)	71 (8.4%)	175 (11.1%)	305 (10.6%)	1,079 (9.0%)
4+	513 (23.4%)	397 (12.6%)	555 (40.1%)	199 (23.5%)	443 (28.1%)	994 (34.6%)	3,101 (25.8%)

Note: Includes children who were admitted to a hospital in England after the first year of age.

5.4.7 Outcomes of Cohort 3 (at least 10 years of follow-up): children with a surgical condition born between 01 January 2005 and 30 November 2012)

In the cohort of children who were born between 2005 and 2012, the 1-year mortality was 15.4% (n=1,378), the 5-year mortality was 16.4% (n=1,469) and the 10-year mortality was 16.7% (n=1,493) (**Table 5.14, Table 5.15 and Table 5.16**). The proportion of survivors who had four or more operations increased from 18.6% (n=1,356) at 1 year, to 29.7% (n=2,189) at 5 years, to 34.6% (n=2,570) at 10 years (**Table 5.17, Table 5.18 and Table 5.19**). The number of infections amongst survivors at 1 year, 5 years and 10 years is outlined in **Table 5.20, Table 5.21 and Table 5.22.**

Table 5.14 Mortality within 1-year of age amongst children with a surgical condition born between 01 January 2005 and 30 November 2012

	Hirschsprung's Disease N=1,414	Gastroschisis N=2,166	Oesophageal Atresia N=1,044	Congenital Diaphragmatic Hernia N=929	Posterior Urethral Valves N=991	Surgical Necrotising Enterocolitis N=2,388	Total N=8,932
Survived	1,382 (97.7%)	2,081 (96.1%)	868 (83.1%)	521 (56.1%)	971 (98.0%)	1,731 (72.5%)	7,554 (84.6%)
Died	32 (2.3%)	85 (3.9%)	176 (16.9%)	408 (43.9%)	20 (2.0%)	657 (27.5%)	1,378 (15.4%)

Data are presented as n (%).

Table 5.15 Mortality within 5-years of age amongst children with a surgical condition born between 01 January 2005 and 30 November 2012

	Hirschsprung's Disease N=1,414	Gastroschisis N=2,166	Oesophageal Atresia N=1,044	Congenital Diaphragmatic Hernia N=929	Posterior Urethral Valves N=991	Surgical Necrotising Enterocolitis N=2,388	Total N=8,932
Survived	1,359 (96.1%)	2,069 (95.5%)	853 (81.7%)	515 (55.4%)	965 (97.4%)	1,702 (71.3%)	7,463 (83.6%)
Died	55 (3.9%)	97 (4.5%)	191 (18.3%)	414 (44.6%)	26 (2.6%)	686 (28.7%)	1,469 (16.4%)

Data are presented as n (%).

Table 5.16 Mortality within 10-years of age amongst children with a surgical condition born between 01 January 2005 and 30 November 2012

	Hirschsprung's Disease N=1,414	Gastroschisis N=2,166	Oesophageal Atresia N=1,044	Congenital Diaphragmatic Hernia N=929	Posterior Urethral Valves N=991	Surgical Necrotising Enterocolitis N=2,388	Total N=8,932
Survived	1,353 (95.7%)	2,069 (95.5%)	848 (81.2%)	513 (55.2%)	961 (97.0%)	1,695 (71.0%)	7,439 (83.3%)
Died	61 (4.3%)	97 (4.5%)	196 (18.8%)	416 (44.8%)	30 (3.0%)	693 (29.0%)	1,493 (16.7%)

Data are presented as n (%).

Table 5.17 Total number of operations within 1-year amongst survivors born between 01 January 2005 and 30 November 2012 and admitted to a hospital in England before the age of 1

	Hirschsprung's Disease N=1,279	Gastroschisis N=2,060	Oesophageal Atresia N=848	Congenital Diaphragmatic Hernia N=513	Posterior Urethral Valves N=888	Surgical Necrotising Enterocolitis N=1,695	Total N=7,283
0	142 (11.1%)	898 (43.6%)	0 (0.0%)	0 (0.0%)	268 (30.2%)	0 (0.0%)	1,308 (18.0%)
1	227 (17.7%)	576 (28.0%)	311 (36.7%)	315 (61.4%)	215 (24.2%)	447 (26.4%)	2,091 (28.7%)
2	311 (24.3%)	275 (13.3%)	165 (19.5%)	112 (21.8%)	235 (26.5%)	471 (27.8%)	1,569 (21.5%)
3	222 (17.4%)	145 (7.0%)	116 (13.7%)	45 (8.8%)	91 (10.2%)	340 (20.1%)	959 (13.2%)
4+	377 (29.5%)	166 (8.1%)	256 (30.2%)	41 (8.0%)	79 (8.9%)	437 (25.8%)	1,356 (18.6%)

Data are presented as n (%).

Table 5.18 Total number of operations within 5-years amongst survivors born between 01 January 2005 and 30 November 2012 and admitted to a hospital in England before the age of 5

	Hirschsprung's Disease N=1,334	Gastroschisis N=2,065	Oesophageal Atresia N=848	Congenital Diaphragmatic Hernia N=513	Posterior Urethral Valves N=927	Surgical Necrotising Enterocolitis N=1,695	Total N=7,382
0	53 (4.0%)	763 (36.9%)	0 (0.0%)	0 (0.0%)	164 (17.7%)	0 (0.0%)	980 (13.3%)
1	199 (14.9%)	569 (27.6%)	160 (18.9%)	277 (54.0%)	149 (16.1%)	387 (22.8%)	1,741 (23.6%)
2	259 (19.4%)	324 (15.7%)	121 (14.3%)	112 (21.8%)	230 (24.8%)	437 (25.8%)	1,483 (20.1%)
3	197 (14.8%)	174 (8.4%)	129 (15.2%)	59 (11.5%)	114 (12.3%)	316 (18.6%)	989 (13.4%)
4+	626 (46.9%)	235 (11.4%)	438 (51.7%)	65 (12.7%)	270 (29.1%)	555 (32.7%)	2,189 (29.7%)

Data are presented as n (%). **Note:** Includes children who were admitted to a hospital in England after the first year of age.

Table 5.19 Total number of operations within 10-years amongst survivors born between 01 January 2005 and 30 November 2012 and admitted to a hospital in England before the age of 10

	Hirschsprung's Disease N=1,349	Gastroschisis N=2,068	Oesophageal Atresia N=848	Congenital Diaphragmatic Hernia N=513	Posterior Urethral Valves N=954	Surgical Necrotising Enterocolitis N=1,695	Total N=7,427
0	8 (0.6%)	730 (35.3%)	0 (0.0%)	0 (0.0%)	63 (6.6%)	0 (0.0%)	801 (10.8%)
1	195 (14.5%)	567 (27.4%)	133 (15.7%)	265 (51.7%)	139 (14.6%)	375 (22.1%)	1,674 (22.5%)
2	244 (18.1%)	329 (15.9%)	103 (12.1%)	109 (21.2%)	177 (18.6%)	416 (24.5%)	1,378 (18.6%)
3	191 (14.2%)	180 (8.7%)	103 (12.1%)	62 (12.1%)	150 (15.7%)	318 (18.8%)	1,004 (13.5%)
4+	711 (52.7%)	262 (12.7%)	509 (60.0%)	77 (15.0%)	425 (44.5%)	586 (34.6%)	2,570 (34.6%)

Data are presented as n (%). **Note:** Includes children who were admitted to a hospital in England after the first year of age.

Table 5.20 Total number of admissions with infection within 1 year amongst survivors born between 01 January 2005 and 30 November 2012 and admitted to a hospital in England before the age of 1

	Hirschsprung's Disease N=1,279	Gastroschisis N=2,060	Oesophageal Atresia N=848	Congenital Diaphragmatic Hernia N=513	Posterior Urethral Valves N=888	Surgical Necrotising Enterocolitis N=1,695	Total N=7,283
0	768 (60.0%)	1,139 (55.3%)	334 (39.4%)	260 (50.7%)	440 (49.5%)	586 (34.6%)	3,527 (48.4%)
1	280 (21.9%)	536 (26.0%)	199 (23.5%)	116 (22.6%)	164 (18.5%)	474 (28.0%)	1,769 (24.3%)
2	108 (8.4%)	223 (10.8%)	121 (14.3%)	58 (11.3%)	127 (14.3%)	259 (15.3%)	896 (12.3%)
3	50 (3.9%)	90 (4.4%)	75 (8.8%)	32 (6.2%)	66 (7.4%)	156 (9.2%)	469 (6.4%)
4+	72 (5.7%)	72 (3.5%)	119 (14.0%)	47 (9.2%)	91 (10.2%)	220 (13.0%)	622 (8.5%)

Data are presented as n (%).

Table 5.21 Total number of admissions with infection within 5 years amongst survivors born between 01 January 2005 and 30 November 2012 and admitted to a hospital in England before the age of 5

	Hirschsprung's Disease N=1,334	Gastroschisis N=2,065	Oesophageal Atresia N=848	Congenital Diaphragmatic Hernia N=513	Posterior Urethral Valves N=927	Surgical Necrotising Enterocolitis N=1,695	Total N=7,382
0	526 (39.4%)	895 (43.3%)	175 (20.6%)	186 (36.3%)	287 (31.0%)	401 (23.7%)	2,470 (33.5%)
1	286 (21.4%)	539 (26.1%)	152 (17.9%)	113 (22.0%)	184 (19.8%)	337 (19.9%)	1,611 (21.8%)
2	172 (12.9%)	295 (14.3%)	110 (13.0%)	60 (11.7%)	120 (12.9%)	258 (15.2%)	1,015 (13.7%)
3	104 (7.8%)	127 (6.2%)	83 (9.8%)	39 (7.6%)	105 (11.3%)	174 (10.3%)	632 (8.6%)
4+	246 (18.4%)	209 (10.1%)	328 (38.7%)	115 (22.4%)	231 (24.9%)	525 (31.0%)	1,654 (22.4%)

Data are presented as n (%). **Note:** Includes children who were admitted to a hospital in England after the first year of age.

Table 5.22 Total number of admissions with infection within 10 years amongst survivors born between 01 January 2005 and 30 November 2012 and admitted to a hospital in England before the age of 10

	Hirschsprung's Disease N=1,349	Gastroschisis N=2,068	Oesophageal Atresia N=848	Congenital Diaphragmatic Hernia N=513	Posterior Urethral Valves N=954	Surgical Necrotising Enterocolitis N=1,695	Total N=7,427
0	456 (33.8%)	829 (40.1%)	155 (18.3%)	170 (33.1%)	253 (26.5%)	357 (21.1%)	2,220 (29.9%)
1	296 (21.9%)	543 (26.3%)	135 (15.9%)	115 (22.4%)	171 (17.9%)	331 (19.5%)	1,591 (21.4%)
2	164 (12.2%)	306 (14.8%)	96 (11.3%)	60 (11.7%)	133 (13.9%)	244 (14.4%)	1,003 (13.5%)
3	121 (9.0%)	134 (6.5%)	88 (10.4%)	38 (7.4%)	96 (10.1%)	181 (10.7%)	658 (8.9%)
4+	312 (23.1%)	256 (12.4%)	374 (44.1%)	130 (25.3%)	301 (31.6%)	582 (34.3%)	1,955 (26.3%)

Data are presented as n (%). **Note:** Includes children who were admitted to a hospital in England after the first year of age.

5.4.8 Outcomes: Operations

Amongst survivors born between 01 January 2005 and 30 November 2021, children with HD and OA had the highest operation rates, with 37.7% (n=1,025) of children with HD and 37.3% (n=666) of children with OA undergoing 4 or more operations within the first year of life. This was followed by children with surgical NEC (30.5%, n=1,162), then PUV (12.2%, n=240), CDH (9.5%, n=104) and gastroschisis (8.4%, n=319) (**Table 5.23**).

Amongst survivors born between 01 January 2005 and 30 November 2012, a similar pattern was seen, as children with OA and HD had the highest proportion undergoing 4 or more operations within the first year of life, 30.2% (n=256) and 29.5% (n=377) respectively (**Table 5.23**). Children with OA and HD continued to carry the highest burden of operations at 5 years and 10 years (**Figure 5.4**). Whilst children with surgical NEC had a high proportion of children undergoing 4 or more operations within one year (25.8%, n=437), this tapers off at 5 and 10 years, whilst children with PUV continue to have a high burden of operations at 10 years (44.5% of children with PUV had 4 or more operations at 10 years, n=425) (**Figure 5.4).** The total number of operations at 1 year, 5 years and 10 years for survivors born between 01 January 2005 and 30 November 2012 are outlined in **Table 5.24**, **Table 5.25** and **Table 5.26**.

Figure 5.4 Proportion of survivors who had 4 or more operations at 1, 5 and 10 years amongst survivors born between 01 January 2005 and 30 November 2012

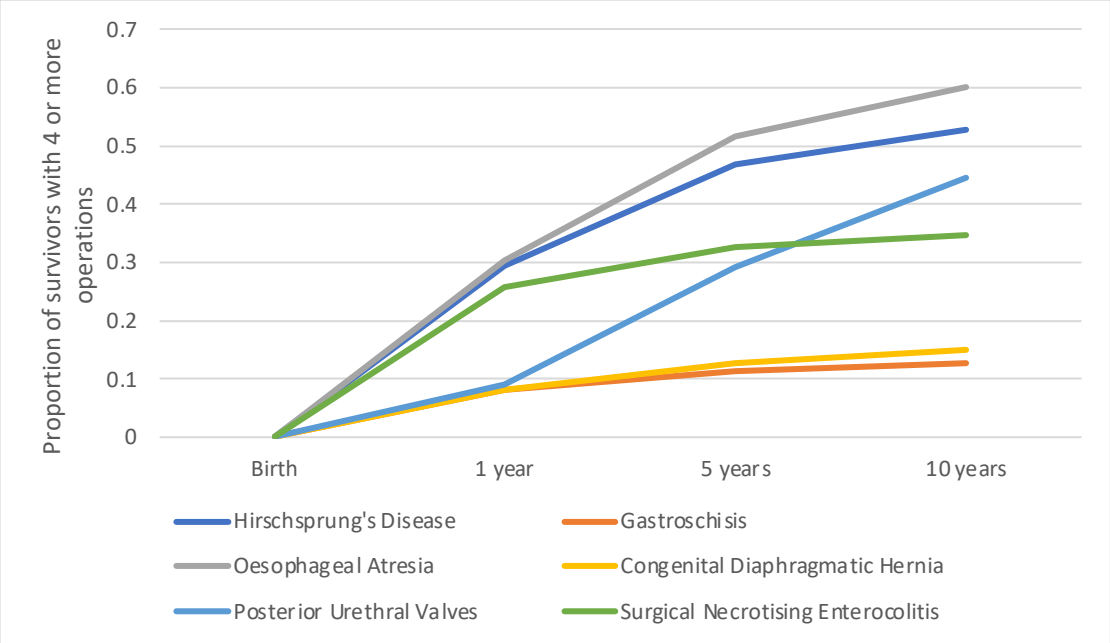


Table 5.23 Total number of operations within 1-year amongst survivors born between 01 January 2005 and 30 November 2021

	Hirschsprung's Disease	Gastroschisis	Oesophageal Atresia	Congenital Diaphragmatic Hernia	Posterior Urethral Valves	Surgical Necrotising Enterocolitis	Total
	N=2,719	N=3,807	N=1,787	N=1,097	N=1,973	N=3,812	N=15,195
0	279 (10.3%)	1,596 (41.9%)	0 (0.0%)	0 (0.0%)	420 (21.3%)	0 (0.0%)	2,295 (15.1%)
1	393 (14.5%)	1,030 (27.1%)	544 (30.4%)	618 (56.3%)	460 (23.3%)	826 (21.7%)	3,871 (25.5%)
2	558 (20.5%)	560 (14.7%)	334 (18.7%)	273 (24.9%)	571 (28.9%)	1,020 (26.8%)	3,316 (21.8%)
3	464 (17.1%)	302 (7.9%)	243 (13.6%)	102 (9.3%)	282 (14.3%)	804 (21.1%)	2,197 (14.5%)
4+	1,025 (37.7%)	319 (8.4%)	666 (37.3%)	104 (9.5%)	240 (12.2%)	1,162 (30.5%)	3,516 (23.1%)

Data are presented as n (%).

Table 5.24 Total number of operations within 1-year amongst survivors born between 01 January 2005 and 30 November 2012

	Hirschsprung's Disease	Gastroschisis	Oesophageal Atresia	Congenital Diaphragmatic Hernia	Posterior Urethral Valves	Surgical Necrotising Enterocolitis	Total
	N=1,279	N=2,060	N=848	N=513	N=888	N=1,695	N=7,283
0	142 (11.1%)	898 (43.6%)	0 (0.0%)	0 (0.0%)	268 (30.2%)	0 (0.0%)	1,308 (18.0%)
1	227 (17.7%)	576 (28.0%)	311 (36.7%)	315 (61.4%)	215 (24.2%)	447 (26.4%)	2,091 (28.7%)
2	311 (24.3%)	275 (13.3%)	165 (19.5%)	112 (21.8%)	235 (26.5%)	471 (27.8%)	1,569 (21.5%)
3	222 (17.4%)	145 (7.0%)	116 (13.7%)	45 (8.8%)	91 (10.2%)	340 (20.1%)	959 (13.2%)
4+	377 (29.5%)	166 (8.1%)	256 (30.2%)	41 (8.0%)	79 (8.9%)	437 (25.8%)	1,356 (18.6%)

Data are presented as n (%). **Note:** Includes children who were admitted to a hospital in England after the first year of age.

Table 5.25 Total number of operations within 5-years amongst survivors born between 01 January 2005 and 30 November 2012

	Hirschsprung's Disease	Gastroschisis	Oesophageal Atresia	Congenital Diaphragmatic Hernia	Posterior Urethral Valves	Surgical Necrotising Enterocolitis	Total
	N=1,334	N=2,065	N=848	N=513	N=927	N=1,695	N=7,382
0	53 (4.0%)	763 (36.9%)	0 (0.0%)	0 (0.0%)	164 (17.7%)	0 (0.0%)	980 (13.3%)
1	199 (14.9%)	569 (27.6%)	160 (18.9%)	277 (54.0%)	149 (16.1%)	387 (22.8%)	1,741 (23.6%)
2	259 (19.4%)	324 (15.7%)	121 (14.3%)	112 (21.8%)	230 (24.8%)	437 (25.8%)	1,483 (20.1%)
3	197 (14.8%)	174 (8.4%)	129 (15.2%)	59 (11.5%)	114 (12.3%)	316 (18.6%)	989 (13.4%)
4+	626 (46.9%)	235 (11.4%)	438 (51.7%)	65 (12.7%)	270 (29.1%)	555 (32.7%)	2,189 (29.7%)

Data are presented as n (%). **Note:** Includes children who were admitted to a hospital in England after the first year of age.

Table 5.26 Total number of operations within 10-years amongst survivors born between 01 January 2005 and 30 November 2012

	Hirschsprung's Disease	Gastroschisis	Oesophageal Atresia	Congenital Diaphragmatic Hernia	Posterior Urethral Valves	Surgical Necrotising Enterocolitis	Total
	N=1,349	N=2,068	N=848	N=513	N=954	N=1,695	N=7,427
0	8 (0.6%)	730 (35.3%)	0 (0.0%)	0 (0.0%)	63 (6.6%)	0 (0.0%)	801 (10.8%)
1	195 (14.5%)	567 (27.4%)	133 (15.7%)	265 (51.7%)	139 (14.6%)	375 (22.1%)	1,674 (22.5%)
2	244 (18.1%)	329 (15.9%)	103 (12.1%)	109 (21.2%)	177 (18.6%)	416 (24.5%)	1,378 (18.6%)
3	191 (14.2%)	180 (8.7%)	103 (12.1%)	62 (12.1%)	150 (15.7%)	318 (18.8%)	1,004 (13.5%)
4+	711 (52.7%)	262 (12.7%)	509 (60.0%)	77 (15.0%)	425 (44.5%)	586 (34.6%)	2,570 (34.6%)

Data are presented as n (%). **Note:** Includes children who were admitted to a hospital in England after the first year of age.

5.4.9 Outcomes: Infections

Amongst survivors born between 01 January 2005 and 30 November 2021, 43.9% (n=6678) did not have any infections within the first year of life. Children with OA had the highest proportion of children having 4 or more infections within the first year of life (15.9%, n=284), closely followed by surgical NEC (14.9%, n=567) and PUV (13.3%, n=263) (**Table 5.27**).

Amongst survivors born between 01 January 2005 and 30 November 2012, the proportion of children with 4 or more infections remained highest amongst children with OA and surgical NEC at 10 years, 44.1% (n=374) and 34.3% (n=582) respectively, and lowest amongst children with gastroschisis (12.4%, n=256) (**Figure 5.5**). The total number of operations at 1 year, 5 years and 10 years for survivors born between 01 January 2005 and 30 November 2012 are outlined in **Table 5.28, Table 5.29** and **Table 5.30**.

Figure 5.5 Proportion of survivors who had 4 or more infections at 1, 5 and 10 years amongst survivors born between 01 January 2005 and 30 November 2012

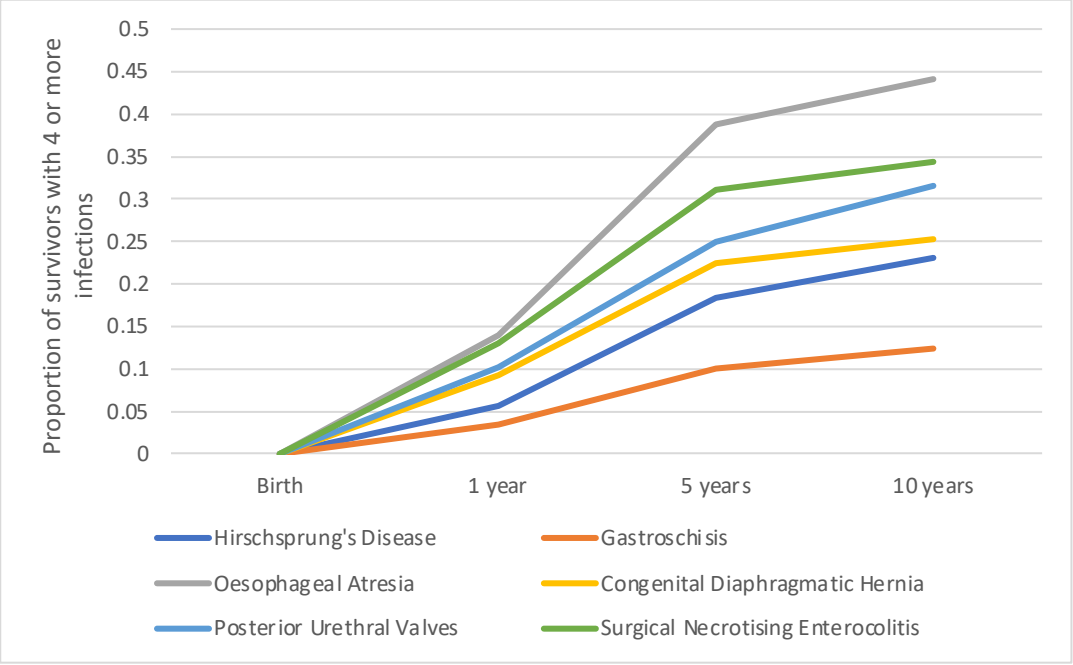


Table 5.27 Total number of infections within 1-year amongst survivors born between 01 January 2005 and 30 November 2021

	Hirschsprung's Disease N=2,719	Gastroschisis N=3,807	Oesophageal Atresia N=1,787	Congenital Diaphragmatic Hernia N=1,097	Posterior Urethral Valves N=1,973	Surgical Necrotising Enterocolitis N=3,812	Total N=15,195
0	1,433 (52.7%)	1,989 (52.2%)	657 (36.8%)	536 (48.9%)	864 (43.8%)	1,199 (31.5%)	6,678 (43.9%)
1	620 (22.8%)	1,027 (27.0%)	415 (23.2%)	266 (24.2%)	416 (21.1%)	1,036 (27.2%)	3,780 (24.9%)
2	293 (10.8%)	417 (11.0%)	256 (14.3%)	116 (10.6%)	285 (14.4%)	636 (16.7%)	2,003 (13.2%)
3	148 (5.4%)	205 (5.4%)	175 (9.8%)	73 (6.7%)	145 (7.3%)	374 (9.8%)	1,120 (7.4%)
4+	225 (8.3%)	169 (4.4%)	284 (15.9%)	106 (9.7%)	263 (13.3%)	567 (14.9%)	1,614 (10.6%)

Data are presented as n (%).

Table 5.28 Total number of infections within 1 year amongst survivors born between 01 January 2005 and 30 November 2012

	Hirschsprung's Disease	Gastroschisis	Oesophageal Atresia	Congenital Diaphragmatic Hernia	Posterior Urethral Valves	Surgical Necrotising Enterocolitis	Total
	N=1,279	N=2,060	N=848	N=513	N=888	N=1,695	N=7,283
0	768 (60.0%)	1,139 (55.3%)	334 (39.4%)	260 (50.7%)	440 (49.5%)	586 (34.6%)	3,527 (48.4%)
1	280 (21.9%)	536 (26.0%)	199 (23.5%)	116 (22.6%)	164 (18.5%)	474 (28.0%)	1,769 (24.3%)
2	108 (8.4%)	223 (10.8%)	121 (14.3%)	58 (11.3%)	127 (14.3%)	259 (15.3%)	896 (12.3%)
3	50 (3.9%)	90 (4.4%)	75 (8.8%)	32 (6.2%)	66 (7.4%)	156 (9.2%)	469 (6.4%)
4+	72 (5.7%)	72 (3.5%)	119 (14.0%)	47 (9.2%)	91 (10.2%)	220 (13.0%)	622 (8.5%)

Data are presented as n (%).

Table 5.29 Total number of infections within 5 years amongst survivors born between 01 January 2005 and 30 November 2012

	Hirschsprung's Disease	Gastroschisis	Oesophageal Atresia	Congenital Diaphragmatic Hernia	Posterior Urethral Valves	Surgical Necrotising Enterocolitis	Total
	N=1,334	N=2,065	N=848	N=513	N=927	N=1,695	N=7,382
0	526 (39.4%)	895 (43.3%)	175 (20.6%)	186 (36.3%)	287 (31.0%)	401 (23.7%)	2,470 (33.5%)
1	286 (21.4%)	539 (26.1%)	152 (17.9%)	113 (22.0%)	184 (19.8%)	337 (19.9%)	1,611 (21.8%)
2	172 (12.9%)	295 (14.3%)	110 (13.0%)	60 (11.7%)	120 (12.9%)	258 (15.2%)	1,015 (13.7%)
3	104 (7.8%)	127 (6.2%)	83 (9.8%)	39 (7.6%)	105 (11.3%)	174 (10.3%)	632 (8.6%)
4+	246 (18.4%)	209 (10.1%)	328 (38.7%)	115 (22.4%)	231 (24.9%)	525 (31.0%)	1,654 (22.4%)

Data are presented as n (%).

Table 5.30 Total number of infections within 10 years amongst survivors born between 01 January 2005 and 30 November 2012

	Hirschsprung's Disease	Gastroschisis	Oesophageal Atresia	Congenital Diaphragmatic Hernia	Posterior Urethral Valves	Surgical Necrotising Enterocolitis	Total
	N=1,349	N=2,068	N=848	N=513	N=954	N=1,695	N=7,427
0	456 (33.8%)	829 (40.1%)	155 (18.3%)	170 (33.1%)	253 (26.5%)	357 (21.1%)	2,220 (29.9%)
1	296 (21.9%)	543 (26.3%)	135 (15.9%)	115 (22.4%)	171 (17.9%)	331 (19.5%)	1,591 (21.4%)
2	164 (12.2%)	306 (14.8%)	96 (11.3%)	60 (11.7%)	133 (13.9%)	244 (14.4%)	1,003 (13.5%)
3	121 (9.0%)	134 (6.5%)	88 (10.4%)	38 (7.4%)	96 (10.1%)	181 (10.7%)	658 (8.9%)
4+	312 (23.1%)	256 (12.4%)	374 (44.1%)	130 (25.3%)	301 (31.6%)	582 (34.3%)	1,955 (26.3%)

Data are presented as n (%).

5.5 Discussion

This is the largest study to date to investigate the long-term outcomes of children in England across six different paediatric surgical conditions using the HES database. The study comprised 18,824 children admitted to NHS hospitals.

5.5.1 Feasibility of utilising the HES database to investigate long-term outcomes

This study demonstrates that it is feasible to utilise the HES database to investigate outcomes of children with a paediatric surgical condition, though there are some notable limitations. Previous studies have validated this data source amongst several adult conditions.[35 292 293] Nonetheless, the potential for diagnostic misclassification due to miscoding remains a cause for concern and the accuracy may vary depending on the diagnosis.[290 292] For instance, the ICD-10 code, *Q79.0 Congenital diaphragmatic hernia*, may be erroneously exchanged with "Q79.1", which represents diaphragmatic eventration and other conditions that fall into the category of "Other congenital malformations". Diaphragmatic eventration is a similar condition to CDH and it can be difficult to differentiate between the two. However, diaphragmatic eventration is a less severe condition and may be managed without an operation.[194] When the study surgical conditions were defined based on ICD-10 diagnostic codes alone, this resulted in implausible condition incidences and outcomes, with 17.2% and 32.2% of children with OA and CDH survivors having had no operations. This suggests that the presence of a qualifying ICD-10 code may be of limited utility on its own for certain conditions, resulting in a low specificity that a child truly has the condition based on the presence of a qualifying ICD-10 code. However, as shown in a validation study by Hannah et al., it may be possible to improve the positive predictive value and sensitivity by using an algorithm and optimal code combinations.[292] In this study, the presence of a corresponding OPCS-4

code may have helped increase the accuracy of including children who truly have the disease. For instance, identifying cases of OA using both the presence of a qualifying ICD-10 diagnosis and a qualifying operation code resulted in an incidence of 18.2 per 100,000 live births, which is similar to the incidence of 19.8 per 100,000 live births reported in a previous cohort study conducted by the British Association of Paediatric Surgeons Congenital Anomalies Surveillance System (BAPSCASS).[301]

5.5.2 Incidences

In this study, the incidences of each surgical condition in England per 100,000 live births was 23.6 for HD (95%CI 22.5-24.6), 29.1 for gastroschisis (95%CI 27.8-30.4), 18.2 for OA (95%CI 17.3-19.3), 16.5 for CDH (95%CI 15.5-17.4), 18.0 for PUV (95%CI 17.0-19.0), and 44.6 for PUV (95%CI 43.1-46.2). The incidences for HD, gastroschisis, OA and PUV in this study are similar to those reported by prospective cohort studies conducted by BAPS CASS, whereas the incidences calculated based on using ICD-10 coding alone resulted in implausible incidences for certain conditions.[2 39 259 301] The incidence of surgical NEC in this study was slightly higher than the incidences reported in previous BAPS CASS cohort studies conducted by Allin et al. and Bethell et al., however, the latter study applied more restrictive inclusion criteria, only including infants if they underwent first surgical intervention within 7 days of diagnosis and cases of spontaneous intestinal perforation were excluded.[38 302] To meet the criteria for surgical NEC, children had to have a qualifying operation code within the first year of life (**Table 5.31**).

Table 5.31 Condition incidences based on Hospital Episode Statistics (HES) data and British Association of Paediatric Surgeons Congenital Anomalies Surveillance System (BAPS-CASS) data

Condition	**Incidence in HES** *per 100,000 live births*	**Incidence in BAPS-CASS studies**
Hirschsprung's disease	23.6 (22.5-24.7)	18
Gastroschisis	29.1 (27.8-30.4)	33.9
Oesophageal atresia	18.2 (17.3-19.3)	19.8
Congenital diaphragmatic hernia	16.5 (15.5-17.4)	20.2
Posterior urethral valves	18.0 (17.0-19.0)	16.2
Surgical necrotising enterocolitis	44.6 (43.1-46.2)	27.9

5.5.3 Long-term outcome: Mortality

It is important to report contemporary outcomes for children with these surgical conditions in order to provide parents with accurate data for prognostication and general counselling. Amongst children born 2005-2021, children with HD had the highest survival rate (98.4%, n=2832), followed by PUV (97.5%, n=2,077), gastroschisis (96.4%, n=3,827), OA (82.5%, n=1,787), surgical NEC (75.8%, n=3,812), and CDH (55.9%, n=1,097). The majority of deaths occurred within the first year of life, resulting in 5-year and 10-year mortality being similar. For children with CDH, the 5-year mortality was 44.6% compared to a 10-year mortality of 44.8%. Similarly, for children with gastroschisis, the 5-year and 10-year mortality were identical (4.5%). These figures may be reassuring to parents and clinicians. Mortality with 1 year of age was similar across all three cohorts and time periods: 14.9% for those born 2005-2021, 14.8% for those born 2005-2017 and 15.4% for those born 2005-2012. For comparison, the pooled proportion for one-year survival from the systematic review (**Chapter 2**) was highest for Hirschsprung's disease 98% (95% confidence interval [CI] 97-100), followed by 96% for gastroschisis (95% CI 95-97), 92% for oesophageal atresia (95% CI 89-95), 77% for congenital diaphragmatic hernia (95% CI 72-82) and 61% for those with surgical necrotising enterocolitis (95% CI 47-76).

5.5.4 Long-term outcome: operations and infections

Amongst survivors, children with OA and HD had the highest burden of children undergoing 4 or more operations. The majority of children with OA and HD had 4 or more operations within 10 years, 60.0% of children with OA (n=509) and 52.7% of children with HD (n=711), compared to only 12.7% of children with gastroschisis (n=262). Whilst children with surgical NEC had more operations within the first year, this tapered off at 5 and 10 years, as opposed to children with PUV, who were less likely to undergo 4 or more operations within the first year of life, but had a relatively high proportion of children having 4 or more operations at 10 years (44.5%, n=425). This may be due to the fact that children with PUV may require cystoscopies later in life. Children with OA had the highest proportion of children who had 4 or more admissions with infections within the first year of life (14%, n=199), compared to only 3.5% of children with gastroschisis (n=72). Understanding the trajectory of these conditions can be useful for both parents and clinicians in understanding the current expected course of disease.

5.5.5 Limitations and strengths

The strength of this study is that it demonstrates the added utility of using routinely collected data, specifically the HES database as a data source, to explore the long-term outcomes of children with a paediatric surgical condition. It is a population-based study encompassing 18,824 children in England between 2005 and 2022.

As discussed previously, one of the limitations of using routinely collected data is inaccuracies in ICD-10 diagnostic coding. However, as shown in this study, it may be possible to enhance the accuracy of the cohort with the inclusion of OPCS-4 codes, which may differ according to the condition involved. Another limitation is the use of OPCS-4

codes, as the way in which OPCS-4 codes are utilised may not accurately reflect the clinical scenario. For instance, infants with gastroschisis may be managed with a silo on the ward, however it is possible that such ward-based procedures may not be as consistently coded with an OPCS-4 procedure code, compared to procedures conducted in an operating theatre. Based on BAPS CASS data, 36% of children with gastroschisis are managed with a silo on the ward.[39] Furthermore, as with the NNRD, the HES database does not include information from operative records, which would provide valuable information to evaluate the management of these surgical conditions.

5.5.5.1 Obtaining markers of condition severity using routinely collected data

Markers of condition severity are important factors that influence outcome. Although these could not be obtained from the NNRD for each study condition, it was possible to derive some condition-specific markers of severity from the HES database, such as pre-operative Hirschsprung-associated enterocolitis (HAEC) for children with HD and complex gastroschisis. However, several important markers of condition severity could not be obtained from the HES database. For instance, right-sided CDH, lung-to-head circumference ratio, patch surgery and use of ECMO are known markers of condition severity for CDH, but were not available or incompletely recorded in the HES database.[303] [304] Similarly, length of bowel resection is an important severity marker for both HD and surgical NEC, however this level of data granularity could not be obtained from ICD-10 or OPCS-4 codes and detailed operative records are not held in the HES database.[91] [305] Thus, whilst at least one condition-specific severity marker could be derived from the HES database, more suitable severity markers may not be routinely collected, highlighting a limitation of this data source.

5.5.5.2 The structure of the HES database: Finished Consultant Episodes and Continuous InPatient Spells

As the HES database is made up of FCEs, there may be more than one FCE record per admission. In order to convert the database into one record per admission, CIPS records may be generated from FCE records, which represent a single inpatient admission including transfers. During this process, some data granularity may be lost, as the CIPS records only contain a maximum of 20 diagnosis fields and 24 operation fields per admission. Nevertheless, the impact of this in the data is likely to be minimal, as few children will have more than 24 operation codes during a single admission and the most common and important diagnoses are captured from the discharge and admission FCE records.

5.6 Conclusion

In this study of children born in England between 2005 and 2022 with a diagnosis of at least one of the six surgical conditions, routine data was found to be an important tool to investigate long-term outcomes for this patient population. A limitation of routine data is that study investigators are limited to existing data items, which may not capture important variables, such as the details of the operative procedure or condition severity. Furthermore, outcomes that are important to parents and clinicians may not be captured, such as quality of life outcomes.

Chapter 6

Investigating whether Hospital Episode Statistics data can be used to develop a model to predict long-term outcomes

6.1 Introduction

As demonstrated in **Chapter 4**, it is feasible to utilise routinely collected data to develop and internally validate multivariable prediction models for short-term outcomes amongst children requiring early surgery. However, important clinical predictors, such as condition severity and operative management may not be captured in routinely collected data, limiting the predictive power and utility of the models. Nevertheless, the possibility to use whole population data and attain a large sample size remains a strength of using routinely collected data, particularly for prediction modelling, where greater sample sizes allow for the development of more robust models.[306]

6.1.1 Prediction modelling of long-term outcomes

Multivariable models to predict long-term outcomes are less common than models to predict short-term outcomes, for the same reasons presented in **Chapter 5** regarding the barriers to collecting long-term outcome data. Nonetheless, several prediction models for long-term outcomes have been developed for adult patients, including for long-term allograft and patient survival following renal transplantation, aphasia outcomes amongst stroke survivors and occupational performance following traumatic brain injury.[307-309] Whilst there are fewer prediction models for short-term outcomes in the field of paediatric surgery compared to other fields of medicine, prediction models for long-term outcomes amongst children requiring surgery are even less common. Furthermore, the majority of these prediction models are developed in relatively small samples, often using data from a single institution.

6.1.2 The implications of small samples in prediction modelling

The issue of small samples presents a challenge in prediction modelling. The methodology regarding the calculation of the sample size required to develop a multivariable prediction model remains an area of controversy and ongoing research. A popular rule of thumb that has been frequently cited is that 10 events per variable (EPVs) are required for binary and time-to-event outcomes.[310 311] Conversely, Riley et al. proposes that a more nuanced approach should be adopted in the sample size calculations for developing prediction models, taking into account the context, outcome incidence and expected predictive performance of the models. It is widely accepted that larger numbers of study participants are required for the development of rigorous and reliable prediction models, which is why using all available data to build these models is recommended, as opposed to splitting data for model building and external validation. The latter approach is generally viewed as inferior and an inadequate form of external validation, as it decreases the data available to develop the model and systematic biases within the database will still exist, even if the database is split randomly.[306]

6.1.3 Prediction modelling using the HES database

Previous studies have shown that it is feasible to develop robust multivariable prediction models using the HES database. A study by Soong et al. developed frailty syndrome models to predict mortality, institutionalisation and emergency readmission using the HES database, including over two million patients over the age of 65 in the analysis. The discrimination of these models as measured by ROC scores were 0.57-0.63 for 30-day readmission to the emergency department, 0.62-0.66 for inpatient mortality and 0.63-0.65 for institutionalisation.[312] Similarly, Billings et al. developed a prediction model to identify patients at high risk of 30-day readmission, using observations from half a million

patients.[313] These examples highlight the potential benefits of using the HES database in prediction modelling, particularly for the modelling of common outcomes amongst adult patients. Further research is required to explore the utility of the HES database in the development of prediction models for long-term outcomes amongst children with a general paediatric surgical condition.

6.2 Aims and objectives

The overall aim of this chapter was to explore whether it is possible to utilise Hospital Episode Statistics (HES) data to develop prediction models for long-term outcomes for children with one of the six study surgical conditions: Hirschsprung's disease (HD), gastroschisis, oesophageal atresia (OA), congenital diaphragmatic hernia (CDH), posterior urethral valves (PUV) and surgical necrotising enterocolitis (NEC).

From this overarching aim, there were three specific objectives:

1. To develop a prediction model for long-term survival amongst children with one of the six study conditions;
2. To develop a prediction model for long-term operations amongst children with one of the six study conditions, and;
3. To develop a prediction model for long-term infections amongst children with one of the six study conditions.

6.3 Methods

The methodology regarding the data source, study participants, predictors and outcomes has been described in further detail in **Chapter 5**. This study follows the "Transparent

reporting of multivariable prediction model for individual prognosis or diagnosis" (TRIPOD) guidelines.[273]

6.3.1 Sample size

As aforementioned, sample size calculation for developing a prediction model remains an area of ongoing research, though the 10 events per variable (EPVs) rule-of-thumb is commonly cited for binary and time-to-event outcomes. Using this guideline, assuming there will be 7 predictors the model (i.e. gestational age, sex, surgical condition, ethnicity, IMD decile, presence of an additional major congenital anomaly and condition severity), this would require 70 deaths. There were 2,705 deaths at 1 year amongst children born between 01 January 2005 and 30 November 2021 (**Chapter 5**), suggesting that the sample size in the HES database is sufficient for the purpose of developing a prediction model, according to the 10 EPV rule. However, for the reasons outlined in the introduction, all available data were used to develop the prediction models.

6.3.2 Choosing the functional form of continuous variables

As previously described in **Chapter 4**, flexible modelling techniques (such as restricted cubic splines) were explored for continuous variables that had a non-linear relationship with the outcome.

6.3.3 Missing data

The proportion of missing data was presented for each predictor. Patterns of missingness were explored and multivariable logistic regression was conducted to investigate whether there were variables that were independent predictors of missingness in the gestational age variable. Variables with greater than 10% missing data were considered to have a

substantial amount of missing data. Both complete case analyses and sensitivity analyses using multiple imputation were conducted to explore the impact of using multiple imputation for variables with greater than 10% missingness on the model.

6.3.4 Multiple imputation

Of the predictors in the prediction model, only gestational age at birth had greater than 10% missing data. As gestational age at birth was not normally distributed, multiple imputation using predictive mean matching (PMM) was conducted to ensure that implausible values were not imputed. Although earlier studies have suggested that 3 to 5 imputations are sufficient, more recent studies recommend that the number of imputations performed be greater than the nominal percentage of missing data (i.e. 20 imputations should be performed if there is 20% of missing data).[314 315] As there was 37% missing data in the gestational age at birth variable, 40 imputations were performed.

6.3.5 Statistical analysis

Statistical analysis was performed using Stata/MP Version 18.0 (StataCorp LLC 2023: Texas, USA). The same variable selection strategy as outlined in **Chapter 4** was used. All predictors that were selected *a priori* were entered into the model.

6.3.6 Choosing the appropriate statistical model

Counts can be modelled using several different models, of which Poisson regression and negative binomial regression are frequently used. An assumption of the Poisson model, which is based on the Poisson distribution, is that the mean is equal to the variance. A common issue that may arise in the data is overdispersion, which occurs when the variance is greater than expected based on the Poisson distribution. Thus, Poisson regression is not

the appropriate model to use in the presence of overdispersion. In such cases, negative binomial regression may be performed, as the model has an additional parameter to account for overdispersion. In order to check for overdispersion, the likelihood-ratio chi-square test of alpha=0 (where alpha is the dispersion parameter) was conducted. Where overdispersion was present, a negative binomial model was used instead of a Poisson model. Follow-up time was measured by date of death or date of censor.

The incidence rate ratio, standard error and 95% confidence interval was reported for each prediction model. A global p-value was calculated for each predictor using the Wald test. Measures of model assessment were reported, including the Akaike Information Criterion (AIC), Bayesian Information Criterion (BIC), log-likelihood value and Cragg & Uhler's R^2 (also known as Nagelkerke's R^2).

6.3.7 Modelling of counts versus binary outcomes

Prediction modelling in healthcare is well described for modelling binary outcomes, as well as linear and time to event outcomes. However, prediction modelling methods for modelling counts is currently underdeveloped, including methods to evaluate the predictive performance and methods for internal validation. Therefore, prediction models using both negative binomial regression and logistic regression were developed to enable evaluation of predictive performance measures.

6.3.8 Prediction modelling using negative binomial regression

The outcomes of interest were mortality, total number of operations and total number of infections. Follow-up time in days was used as the exposure variable, to take into account the expected increased incidence of the outcome over longer follow-up times.

The incident rate ratio, standard error and 95% confidence interval were reported for each prediction model using negative binomial regression, along with the constant, which represents the 'baseline' estimate of incidence. A global p-value was calculated for each predictor using the Wald test. Measures of model fit were reported, including the AIC, BIC, and log-likelihood value. A measure of overall model performance was reported using Cragg & Uhler's R^2 (also known as Nagelkerke's R^2).

6.3.9 Prediction modelling using logistic regression

As children had differing lengths of follow-up and the risk of an outcome occurring increases over time, the time-point of one year was used. One-year outcomes were assessed for children who had an admission within the first year of life. The outcomes of interest were survival at one year of age, 3 or more operations within the first year of life, and presence of an infection within the first year of life. For operations, the outcome was having 3 or more operations, as this is more than expected for children with one of the six study conditions.

The adjusted odds ratio, standard error and 95% confidence interval were reported for each prediction model using multivariable logistic regression, along with the constant. A global p-value was calculated for each predictor using the Wald test. For discrimination, the area under the receiver operating characteristic (ROC) curve was reported. Calibration was assessed using two different methods. Firstly, the calibration belt plot was plotted, and the test statistic calculated. The calibration belt was plotted in Stata (package name: SJ17-4:gr0071) using the method developed by Nattino et al.[272] Additionally, a calibration plot, the ratio of expected and observed events (E:O), calibration-in-the-large (CITL), and

calibration slope were obtained to assess the calibration of the prediction model. The following measures of goodness-of-fit and overall model performance was reported: AIC, BIC, likelihood-value, Brier score and Cragg & Uhler's R^2 (also known as Nagelkerke's R^2).

6.3.10 Internal validation of prediction models

Internal validation was conducted using a bootstrapping approach using a total of 100 bootstrap samples. More details of this method have been previously described in **Chapter 4**.

6.4 Results

6.4.1 Participants

The flow of participants and development of the cohort is described in detail in **Chapter 5**.

Of 18,824 children included in the final cohort in Chapter 5, 28 children were excluded due to having a follow-up time of 0 days. Of 18,796 children available for inclusion in the multivariable prediction modelling using negative binomial regression, 11,842 children were included in the complete case analysis and 17,985 children were included in the multiple imputation analysis (**Figure 6.1**). The characteristics of this cohort, along with the proportion of missing data for each variable, are outlined in **Table 6.1**. In this cohort, 16.0% of children died (n=3,012), with the median age at death being 35 days. The median number of operations was 2 (IQR 1-5), and the median number of infections was 1 (IQR 0-3). The median follow-up time was 2,892 days (IQR 944-4628) (**Table 6.2**).

Figure 6.1 Participant flow diagram

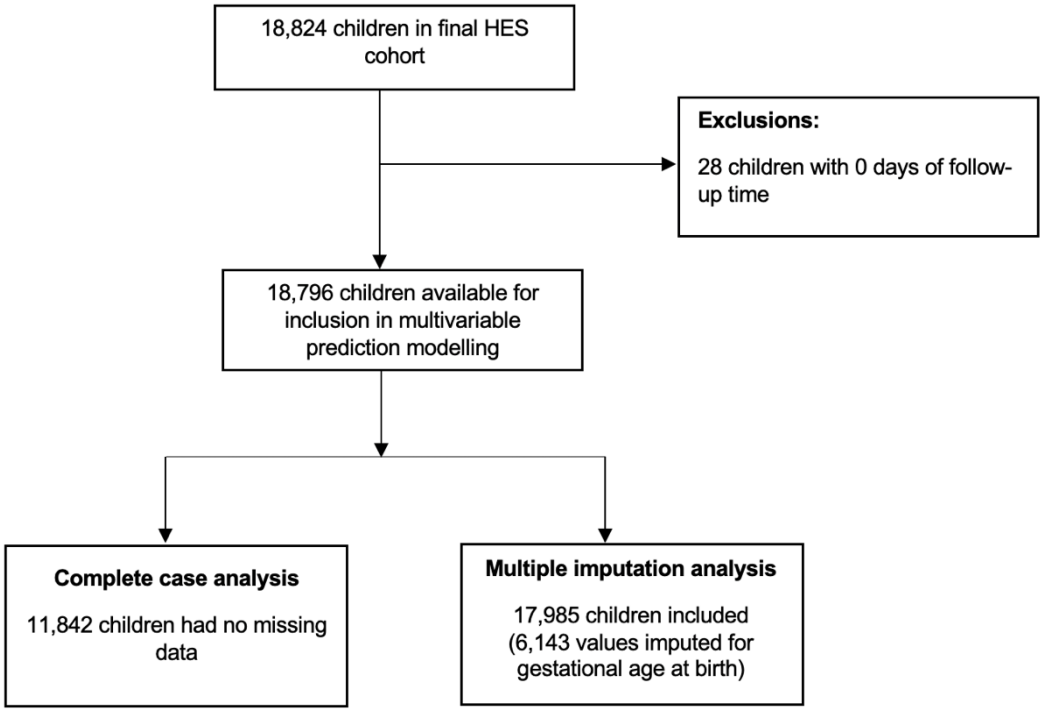


Table 6.1 Characteristics of surgical neonates in England

	Hirschsprung's Disease	Gastroschisis	Oesophageal Atresia	Congenital Diaphragmatic Hernia	Posterior Urethral Valves	Surgical Necrotising Enterocolitis	Total
	N=2,963	N=4,096	N=2,270	N=2,045	N=2,192	N=5,230	N=18,796
Gestational age (in weeks)	39 (38-40)	36 (35-37)	37 (34-39)	38 (36-39)	38 (37-40)	27 (25-32)	37 (32-39)
Missing	1,050 (35.4%)	1,452 (35.5%)	813 (35.8%)	709 (34.7%)	770 (35.1%)	1,850 (35.4%)	6,644 (35.4%)
Sex							
Male	2,185 (73.7%)	2,112 (51.6%)	1,305 (57.5%)	1,177 (57.6%)	2,191 (100.0%)	3,164 (60.5%)	12,134 (64.6%)
Female	778 (26.3%)	1,977 (48.3%)	963 (42.4%)	863 (42.2%)	0 (0.0%)	2,063 (39.4%)	6,644 (35.3%)
Indeterminate	0 (0.0%)	5 (0.1%)	1 (0.0%)	2 (0.1%)	0 (0.0%)	1 (0.0%)	9 (0.0%)
Missing	0 (0.0%)	2 (0.0%)	1 (0.0%)	3 (0.1%)	1 (0.0%)	2 (0.0%)	9 (0.0%)
Additional major congenital anomaly							
No additional major congenital anomaly	2,185 (73.7%)	3,041 (74.2%)	564 (24.8%)	1,036 (50.7%)	1,725 (78.7%)	1,977 (37.8%)	10,528 (56.0%)
Additional major congenital anomaly	778 (26.3%)	1,055 (25.8%)	1,706 (75.2%)	1,009 (49.3%)	467 (21.3%)	3,253 (62.2%)	8,268 (44.0%)
Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Ethnicity							
White	2,192 (74.0%)	3,568 (87.1%)	1,751 (77.1%)	1,392 (68.1%)	1,354 (61.8%)	3,502 (67.0%)	13,759 (73.2%)
Mixed	146 (4.9%)	189 (4.6%)	85 (3.7%)	62 (3.0%)	118 (5.4%)	270 (5.2%)	870 (4.6%)
Asian or Asian British	254 (8.6%)	65 (1.6%)	221 (9.7%)	297 (14.5%)	398 (18.2%)	672 (12.8%)	1,907 (10.1%)
Black or Black British	162 (5.5%)	64 (1.6%)	69 (3.0%)	71 (3.5%)	182 (8.3%)	486 (9.3%)	1,034 (5.5%)
Other	125 (4.2%)	83 (2.0%)	81 (3.6%)	67 (3.3%)	81 (3.7%)	170 (3.3%)	607 (3.2%)
Unknown	84 (2.8%)	127 (3.1%)	63 (2.8%)	156 (7.6%)	59 (2.7%)	130 (2.5%)	619 (3.3%)
IMD decile	4.0 (2.0-7.0)	4.0 (2.0-6.0)	5.0 (2.0-7.0)	4.0 (2.0-7.0)	4.0 (2.0-7.0)	4.0 (2.0-6.0)	4.0 (2.0-7.0)
Missing	145 (4.9%)	340 (8.3%)	77 (3.4%)	75 (3.7%)	67 (3.1%)	100 (1.9%)	804 (4.3%)

Data are presented as median (IQR) for continuous measures, and n (%) for categorical measures.

Table 6.2 Outcomes of surgical neonates in England

	Hirschsprung's Disease N=2,963	Gastroschisis N=4,096	Oesophageal Atresia N=2,270	Congenital Diaphragmatic Hernia N=2,045	Posterior Urethral Valves N=2,192	Surgical Necrotising Enterocolitis N=5,230	Total N=18,796
Mortality							
Survival	2,874 (97.0%)	3,932 (96.0%)	1,848 (81.4%)	1,126 (55.1%)	2,122 (96.8%)	3,882 (74.2%)	15,784 (84.0%)
Mortality	89 (3.0%)	164 (4.0%)	422 (18.6%)	919 (44.9%)	70 (3.2%)	1,348 (25.8%)	3,012 (16.0%)
Age at death (in days)	331 (90-880)	41 (20-120)	33 (18-119)	21 (11-30)	30 (16-300)	53 (30-102)	35 (19-86)
Total number of operations	4 (2-7)	1 (0-2)	4 (2-8)	1 (0-2)	3 (2-5)	3 (2-4)	2 (1-5)
Total number of admissions with infections	1 (0-4)	1 (0-2)	2 (0-5)	0 (0-2)	2 (0-4)	1 (0-4)	1 (0-3)
Follow-up time (in days)	3379 (1796-4809)	3683 (1994-5083)	2618 (700-4536)	700 (23-3652)	3226 (1765-4809)	2222 (242-4202)	2892 (944-4628)

Data are presented as median (IQR) for continuous measures, and n (%) for categorical measures.

6.4.2 Model specification: Mortality

As overdispersion was present, a negative binomial regression was used instead of Poisson regression (likelihood-ratio test of alpha=0: 6762.32, $p<0.001$). Predictors included gestational age at birth (in weeks), surgical condition, sex, presence of an additional major congenital anomaly, ethnicity, IMD decile and condition severity. Gestational age was modelled using restricted cubic splines. Due to the high proportion of missingness in both the gestational age and birthweight variables, a small-for-gestational-age variable could not be included in the model. The full prediction model for mortality using negative binomial regression is presented in **Table 6.3**. The Akaike Information Criterion (AIC), Bayesian Information Criterion (BIC) and the log-likelihood value are reported in **Table 6.4**.

Table 6.3 Multivariable prediction model for mortality using negative binomial regression

Predictors	IRR	SE	95% CI	p-value
Gestational age at birth (in weeks)*				<0.001
24-35 weeks	1.01	0.04	0.94-1.08	
35-38 weeks	0.77	0.04	0.69-0.86	
38-41 weeks	8.33	8.17	1.22-57.00	
Surgical condition				<0.001
Hirschsprung's Disease (Reference)	-	-	-	
Gastroschisis	1.53	0.41	0.91-2.57	
Oesophageal Atresia	64.63	16.87	38.74-107.81	
Congenital Diaphragmatic Hernia	1014.38	244.19	632.83-1625.97	
Posterior Urethral Valves	1.45	0.44	0.80-2.61	
Surgical Necrotising Enterocolitis	34.42	8.99	20.63-57.42	
Sex				0.048
Male (Reference)	-	-	-	
Female	1.35	0.16	1.06-1.71	
Indeterminate	2.35	5.04	0.04-156.43	
Additional major congenital anomaly				
No additional major congenital anomaly (Reference)	-	-	-	
Additional major congenital anomaly	2.16	0.27	1.69-2.75	<0.001
Ethnicity				<0.001
White (Reference)	-	-	-	
Mixed	1.28	0.34	0.76-2.15	
Asian or Asian British	1.81	0.34	1.25-2.62	
Black or Black British	1.58	0.39	0.97-2.58	
Other	0.99	0.32	0.52-1.88	
Unknown	27.43	11.76	11.84-63.56	
IMD decile	0.96	0.02	0.92-1.00	0.068
Condition severity	1.81	0.24	1.39-2.35	<0.001
_cons	0.00	0.00	0.00	

IRR = incidence rate ratio; SE = standard error; CI = confidence interval. Wald test used to calculate global p-values. **_cons** represents the estimate when all predictors in the model are evaluated at zero. *Gestational age modelled using restricted cubic splines, therefore coefficients cannot be interpreted in the same manner as a linear term.

Table 6.4 Measures of model assessment for the multivariable prediction model for mortality using negative binomial regression

Model assessment	Value
Akaike Information Criterion (AIC)	16549.82
Bayesian Information Criterion (BIC)	16697.41
Log-likelihood value (Full Model)	-8254.912
Cragg & Uhler's R^2	0.162

6.4.3 Model specification: Number of operations

As with the prediction model for mortality, overdispersion was present for the prediction model for total operations (likelihood-ratio test of alpha=0: 25000, $p<0.001$), thus a negative binomial regression model was fitted. The full prediction model for mortality using negative binomial regression is presented in **Table 6.5**. Predictors included gestational age at birth (in weeks), surgical condition, sex, presence of an additional major congenital anomaly, ethnicity, IMD decile and condition severity. The Akaike Information Criterion (AIC), Bayesian Information Criterion (BIC) and the log-likelihood value is reported in **Table 6.6**.

Table 6.5 Multivariable prediction model for total number of operations using negative binomial regression

Predictors	**IRR**	**SE**	**95% CI**	**p-value**
Gestational age at birth (in weeks)	0.93	0.00	0.93-0.94	<0.001
Surgical condition				<0.001
Hirschsprung's Disease (Reference)	-	-	-	
Gastroschisis	0.19	0.01	0.17-0.21	
Oesophageal Atresia	0.73	0.04	0.66-0.80	
Congenital Diaphragmatic Hernia	0.50	0.03	0.44-0.57	
Posterior Urethral Valves	0.49	0.02	0.44-0.53	
Surgical Necrotising Enterocolitis	0.63	0.03	0.56-0.69	
Sex				<0.001
Male (Reference)	-	-	-	
Female	0.89	0.03	0.84-0.94	
Indeterminate	0.78	0.80	0.10-5.87	
Additional major congenital anomaly				<0.001
No additional major congenital anomaly (Reference)	-	-	-	
Additional major congenital anomaly	1.53	0.05	1.44-1.62	
Ethnicity				<0.001
White (Reference)	-	-	-	
Mixed	1.13	0.07	1.00-1.27	
Asian or Asian British	1.17	0.05	1.07-1.27	
Black or Black British	1.12	0.07	0.99-1.27	
Other	1.03	0.08	0.88-1.21	
Unknown	1.91	0.28	1.43-2.56	
IMD decile	0.99	0.00	0.98-1.00	0.025
Condition severity	1.56	0.05	1.46-1.67	<0.001
_cons	0.04	0.01	0.03-0.06	

IRR = incidence rate ratio; SE = standard error; CI = confidence interval. Wald test used to calculate global p-values. **_cons** represents the estimate when all predictors in the model are evaluated at zero.

Table 6.6 Measures of model assessment for the multivariable prediction model for total number of operations using negative binomial regression

Model assessment	**Value**
Akaike Information Criterion (AIC)	64513.24
Bayesian Information Criterion (BIC)	64646.07
Log-likelihood value (Full Model)	-32238.621
Cragg & Uhler's R^2	0.233

6.4.4 Model specification: Number of infections

As overdispersion was present, a negative binomial regression was used instead of Poisson regression (likelihood-ratio test of alpha=0: 30000, $p<0.001$). The full prediction model for mortality using negative binomial regression is presented in **Table 6.7**. Predictors included gestational age at birth (in weeks), surgical condition, sex, presence of an additional major congenital anomaly, ethnicity, IMD decile and condition severity. Gestational age was modelled using restricted cubic splines. The Akaike Information Criterion (AIC), Bayesian Information Criterion (BIC) and the log-likelihood value is reported in **Table 6.8**.

Table 6.7 Multivariable prediction model for total number of infections using negative binomial regression

Predictors	IRR	SE	95% CI	p-value
Gestational age at birth (in weeks)*				<0.001
24-35 weeks	0.96	0.01	0.94-0.98	
35-38 weeks	1.02	0.02	0.99-1.06	
38-41 weeks	0.39	0.09	0.24-0.62	
Surgical condition				<0.001
Hirschsprung's Disease (Reference)	-	-	-	
Gastroschisis	0.44	0.02	0.40-0.48	
Oesophageal Atresia	0.91	0.05	0.82-1.02	
Congenital Diaphragmatic Hernia	0.67	0.04	0.59-0.75	
Posterior Urethral Valves	1.14	0.06	1.03-1.26	
Surgical Necrotising Enterocolitis	0.91	0.05	0.82-1.02	
Sex				0.003
Male (Reference)	-	-	-	
Female	0.90	0.03	0.84-0.95	
Additional major congenital anomaly				<0.001
No additional major congenital anomaly (Reference)	-	-	-	
Additional major congenital anomaly	2.10	0.07	1.97-2.24	
Ethnicity				<0.001
White (Reference)	-	-	-	
Mixed	1.03	0.07	0.90-1.17	
Asian or Asian British	1.04	0.05	0.94-1.14	
Black or Black British	0.71	0.05	0.62-0.81	
Other	0.79	0.07	0.67-0.94	
Unknown	0.51	0.10	0.35-0.76	
IMD decile	0.98	0.01	0.97-0.99	<0.001
Condition severity	1.63	0.06	1.51-1.75	<0.001
_cons	0.01	0.00	0.00-0.01	

IRR = incidence rate ratio; SE = standard error; CI = confidence interval. Wald test used to calculate global p-values. **_cons** represents the estimate when all predictors in the model are evaluated at zero. *Gestational age modelled using restricted cubic splines, therefore coefficients cannot be interpreted in the same manner as a linear term.

Table 6.8 Measures of model assessment for the multivariable prediction model for total number of operations using negative binomial regression

Model assessment	Value
Akaike Information Criterion (AIC)	51336.31
Bayesian Information Criterion (BIC)	51483.9
Log-likelihood value (Full Model)	-25648.16
Cragg & Uhler's R^2	0.158

6.4.5 Handling of missing data

All predictors that were entered into the model had less than 5% of missing data, with the exception of gestational age at birth, where 35.4% of children had missing data (n=6,644) (**Table 6.9**). Surgical condition, ethnicity and IMD decile were independently predictive of missingness in the gestational age variable, suggesting that missing values in the gestational age variable were not missing completely at random (MCAR), though could be either missing at random (MAR) or missing not at random (MNAR) (**Table 6.10**).

Table 6.9 Proportion of missing data for each predictor

Predictor	**Missingness (n, %)** **N=18,796**
Gestational age at birth	6,644 (35.35%)
Surgical condition	0 (0%)
Sex	9 (0.05%)
Additional major congenital anomaly	0 (0%)
Ethnicity	619 (3.29%)
IMD decile	804 (4.28%)
Condition severity	0 (0%)

Table 6.10 Pattern of missingness for gestational age at birth

	Adjusted Odds ratio	**SE**	**95% CI**	**p-value**
Death	0.94	0.05	0.86-1.04	0.240
Total number of operations	1.00	0.00	0.99-1.00	0.345
Total number of infections	1.00	0.00	1.00-1.01	0.644
Surgical condition				0.026
Hirschsprung's Disease (Reference)	-	-	-	
Gastroschisis	1.17	0.07	1.04-1.30	
Oesophageal Atresia	1.10	0.07	0.97-1.25	
Congenital Diaphragmatic Hernia	1.01	0.07	0.88-1.16	
Posterior Urethral Valves	1.00	0.06	0.88-1.13	
Surgical Necrotising Enterocolitis	1.11	0.06	1.00-1.23	
Sex				0.517
Male (Reference)	-	-	-	
Female	0.96	0.03	0.90-1.03	
Indeterminate	0.84	0.67	0.18-3.97	
Additional major congenital anomaly				0.132
No additional major congenital anomaly (Reference)	-	-	-	
Additional major congenital anomaly	0.95	0.03	0.88-1.02	
Ethnicity				<0.001
White (Reference)	-	-	-	
Mixed	1.07	0.08	0.93-1.24	
Asian or Asian British	1.10	0.06	0.99-1.23	
Black or Black British	1.52	0.10	1.33-1.74	
Other	1.35	0.12	1.13-1.61	
Unknown	3.18	0.32	2.62-3.86	
IMD decile	1.03	0.01	1.01-1.04	<0.001
Condition severity	1.04	0.04	0.96-1.12	0.380

IRR = incidence rate ratio; SE = standard error; CI = confidence interval. Wald test used to calculate global p-values.

6.4.6 Sensitivity analysis: Complete-case analyses compared with multiple imputation analyses

The estimates from the complete-case analyses were similar to the multiple imputation analyses using predictive mean matching to impute values for gestational age at birth, suggesting that the missing values in the gestational age variable are missing at random (MAR) or that the mechanism of missingness has not altered or biased the multivariable association. The complete case analysis and multiple imputation analysis for the prediction models for mortality, total operations and total infections are presented in **Table 6.11, Table 6.12 and Table 6.13**.

Table 6.11 Complete case analysis and multiple imputation for the multivariable prediction model for mortality

	Complete case analysis			Multiple imputation analysis		
Predictors	**IRR**	**SE**	**95% CI**	**IRR**	**SE**	**95% CI**
Gestational age at birth (in weeks)*						
24-35 weeks	1.01	0.04	0.94-1.08	1.01	0.04	0.94-1.08
35-38 weeks	0.77	0.04	0.69-0.86	0.77	0.04	0.69-0.86
38-41 weeks	8.33	8.17	1.22-57.00	8.33	8.17	1.22-57.00
Surgical condition						
Hirschsprung's Disease (Reference)	-	-	-	-	-	-
Gastroschisis	1.53	0.41	0.91-2.57	1.53	0.41	0.91-2.57
Oesophageal Atresia	64.63	16.87	38.74-107.81	64.63	16.87	38.74-107.81
Congenital Diaphragmatic Hernia	1014.38	244.19	632.83-1625.97	1014.38	244.19	632.83-1625.97
Posterior Urethral Valves	1.45	0.44	0.80-2.61	1.45	0.44	0.80-2.61
Surgical Necrotising Enterocolitis	34.42	8.99	20.63-57.42	34.42	8.99	20.63-57.42
Sex						
Male (Reference)	-	-	-	-	-	-
Female	1.35	0.16	1.06-1.71	1.35	0.16	1.06-1.71
Indeterminate	2.35	5.04	0.04-156.43	2.35	5.04	0.04-156.43
Additional major congenital anomaly						
No additional major congenital anomaly (Reference)	-	-	-	-	-	-
Additional major congenital anomaly	2.16	0.27	1.69-2.75	2.16	0.27	1.69-2.75
Ethnicity						
White (Reference)	-	-	-	-	-	-
Mixed	1.28	0.34	0.76-2.15	1.28	0.34	0.76-2.15
Asian or Asian British	1.81	0.34	1.25-2.62	1.81	0.34	1.25-2.62
Black or Black British	1.58	0.39	0.97-2.58	1.58	0.39	0.97-2.58
Other	0.99	0.32	0.52-1.88	0.99	0.32	0.52-1.88
Unknown	27.43	11.76	11.84-63.56	27.43	11.76	11.84-63.56
IMD decile	0.96	0.02	0.92-1.00	0.96	0.02	0.92-1.00
Condition severity	1.81	0.24	1.39-2.35	1.81	0.24	1.39-2.35
_cons	0.00	0.00	0.00	0.00	0.00	0.00-0.00

IRR = incidence rate ratio; SE = standard error; CI = confidence interval. *Gestational age modelled using restricted cubic splines, therefore coefficients cannot be interpreted in the same manner as a linear term. Note: The results for complete case analysis and multiple imputation analysis were the same.

Table 6.12 Complete case analysis and multiple imputation for the multivariable prediction model for total operations

	Complete case analysis			Multiple imputation analysis		
Predictors	**IRR**	**SE**	**95% CI**	**IRR**	**SE**	**95% CI**
Gestational age at birth (in weeks)	0.93	0.00	0.93-0.94	0.94	0.00	0.93-0.95
Surgical condition						
Hirschsprung's Disease (Reference)	-	-	-	-	-	-
Gastroschisis	0.19	0.01	0.17-0.21	0.20	0.01	0.18-0.21
Oesophageal Atresia	0.73	0.04	0.66-0.80	0.75	0.03	0.70-0.82
Congenital Diaphragmatic Hernia	0.50	0.03	0.44-0.57	0.53	0.03	0.47-0.58
Posterior Urethral Valves	0.49	0.02	0.44-0.53	0.49	0.02	0.45-0.53
Surgical Necrotising Enterocolitis	0.63	0.03	0.56-0.69	0.71	0.04	0.64-0.79
Sex						
Male (Reference)	-	-	-	-	-	-
Female	0.89	0.03	0.84-0.94	0.90	0.02	0.86-0.94
Indeterminate	0.78	0.80	0.10-5.87	1.85	1.61	0.33-10.23
Additional major congenital anomaly						
No additional major congenital anomaly (Reference)	-	-	-	-	-	-
Additional major congenital anomaly	1.53	0.05	1.44-1.62	1.63	0.04	1.55-1.71
Ethnicity						
White (Reference)	-	-	-	-	-	-
Mixed	1.13	0.07	1.00-1.27	1.11	0.06	1.00-1.23
Asian or Asian British	1.17	0.05	1.07-1.27	1.12	0.04	1.04-1.21
Black or Black British	1.12	0.07	0.99-1.27	1.05	0.05	0.95-1.16
Other	1.03	0.08	0.88-1.21	1.01	0.07	0.89-1.15
Unknown	1.91	0.28	1.43-2.56	1.52	0.15	1.25-1.86
IMD decile	0.99	0.00	0.98-1.00	0.99	0.00	0.99-1.00
Condition severity	1.56	0.05	1.46-1.67	1.58	0.05	1.49-1.67
_cons	0.04	0.01	0.03-0.06	0.03	0.00	0.02-0.04

IRR = incidence rate ratio; SE = standard error; CI = confidence interval.

Table 6.13 Complete case analysis and multiple imputation for the multivariable prediction model for total infections

	Complete case analysis			Multiple imputation analysis		
Predictors	**IRR**	**SE**	**95% CI**	**IRR**	**SE**	**95% CI**
Gestational age at birth (in weeks)*						
24-35 weeks	0.96	0.01	0.94-0.98	0.96	0.01	0.94-0.98
35-38 weeks	1.02	0.02	0.99-1.06	1.02	0.02	0.99-1.06
38-41 weeks	0.39	0.09	0.24-0.62	0.39	0.09	0.24-0.62
Surgical condition						
Hirschsprung's Disease (Reference)	-	-	-	-	-	-
Gastroschisis	0.44	0.02	0.40-0.48	0.44	0.02	0.40-0.48
Oesophageal Atresia	0.91	0.05	0.82-1.02	0.91	0.05	0.82-1.02
Congenital Diaphragmatic Hernia	0.67	0.04	0.59-0.75	0.67	0.04	0.59-0.75
Posterior Urethral Valves	1.14	0.06	1.03-1.26	1.14	0.06	1.03-1.26
Surgical Necrotising Enterocolitis	0.91	0.05	0.82-1.02	0.91	0.05	0.82-1.02
Sex						
Male (Reference)	-	-	-	-	-	-
Female	0.90	0.03	0.84-0.95	0.90	0.03	0.84-0.95
Additional major congenital anomaly						
No additional major congenital anomaly (Reference)	-	-	-	-	-	-
Additional major congenital anomaly	2.10	0.07	1.97-2.24	2.10	0.07	1.97-2.24
Ethnicity						
White (Reference)	-	-	-	-	-	-
Mixed	1.03	0.07	0.90-1.17	1.03	0.07	0.90-1.17
Asian or Asian British	1.04	0.05	0.94-1.14	1.04	0.05	0.94-1.14
Black or Black British	0.71	0.05	0.62-0.81	0.71	0.05	0.62-0.81
Other	0.79	0.07	0.67-0.94	0.79	0.07	0.67-0.94
Unknown	0.51	0.10	0.35-0.76	0.51	0.10	0.35-0.76
IMD decile	0.98	0.01	0.97-0.99	0.98	0.01	0.97-0.99
Condition severity	1.63	0.06	1.51-1.75	1.63	0.06	1.51-1.75
_cons	0.01	0.00	0.00-0.01	0.01	0.00	0.00-0.01

IRR = incidence rate ratio; SE = standard error; CI = confidence interval. *Gestational age modelled using restricted cubic splines, therefore coefficients cannot be interpreted in the same manner as a linear term. Note: The results for complete case analysis and multiple imputation analysis were the same.

6.4.7 Prediction modelling using multivariable logistic regression

One-year outcomes were modelled using multivariable logistic regression. The characteristics and outcomes for this cohort are outlined in **Table 6.14** and **Table 6.15**.

Table 6.14 Characteristics of surgical neonates in England who had an admission in the first year of life

	Hirschsprung's Disease	Gastroschisis	Oesophageal Atresia	Congenital Diaphragmatic Hernia	Posterior Urethral Valves	Surgical Necrotising Enterocolitis	Total
	N=2,764	N=3,952	N=2,167	N=1,962	N=2,027	N=5,029	N=17,901
Gestational age (in weeks)	39 (38-40)	36 (35-37)	37 (34-39)	38 (36-39)	38 (37-40)	27 (25-32)	37 (32-39)
Missing	906 (32.8%)	1,393 (35.3%)	776 (35.8%)	672 (34.3%)	650 (32.1%)	1,792 (35.6%)	6,189 (34.6%)
Sex							
Male	2,048 (74.1%)	2,033 (51.4%)	1,244 (57.4%)	1,130 (57.6%)	2,027 (100.0%)	3,036 (60.4%)	11,518 (64.3%)
Female	716 (25.9%)	1,912 (48.4%)	922 (42.5%)	827 (42.2%)	0 (0.0%)	1,990 (39.6%)	6,367 (35.6%)
Indeterminate	0 (0.0%)	5 (0.1%)	1 (0.0%)	2 (0.1%)	0 (0.0%)	1 (0.0%)	9 (0.1%)
Missing	0 (0.0%)	2 (0.1%)	0 (0.0%)	3 (0.2%)	0 (0.0%)	2 (0.0%)	7 (0.0%)
Additional major congenital anomaly							
No additional major congenital anomaly	2,034 (73.6%)	2,936 (74.3%)	542 (25.0%)	1,006 (51.3%)	1,588 (78.3%)	1,894 (37.7%)	10,000 (55.9%)
Additional major congenital anomaly	730 (26.4%)	1,016 (25.7%)	1,625 (75.0%)	956 (48.7%)	439 (21.7%)	3,135 (62.3%)	7,901 (44.1%)
Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Ethnicity							
White	2,089 (75.6%)	3,439 (87.0%)	1,679 (77.5%)	1,343 (68.5%)	1,277 (63.0%)	3,386 (67.3%)	13,213 (73.8%)
Mixed	139 (5.0%)	181 (4.6%)	82 (3.8%)	56 (2.9%)	106 (5.2%)	248 (4.9%)	812 (4.5%)
Asian or Asian British	234 (8.5%)	60 (1.5%)	202 (9.3%)	278 (14.2%)	373 (18.4%)	644 (12.8%)	1,791 (10.0%)
Black or Black British	151 (5.5%)	63 (1.6%)	66 (3.0%)	69 (3.5%)	166 (8.2%)	462 (9.2%)	977 (5.5%)
Other	101 (3.7%)	83 (2.1%)	77 (3.6%)	63 (3.2%)	69 (3.4%)	163 (3.2%)	556 (3.1%)
Unknown	50 (1.8%)	126 (3.2%)	61 (2.8%)	153 (7.8%)	36 (1.8%)	126 (2.5%)	552 (3.1%)
IMD decile	4.0 (2.0-7.0)	4.0 (2.0-6.0)	5.0 (2.0-7.0)	4.0 (2.0-7.0)	4.0 (2.0-7.0)	4.0 (2.0-6.0)	4.0 (2.0-7.0)
Missing	93 (3.4%)	324 (8.2%)	75 (3.5%)	70 (3.6%)	40 (2.0%)	98 (2.0%)	700 (3.9%)

Data are presented as median (IQR) for continuous measures, and n (%) for categorical measures.

Table 6.15 Outcomes of surgical neonates

	Hirschsprung's Disease N=2,764	Gastroschisis N=3,952	Oesophageal Atresia N=2,167	Congenital Diaphragmatic Hernia N=1,962	Posterior Urethral Valves N=2,027	Surgical Necrotising Enterocolitis N=5,029	Total N=17,901
Mortality							
Survival	2,678 (96.9%)	3,790 (95.9%)	1,757 (81.1%)	1,078 (54.9%)	1,958 (96.6%)	3,728 (74.1%)	14,989 (83.7%)
Mortality	86 (3.1%)	162 (4.1%)	410 (18.9%)	884 (45.1%)	69 (3.4%)	1,301 (25.9%)	2,912 (16.3%)
Total number of operations	3 (1-4)	1 (0-2)	2 (1-4)	1 (0-2)	2 (1-3)	2 (1-4)	2 (1-3)
Total number of infections	0 (0-1)	0 (0-1)	1 (0-2)	0 (0-1)	1 (0-2)	1 (0-2)	1 (0-2)

Data are presented as median (IQR) for continuous measures, and n (%) for categorical measures.

6.4.8 Model specification: Survival at 1-year

The full prediction model for survival at 1-year using multivariable logistic regression is presented in **Table 6.16**. Predictors included gestational age at birth (in weeks), surgical condition, sex, presence of an additional major congenital anomaly, ethnicity, IMD decile and condition severity. Gestational age was modelled using restricted cubic splines.

Table 6.16 Multivariable prediction model for survival at 1 year using logistic regression

Predictors	**Adjusted OR**	**SE**	**95% CI**	**p-value**
Gestational age at birth (in weeks)*				<0.001
24-34 weeks	1.11	0.02	1.07-1.15	
34-38 weeks	1.01	0.03	0.95-1.08	
38-41 weeks	1.59	0.57	0.79-3.22	
Surgical condition				<0.001
Hirschsprung's Disease (Reference)	-	-	-	
Gastroschisis	0.96	0.17	0.67-1.36	
Oesophageal Atresia	0.20	0.03	0.15-0.28	
Congenital Diaphragmatic Hernia	0.05	0.01	0.03-0.06	
Posterior Urethral Valves	1.02	0.22	0.67-1.54	
Surgical Necrotising Enterocolitis	0.33	0.05	0.24-0.45	
Sex				0.079
Male (Reference)	-	-	-	
Female	0.88	0.05	0.79-0.99	
Indeterminate	0.37	0.39	0.04-3.01	
Additional major congenital anomaly				0.011
No additional major congenital anomaly (Reference)	-	-	-	
Additional major congenital anomaly	0.85	0.05	0.75-0.96	
Ethnicity				<0.001
White (Reference)	-	-	-	
Mixed	0.85	0.12	0.65-1.11	
Asian or Asian British	0.72	0.06	0.61-0.86	
Black or Black British	0.66	0.08	0.52-0.83	
Other	0.89	0.15	0.64-1.24	
Unknown	0.09	0.02	0.06-0.14	
IMD Decile	1.03	0.01	1.01-1.06	0.002
Condition severity	0.61	0.04	0.54-0.69	<0.001
_cons	0.65	0.36	0.22-1.91	

OR = odds ratio; SE = standard error; CI = confidence interval; _cons = constant. Wald test used to calculate global p-values. *Gestational age modelled using restricted cubic splines, therefore coefficients cannot be interpreted in the same manner as a linear term

6.4.8.1 Model performance: Survival at 1-year

The area under ROC curve for the prediction model for one-year survival was 0.82, suggesting excellent discrimination (where 0.7-0.8 is acceptable, 0.8-0.9 is excellent and >0.9 is outstanding) (**Figure 6.2**).[280 281] Calibration was also good, as shown in the calibration belt plot (test statistic 0.10, p-value=0.75, **Figure 6.3**) and calibration plot (calibration-in-the-large 0.00, calibration slope 1.00, **Figure 6.4**). The AIC, BIC and the log-likelihood value is reported in **Table 6.17**, along with measures of overall model performance (i.e. the Brier score and Nagelkerke's R^2).

Figure 6.2 Receiver operating characteristic curve for the prediction model for one-year survival

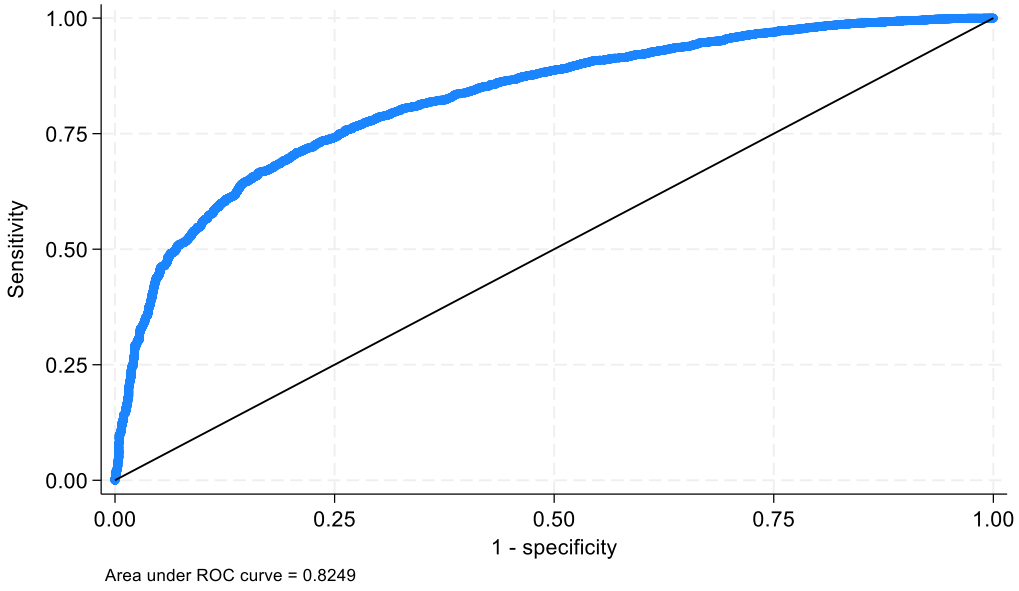


Figure 6.3 Evaluating the calibration of the prediction model for one-year survival using a calibration belt plot

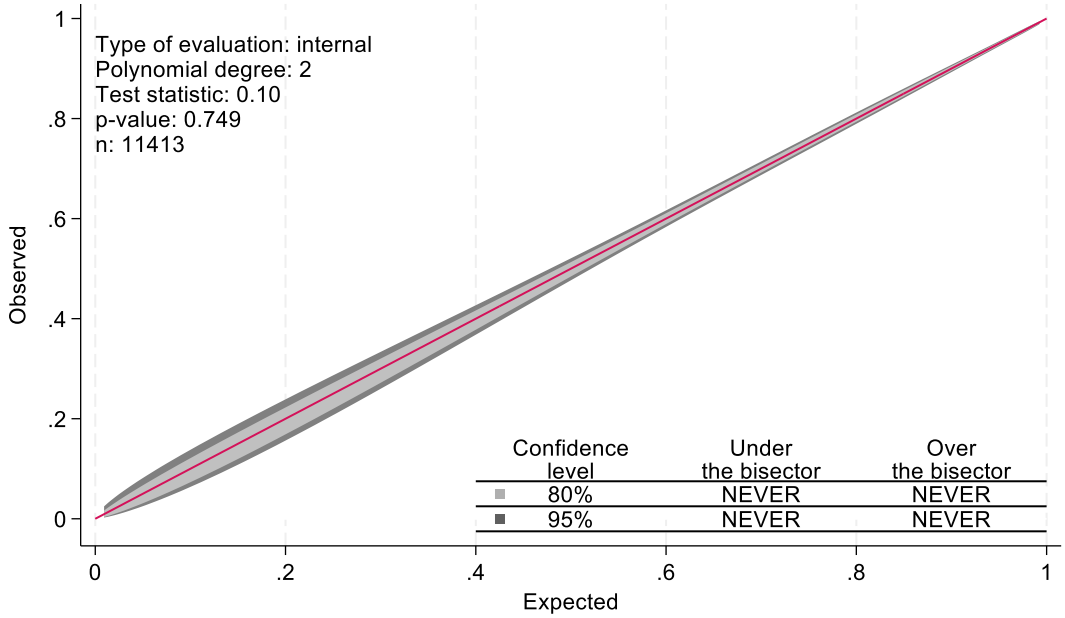
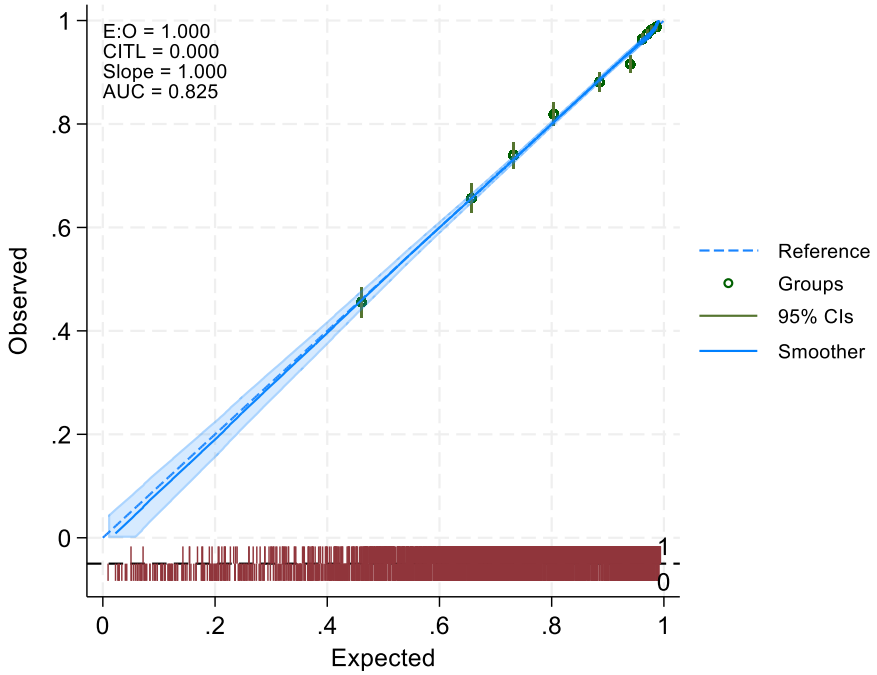


Figure 6.4 Evaluating the calibration of the prediction model for one-year survival using a calibration plot



E:O = Ratio of expected and observed events for model calibration; CITL = calibration-in-the-large for model calibration; Slope = calibration slope for model calibration; AUC = area under the receiver operating characteristic (ROC) curve

Table 6.17 Measures of model assessment for the multivariable prediction model for one-year survival using logistic regression

Model assessment	Value
Akaike Information Criterion (AIC)	7846.686
Bayesian Information Criterion (BIC)	7986.194
Log-likelihood value (Full Model)	-3904.343
Cragg & Uhler's R^2 (Nagelkerke's R^2)	0.313
Brier score	0.1065

6.4.8.2 Internal validation: One-year survival prediction model

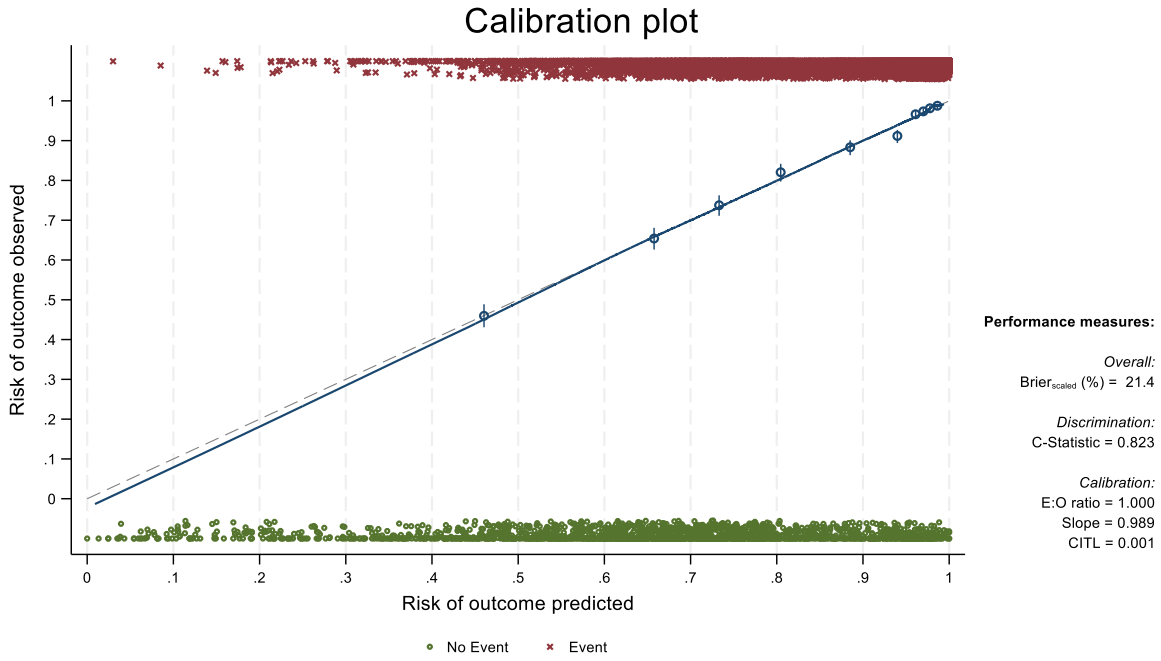
The optimism-adjusted C-statistic was 0.823, which was calculated from 100 bootstrap samples. The bootstrap performance for calibration was similar to the apparent performance (CITL 0.001, slope 0.989). The results of internal validation using a bootstrap validation approach, including the apparent performance, bootstrap performance and shrinkage factors, are presented in **Table 6.18**. The bootstrap performance and apparent performance was similar. The calibration plot is presented in **Figure 6.5**.

Table 6.18 Internal validation using a bootstrap validation approach: Apparent performance, bootstrap performance and shrinkage factors

Apparent performance			Bootstrap performance (Optimism adjusted)		
	Value	95% CI		Value	Bootstrap 95% CI
Overall:			**Overall:**		
Brier scaled (%)	21.8		Brier scaled (%)	21.4	
Discrimination:			**Discrimination:**		
C-Statistic	0.825	0.815-0.835	C-Statistic	0.823	0.812-0.832
Calibration:			**Calibration:**		
E:O ratio	1.000		E:O ratio	1.000	0.994-1.007
CITL	0.000	-0.056-0.056	CITL	0.001	-0.057-0.051
Slope	1.000	0.949-1.051	Slope	0.989	0.939-1.033
Shrinkage factors					
Heuristic shrinkage	0.992				
Bootstrap shrinkage	0.989				

E:O = Ratio of expected and observed events for model calibration; CITL = calibration-in-the-large for model calibration; Slope = calibration slope for model calibration

Figure 6.5 Calibration plot of observed against expected probabilities



6.4.9 Model specification: 3 or more operations within the first year of life

The full prediction model for 3 or more operations within the first year of life using multivariable logistic regression is presented in **Table 6.19**. Predictors included gestational age at birth (in weeks), surgical condition, sex, presence of an additional major congenital anomaly, ethnicity, IMD decile and condition severity.

Table 6.19 Multivariable prediction model for 3 or more operations in the first year of life using logistic regression

Predictors	Adjusted OR	SE	95% CI	p-value
Gestational age at birth (in weeks)	0.99	0.01	0.98-1.00	0.021
Surgical condition				<0.001
Hirschsprung's Disease (Reference)	-	-	-	
Gastroschisis	0.16	0.01	0.14-0.18	
Oesophageal Atresia	0.48	0.04	0.41-0.56	
Congenital Diaphragmatic Hernia	0.10	0.01	0.08-0.12	
Posterior Urethral Valves	0.27	0.02	0.23-0.32	
Surgical Necrotising Enterocolitis	0.54	0.04	0.46-0.63	
Sex				0.138
Male (Reference)	-	-	-	
Female	0.93	0.04	0.85-1.02	
Indeterminate	-	-	-	
Additional major congenital anomaly				<0.001
No additional major congenital anomaly (Reference)	-	-	-	
Additional major congenital anomaly	1.74	0.08	1.59-1.90	
Ethnicity				<0.001
White (reference)				
Mixed	0.96	0.09	0.79-1.16	
Asian or Asian British	0.93	0.06	0.81-1.06	
Black or Black British	0.75	0.07	0.62-0.90	
Other	0.97	0.12	0.76-1.23	
Unknown	0.28	0.06	0.18-0.44	
IMD decile	0.99	0.01	0.98-1.00	0.182
Condition severity	1.22	0.06	1.10-1.35	<0.001
_cons	1.99	0.45	1.28-3.09	

OR = odds ratio; SE = standard error; CI = confidence interval; _cons = constant. Wald test used to calculate global p-values.

6.4.9.1 Model performance: 3 or more operations within the first year of life

The area under ROC curve for the prediction model for 3 or more operations within the first year of life was 0.71, suggesting acceptable discrimination (where 0.7-0.8 is acceptable, 0.8-0.9 is excellent and >0.9 is outstanding) (**Figure 6.6**).[280 281] Model calibration is shown in the calibration belt plot (test statistic 33.50, p-value<0.001, **Figure 6.7**) and calibration plot (calibration-in-the-large 0.00, calibration slope 1.00, **Figure 6.8**). The AIC, BIC and the log-likelihood value is reported in **Table 6.20**, along with measures of overall model performance (i.e. the Brier score and Nagelkerke's R^2).

Figure 6.6 Receiver operating characteristic curve for the prediction model for 3 or more operations within the first year of life

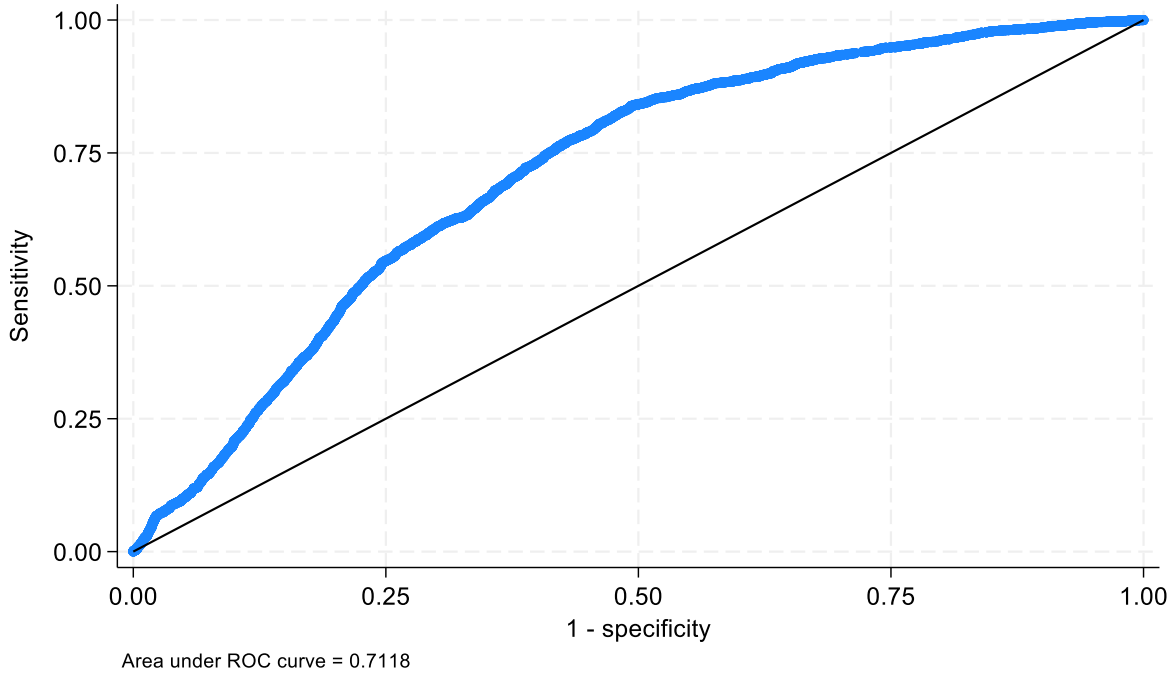


Figure 6.7 Evaluating the calibration of the prediction model for 3 or more operations within the first year of life using a calibration belt plot

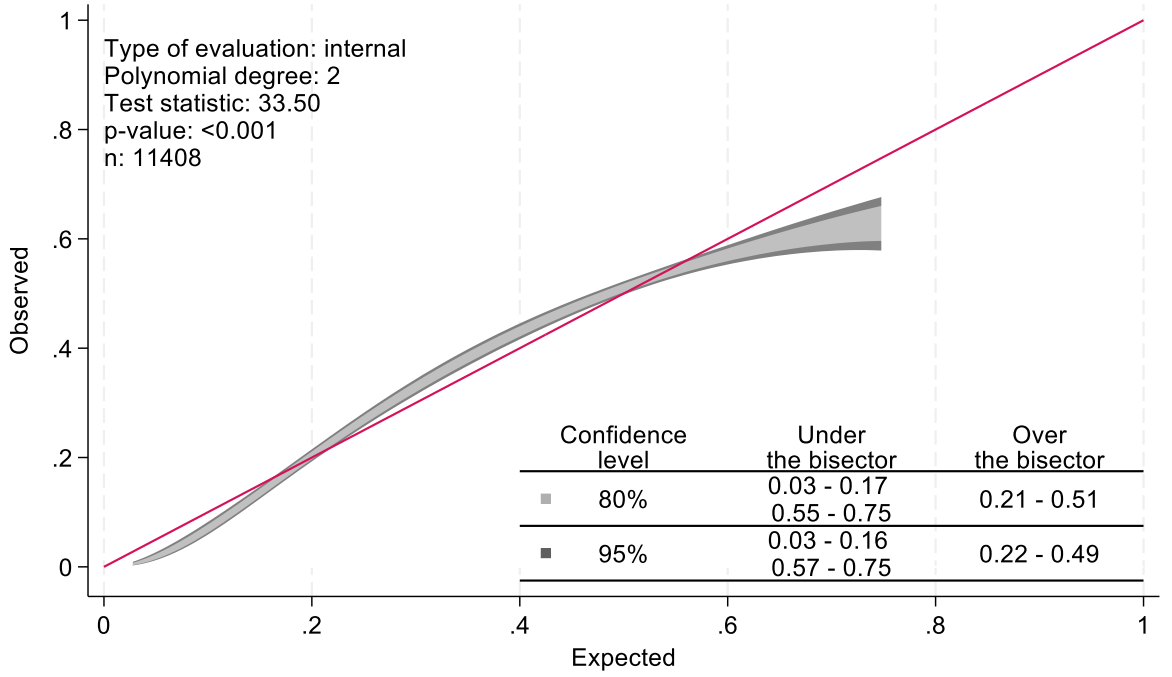
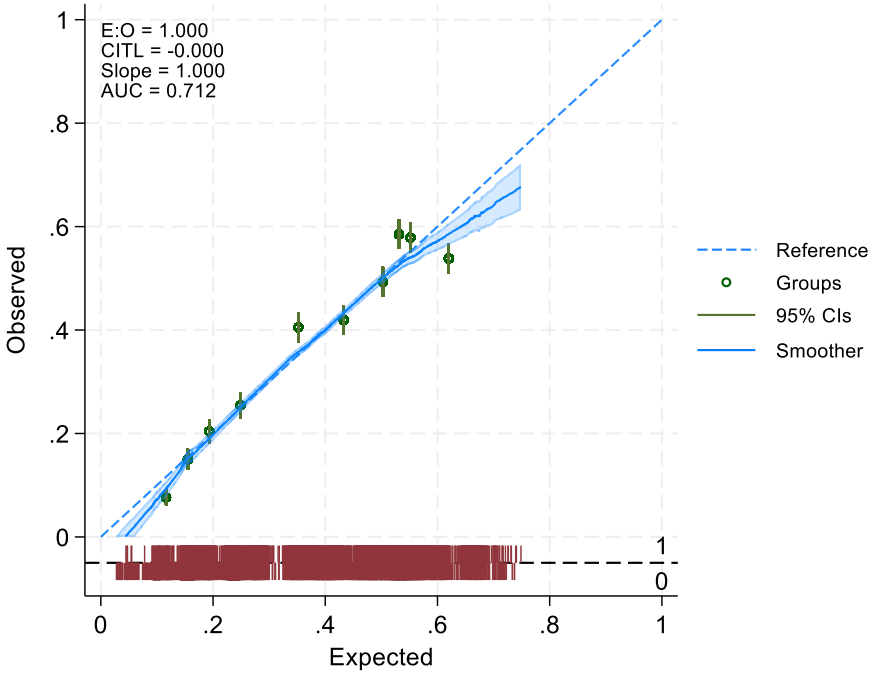


Figure 6.8 Evaluating the calibration of the prediction model for 3 or more operations within the first year of life using a calibration plot



E:O = Ratio of expected and observed events for model calibration; CITL = calibration-in-the-large for model calibration; Slope = calibration slope for model calibration; AUC = area under the receiver operating characteristic (ROC) curve

Table 6.20 Measures of model assessment for the multivariable prediction model for 3 or more operations within the first year of life using logistic regression

Model assessment	**Value**
Akaike Information Criterion (AIC)	13480.99
Bayesian Information Criterion (BIC)	13598.46
Log-likelihood value (Full Model)	-6724.493
Cragg & Uhler's R^2 (Nagelkerke's R^2)	0.178
Brier score	0.2033

6.4.9.2 Internal validation: prediction model for 3 or more operations

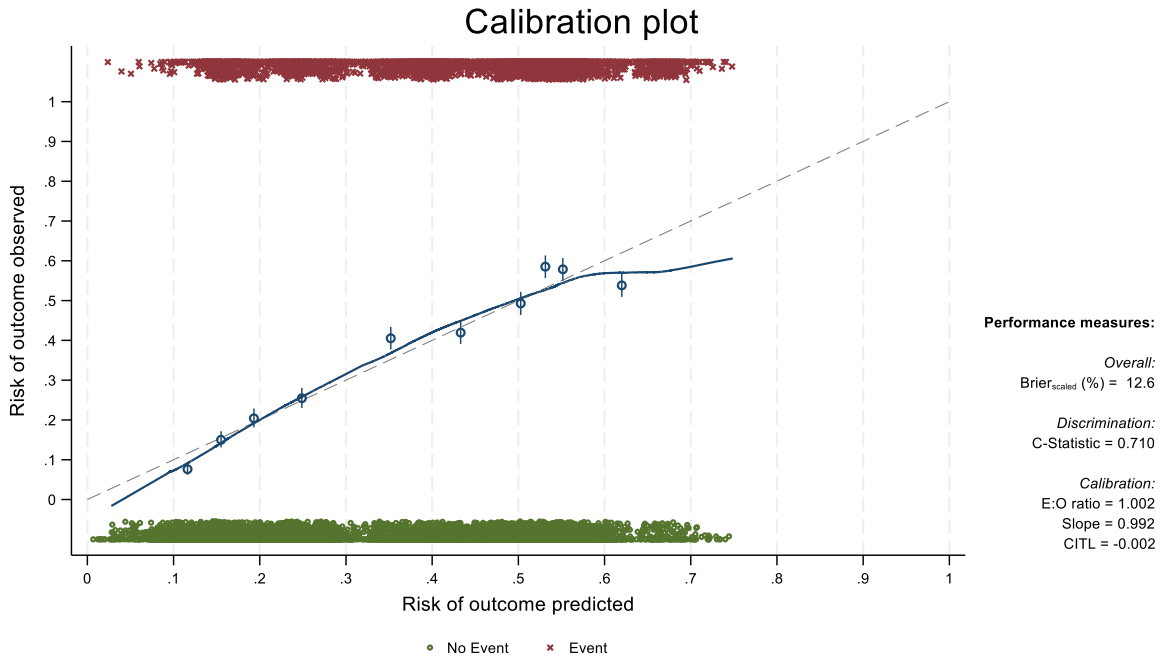
The optimism-adjusted C-statistic was 0.710, compared to the apparent performance C-statistic of 0.712. The optimism-adjusted calibration-in-the-large and optimism-adjusted calibration slope was -0.002 and 0.992 respectively. The results of internal validation using a bootstrap validation approach, including the apparent performance, bootstrap performance and shrinkage factors, are presented in **Table 6.21**. The calibration plot is presented in **Figure 6.9**.

Table 6.21 Internal validation of prediction model for operations using a bootstrap validation approach: Apparent performance, bootstrap performance and shrinkage factors

Apparent performance			**Bootstrap performance (Optimism adjusted)**		
	Value	**95% CI**		**Value**	**Bootstrap 95% CI**
Overall:			**Overall:**		
Brier scaled (%)	12.8		Brier scaled (%)	12.6	
Discrimination:			**Discrimination:**		
C-Statistic	0.712	0.702-0.721	C-Statistic	0.710	0.700-0.720
Calibration:			**Calibration:**		
E:O ratio	1.000		E:O ratio	1.002	0.994-1.007
CITL	-0.000	-0.041-0.041	CITL	-0.002	-0.047-0.037
Slope	1.000	0.946-1.054	Slope	0.992	0.940-1.041
Shrinkage factors					
Heuristic shrinkage	0.991				
Bootstrap shrinkage	0.992				

E:O = Ratio of expected and observed events for model calibration; CITL = calibration-in-the-large for model calibration; Slope = calibration slope for model calibration

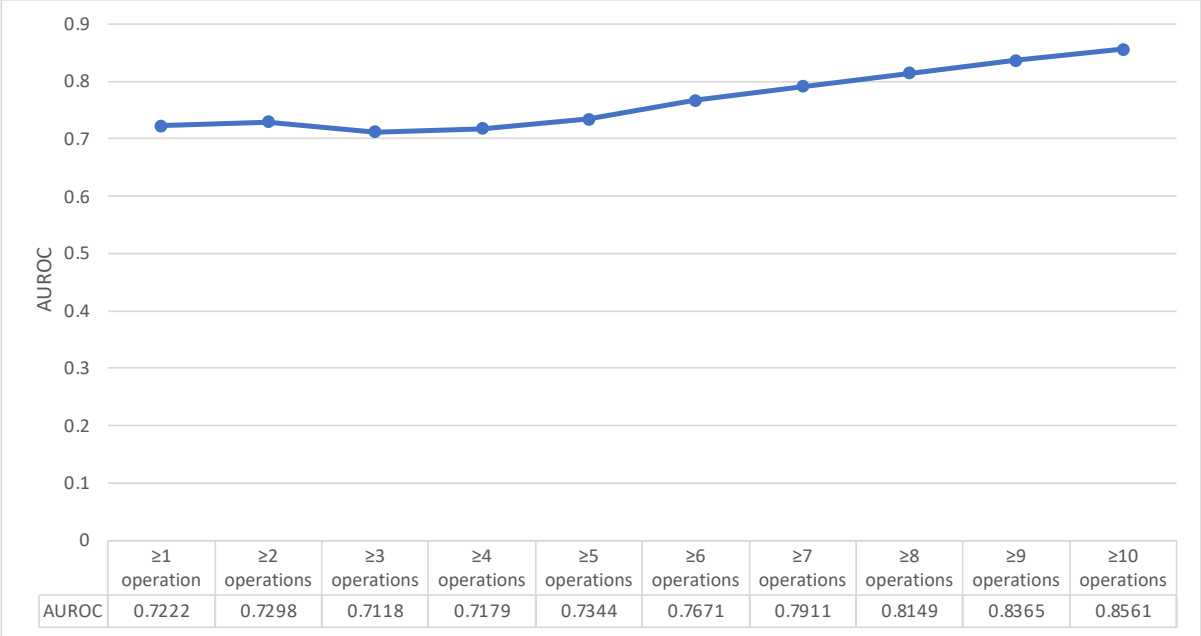
Figure 6.9 Internal validation of prediction model for operations: Calibration plot of observed against expected probabilities



6.4.9.3 Exploring different cut-off points for dichotomising number of operations

As a higher cut-off for the number of operations is used, the discrimination of the model increases (**Figure 6.10**).

Figure 6.10 Exploring different cut-off points for dichotomising number of operations: plot of dichotomised threshold of number of operations against area under the receiver operating characteristic (AUROC) curve



	≥1 operation	≥2 operations	≥3 operations	≥4 operations	≥5 operations	≥6 operations	≥7 operations	≥8 operations	≥9 operations	≥10 operations
AUROC	0.7222	0.7298	0.7118	0.7179	0.7344	0.7671	0.7911	0.8149	0.8365	0.8561

6.4.10 Model specification: infection within the first year of life

The full prediction model for infection within the first year of life using multivariable logistic regression is presented in **Table 6.22**. Predictors included gestational age at birth (in weeks), surgical condition, sex, presence of an additional major congenital anomaly, ethnicity, IMD decile and condition severity. Gestational age was modelled using restricted cubic splines.

Table 6.22 Multivariable prediction model for infection in the first year of life using logistic regression

Predictors	Adjusted OR	SE	95% CI	p-value
Gestational age at birth (in weeks)*				0.039
24-34 weeks	1.05	0.02	1.01-1.08	
34-38 weeks	0.94	0.02	0.90-0.99	
38-41 weeks	1.53	0.35	0.98-2.39	
Surgical condition				<0.001
Hirschsprung's Disease (Reference)	-	-	-	
Gastroschisis	1.03	0.07	0.90-1.18	
Oesophageal Atresia	0.99	0.08	0.85-1.15	
Congenital Diaphragmatic Hernia	0.44	0.04	0.38-0.51	
Posterior Urethral Valves	1.33	0.10	1.15-1.54	
Surgical Necrotising Enterocolitis	1.42	0.11	1.21-1.65	
Sex				<0.001
Male (Reference)	-	-	-	
Female	0.87	0.04	0.80-0.94	
Indeterminate	-	-	-	
Additional major congenital anomaly				<0.001
No additional major congenital anomaly (Reference)	-	-	-	
Additional major congenital anomaly	1.85	0.08	1.70-2.02	
Ethnicity				<0.001
White (Reference)	-	-	-	
Mixed	0.87	0.08	0.73-1.04	
Asian or Asian British	0.97	0.06	0.85-1.11	
Black or Black British	0.70	0.06	0.59-0.83	
Other	0.75	0.09	0.59-0.94	
Unknown	0.22	0.04	0.15-0.32	
IMD decile	0.97	0.01	0.96-0.98	<0.001
Condition severity	1.30	0.07	1.18-1.43	<0.001
_cons	0.30	0.13	0.13-0.72	

OR = odds ratio; SE = standard error; CI = confidence interval; _cons = constant. Wald test used to calculate global p-values. *Gestational age modelled using restricted cubic splines, therefore coefficients cannot be interpreted in the same manner as a linear term.

6.4.10.1 Model performance: infection within the first year of life

The area under ROC curve for the infection within the first year of life was 0.64, suggesting poor discrimination (where 0.7-0.8 is acceptable, 0.8-0.9 is excellent and >0.9 is outstanding) (**Figure 6.11**).[280 281] However, model calibration was good, as shown in the calibration belt plot (test statistic 0.39, p-value=0.53, **Figure 6.12**) and calibration plot (calibration-in-the-large -0.00, calibration slope 1.00, **Figure 6.13**). The AIC, BIC and the log-likelihood value is reported in **Table 6.23**, along with measures of overall model performance (i.e. the Brier score and Nagelkerke's R^2).

Figure 6.11 Receiver operating characteristic curve for the prediction model for 3 or more operations within the first year of life

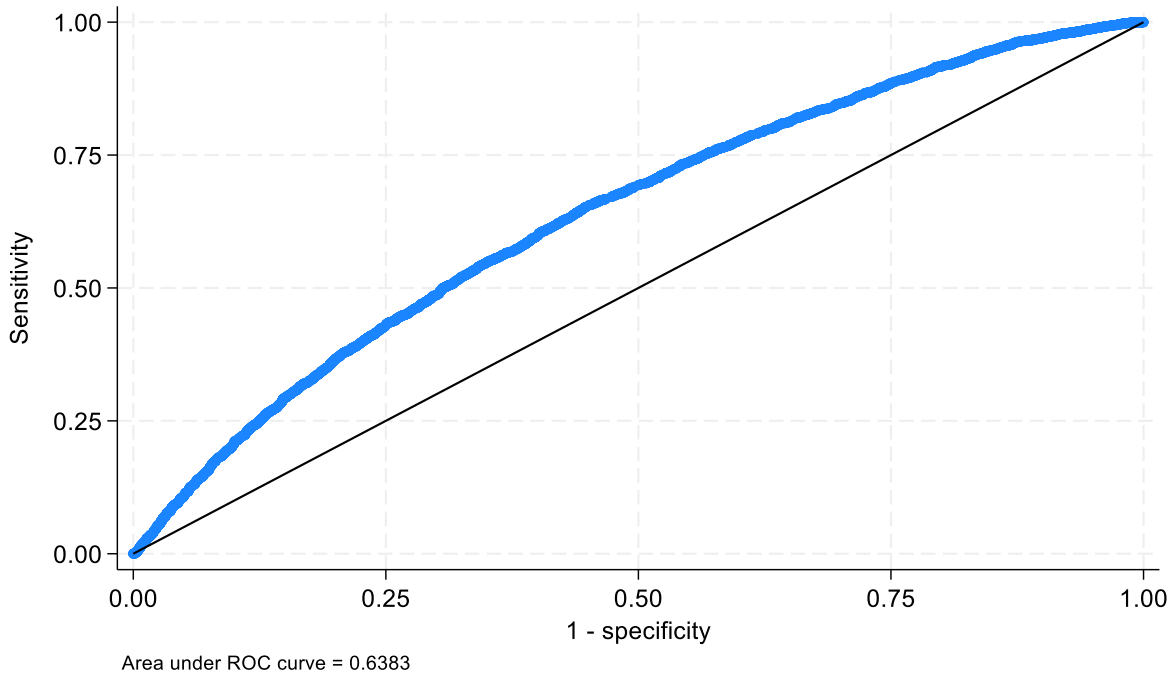


Figure 6.12 Evaluating the calibration of the prediction model for infection within the first year of life using a calibration belt plot

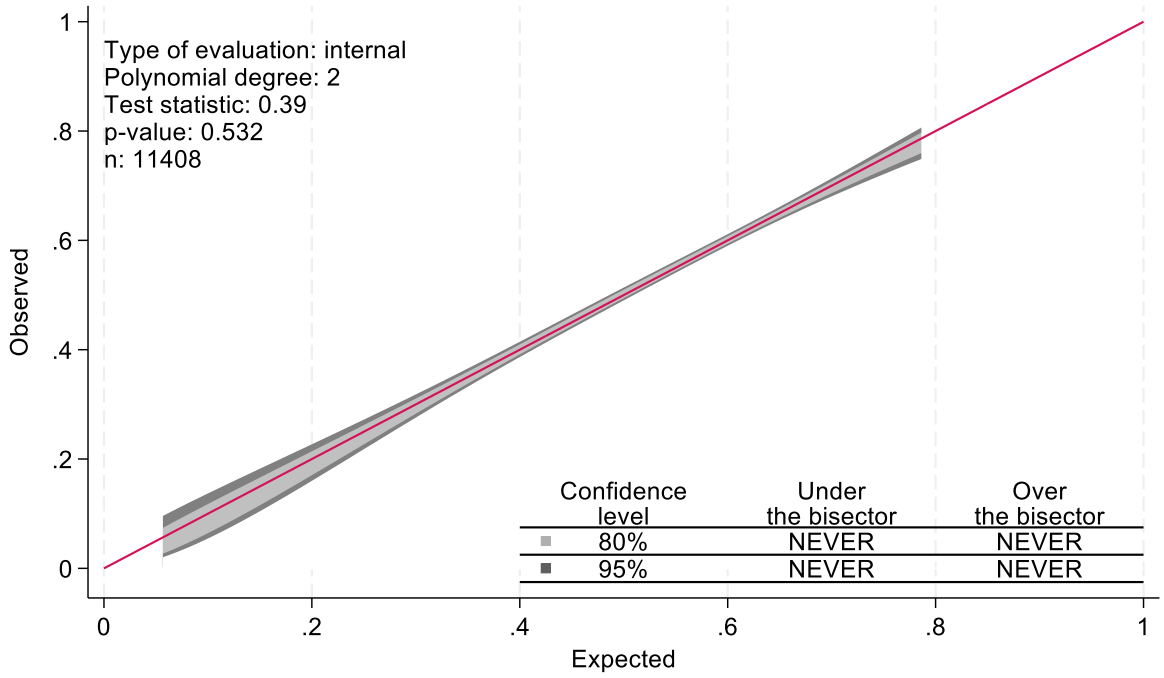
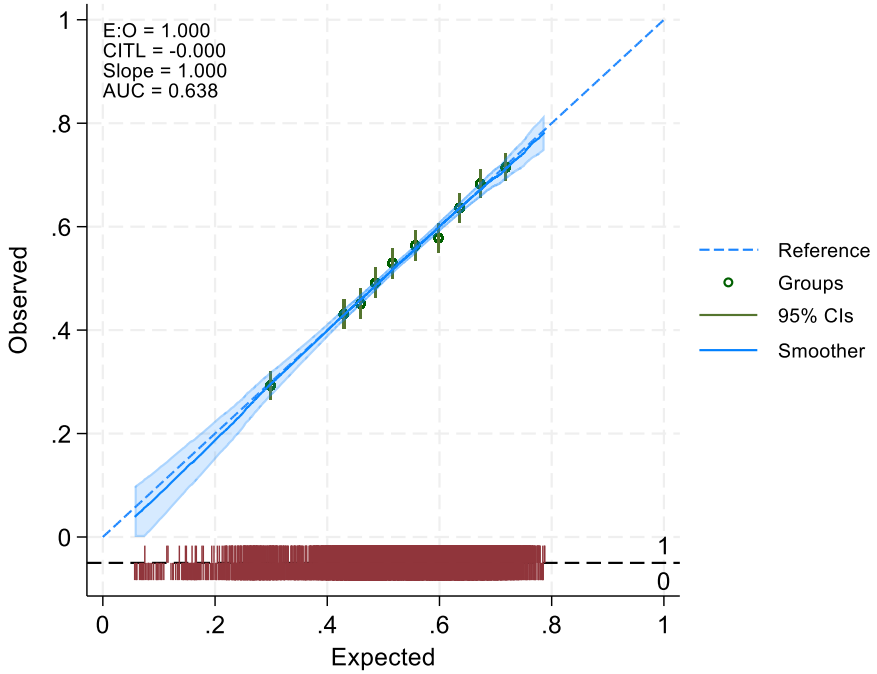


Figure 6.13 Evaluating the calibration of the prediction model for infection within the first year of life using a calibration plot



E:O = Ratio of expected and observed events for model calibration; CITL = calibration-in-the-large for model calibration; Slope = calibration slope for model calibration; AUC = area under the receiver operating characteristic (ROC) curve

Table 6.23 Measures of model assessment for the multivariable prediction model for one-year survival using logistic regression

Model assessment	Value
Akaike Information Criterion (AIC)	15079.6
Bayesian Information Criterion (BIC)	15211.76
Log-likelihood value (Full Model)	-7521.8
Cragg & Uhler's R^2 (Nagelkerke's R^2)	0.080
Brier score	0.2336

6.4.10.2 Internal validation: One-year infection prediction model

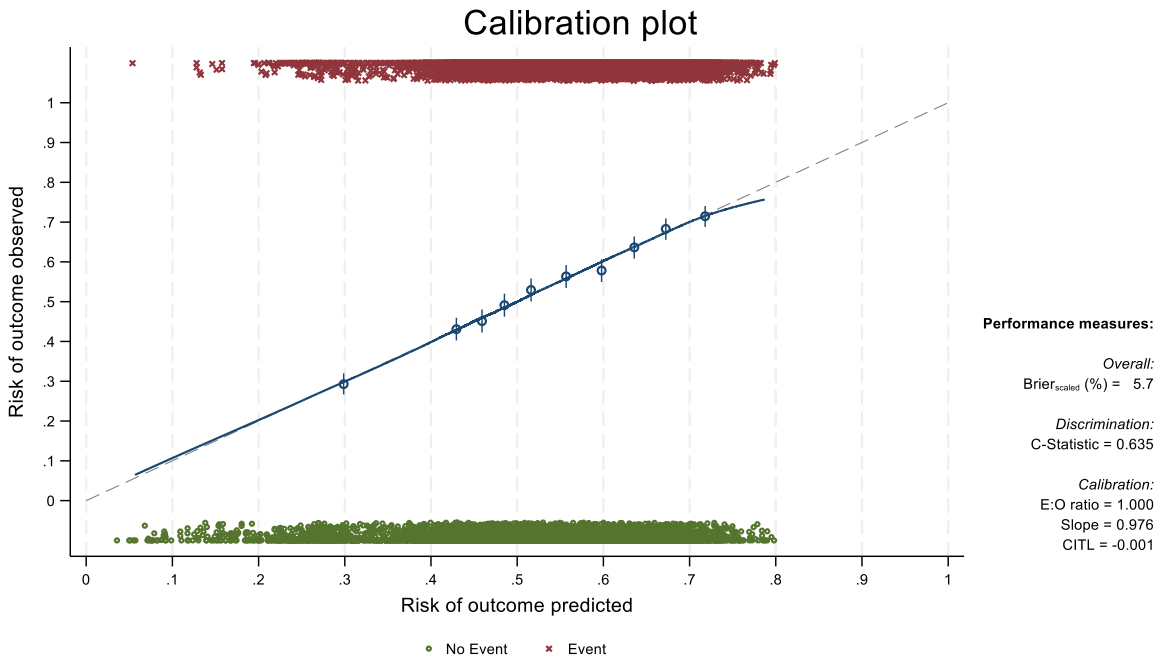
The optimism-adjusted C-statistic was 0.635, compared to the apparent performance C-statistic of 0.638. The optimism-adjusted calibration-in-the-large and optimism-adjusted calibration slope was -0.001 and 0.976 respectively. The results of internal validation using a bootstrap validation approach, including the apparent performance, bootstrap performance and shrinkage factors, are presented in **Table 6.24**. The calibration plot is presented in **Figure 6.14**.

Table 6.24 Internal validation using a bootstrap validation approach: Apparent performance, bootstrap performance and shrinkage factors

Apparent performance			Bootstrap performance (Optimism adjusted)		
	Value	95% CI		Value	Bootstrap 95% CI
Overall:			**Overall:**		
Brier scaled (%)	6.0		Brier scaled (%)	5.7	
Discrimination:			**Discrimination:**		
C-Statistic	0.638	0.628-0.648	C-Statistic	0.635	0.625-0.645
Calibration:			**Calibration:**		
E:O ratio	1.000		E:O ratio	1.000	0.985-1.019
CITL	-0.000	-0.038-0.038	CITL	-0.001	-0.057-0.035
Slope	1.000	0.922-1.078	Slope	0.976	0.902-1.068
Shrinkage factors					
Heuristic shrinkage	0.976				
Bootstrap shrinkage	0.976				

E:O = Ratio of expected and observed events for model calibration; CITL = calibration-in-the-large for model calibration; Slope = calibration slope for model calibration

Figure 6.14 Internal validation of prediction model for infections: Calibration plot of observed against expected probabilities



6.5 Discussion

6.5.1 Main findings

To date, this is the largest study to develop and internally validate multivariable prediction models for long-term outcomes of children with a paediatric surgical condition in England. This study demonstrates that it is feasible to utilise HES data for prediction modelling in paediatric surgery, though the discrimination and calibration of the models vary. Several predictors of long-term outcomes were found and common across differing outcomes. The variables that were included in the prediction models were gestational age at birth, surgical condition, sex, presence of an additional major congenital anomaly, ethnicity, IMD decile and condition severity. The multivariable logistic regression model for survival at 1 year had excellent discrimination (AUROC 0.82), along with good calibration (CITL 0.00, calibration slope 1.00). The multivariable logistic regression model for three or greater operations had acceptable discrimination (AUROC 0.71) and good calibration (CITL 0.00, calibration slope 1.00). However, the multivariable logistic regression for infection within the first year of life had poor discrimination (AUROC 0.64), though good calibration (CITL 0.00, calibration slope 1.00). These findings suggest it is possible to predict the outcomes of one-year survival and three or greater operations, even in the absence of predictors pertaining to operative management or more condition-specific data.

6.5.2 Modelling count versus binary outcomes

Although the modelling of counts was ideal for the outcomes of interest in this study, such as total number of operations and total number of infections, the literature on prediction modelling of count data in healthcare is currently underdeveloped.[316] Poisson regression and negative binomial regression are two models commonly used to model count data, however the literature on using Poisson regression for healthcare prediction modelling is

sparse, and even less developed for negative binomial regression. In a study by Halfon et al., a Poisson model was used to predict risk of falls amongst hospitalised patients, however only the first fall was modelled (i.e. a binary outcome), as opposed to modelling a count.[317] Though there are studies outside of the field of healthcare that predict count data, in particular modelling of wildfires and traffic accidents, methods to report prediction model performance, and importantly, internal validation is underreported or reported heterogeneously.[318-320] Both model performance measures and internal validation are crucial important aspects of transparent model reporting according to the TRIPOD guidelines.[273]

As the methodology for prediction modelling in healthcare is well-developed for logistic regression, models using both count data and binary outcomes are presented. The outcomes of interest in this study naturally lend themselves to a clinically meaningful binary form, as it is of interest whether a child dies or survives, had an infection or not, and had more operations than expected (i.e. 3 or more operations). As children had varying lengths of follow-up time and the likelihood of having an event increases over time, the time-point of one year was used. Although the dichotomisation of linear predictors and outcomes is commonly conducted, usually for the reason of achieving perceived simplicity, there are a number of disadvantages of dichotomisation that must be considered. For instance, it creates an artificial step-function and can lead to the loss of information. Altman et al. cautions against the dichotomisation of predictors, particularly when more appropriate statistical methods exist for choosing the functional form of continuous variables exist.[321] However, in the absence of well-established tools to internally validate and report the overall performance of prediction models for count data, using logistic regression for clinically important outcomes remains a sensible and practical

alternative. Importantly, this highlights a gap in the current literature. Whilst prediction modelling methods and techniques in healthcare have been well-described for binary outcomes, and to a lesser extent linear outcomes and time to event outcomes, more research and development is required into prediction modelling methodologies for count data.[322 323]

6.5.3 Limitations

One of the limitations of this study is that predictors were limited by data available in the HES database. Similarly to the NNRD database, details from operative notes were not available, along with other management factors known to have an important impact on long-term outcome. Furthermore, it was challenging to obtain suitable markers of condition severity. For instance, prenatal lung-to-head ratio and size of the diaphragmatic defect are markers of condition severity for children with CDH, but were not routinely collected or available in the HES database. As the HES database is based in England, the generalisability of these findings to other settings and countries is unknown. Missing data is a common issue encountered when using routinely collected data. Although the proportion of missing data was low for most of the *a priori* selected predictors, 37% of children in this study had missing data for gestational age at birth. However, the coefficients were largely similar between the complete case analyses and sensitivity analyses using multiple imputation, suggesting that the missingness in the gestational age variable did not result in biased estimates. A small-for-gestational-age variable could not be included in the models due to high proportions of missingness in both the birthweight and gestational age variables.

Although restricted cubic splines are a good solution for modelling continuous variables that have a nonlinear relationship with the outcome of interest, and can improve the performance of a prediction model, they nonetheless add complexity to the model and coefficients cannot be interpreted in the same manner as linear terms. Thus, the added complexity and improved performance comes at the cost of interpretability.

6.5.4 Significance

Despite the lack of granular data, a prediction model for one-year survival with good discrimination and calibration was developed, even in the absence of operative details. An advantage of this prediction model is its simplicity and ability to use demographic predictors and characteristics to predict long-term survival. Such models can be useful for benchmarking, comparing management factors and comparing research populations, such as between centres and hospitals. Importantly, they take into account that certain demographic characteristics may have an important impact on long-term outcomes, which should be considered in order to make meaningful comparisons. The poor discrimination of the prediction model for infection with the first year of life suggests that there are other factors that are not included this model or are currently unmeasured. Further studies are required to elucidate whether it is possible to optimise the model for one-year infection using other predictors.

Although it would be reasonable to build condition-specific prediction models, this study demonstrates that it is possible to build models that comprise of common predictors across surgical conditions. Although it is perhaps possible to improve the predictive performance of these models by individualising them to the specific condition, the results of this study

show that it is still possible to have good predictive performance even when using general demographic factors.

6.5.5 Implications for further research

External validation of prediction models presents its own challenges, including the availability of other databases and the costs associated with accessing additional databases, and important predictors in the developed model may not be available in other databases. Nonetheless, before these models can be used in clinical practice or applied to other settings, external validation of these models is required in a differing database to assess the generalisability of the model. Validation of these models should be encouraged in other settings and countries, which may have differing patient case-mixes and management practices. Furthermore, exploring the significance and impact of adding new predictions, such as operative data, is an important aspect of model updating. In order to build robust and clinically relevant prediction models in paediatric surgery, further research is required to build databases containing important management factors and condition-specific severity factors. There exist new opportunities to create multimodal databases, holding different types of data and outcomes, such as operative data, quality of life outcomes and parent-reported outcomes, which may strengthen the utility and predictive performance of prediction models.

Chapter 7

Discussion

7.1 Summary of key findings

7.1.1 Existing literature on long-term outcomes following childhood surgery

In **Chapter 2**, a systematic review was conducted to explore the long-term outcomes of children diagnosed with one of the six study conditions, and to identify factors associated with outcome variation. Of 27,934 records identified, 156 studies across the six study conditions were included in the systematic review. Out of the long-term outcome domains (namely survival, quality of life, developmental outcomes, re-operation, episodes of infection and readmission), only survival was consistently reported across the six study conditions (75 out of 159 studies, 47.2%). Reporting on developmental and quality of life outcomes from large-scale studies was particularly sparse in the existing literature. The pooled proportion for one-year survival was highest amongst those with HD at 98% (95%CI 97-100), followed by 96% for those with gastroschisis (95%CI 95-97), 92% for those with OA (95%CI 89-95), 77% for those with CDH (95%CI 72-82) and 61% for those with surgical NEC (95%CI 47-76). However, there was substantial evidence of heterogeneity between studies for the outcome of survival, with the exception of gastroschisis (I^2=0.00%, p=0.86 for gastroschisis studies). Thus, even for the most commonly reported outcome of one-year long-term survival, it was challenging to produce a meaningful summary estimate for most of the surgical conditions of interest due to the paucity of reporting or significant heterogeneity between studies.

Nonetheless, several factors were found to be associated with variation in long-term outcomes from the systematic review, which were used to inform the development of a directed acyclic graph. From the theoretical framework of the directed acyclic graph, the minimal sufficient adjustment set for estimating the total effect of surgical condition on long-term outcome included the following five factors: gestational age, sex, ethnicity,

presence of a major congenital anomaly, and socio-economic status. These were common factors that were associated with multiple outcomes across surgical conditions. The associations between these candidate predictors and outcomes in paediatric surgery were tested in subsequent chapters (**Chapters 4** and **6**) using the NNRD and HES databases through the development of multivariable prediction models for both short-term and long-term outcomes amongst children with a surgical condition of interest.

7.1.2 The feasibility of utilising the National Neonatal Research Database to explore outcomes following childhood surgery

As the findings of the systematic review demonstrated in **Chapter 2**, outcomes were often reported heterogeneously, and it was challenging to aggregate outcome data in the field of paediatric surgery. The NNRD is a database of routinely collected data from neonatal units across the United Kingdom and presented a potential solution to addressing some of these barriers faced in paediatric surgical research. Thus, in **Chapter 3**, the feasibility and utility of the NNRD to explore outcomes of surgical neonates was investigated. Using NNRD data, the population-based incidence, characteristics and outcomes of surgical neonates were described for those admitted to neonatal care in England and Wales from 2012-2020. The condition incidences of HD and PUV estimated from NNRD data were considerably lower compared to other studies, such as the previous prospective cohort studies undertaken by BAPSCASS.[2 259] This highlights one of the weaknesses of utilising NNRD data to investigate children with certain paediatric surgical conditions, as the database only captures the children who present in the neonatal period and are admitted to a neonatal unit in the UK. Although this would capture most children with surgical NEC, OA and CDH, this poses a problem for conditions such as HD and PUV, which may present later in childhood, and even into adulthood in some cases. Nevertheless, the characteristics and

outcomes of this cohort were comparable to what has been previously reported in the literature, as described in **Chapter 3**. Whilst it was possible to ascertain certain short-term outcomes using NNRD data, such as survival, late-onset sepsis and severe brain injury, which belong to the COIN outcome set, it was not feasible to investigate other important outcomes of interest, such as number of operations and number of episodes of infections. Furthermore, there was a lack of operative data, which is critical to collect when investigating factors associated with outcomes following childhood surgery.

Whilst data on neonatal characteristics were generally comprehensive in the NNRD, such as gestational age, birthweight and birth characteristics, there was a lack of granular data on condition-specific severity factors relating to the study conditions, which are clinically important factors associated with outcome variation. Although some variables had a high proportion of missing data, such as mother's blood group, many of the candidate predictors identified from the directed acyclic graph in **Chapter 2** had high levels of complete data (i.e. missing data less than 10%), with the exception of the variable for mother's ethnicity. Finally, it was not possible to explore outcomes beyond the neonatal period of this cohort of infants. Although the NNRD does hold two-year outcome data, including neurodevelopmental outcomes, this was largely missing for this cohort of infants, likely due to the fact that a large proportion of these term surgical infants would not meet the hospital's criteria for two-year follow-up, which is often limited to preterm infants or term infants with high likelihood of neurodevelopmental delay such as infants with hypoxic ischaemic encephalopathy.

7.1.3 The feasibility of utilising NNRD data to develop multivariable prediction models

The findings from **Chapter 4** demonstrate that it is feasible to develop and internally validate rigorous prediction models for certain neonatal outcomes, specifically survival, late-onset sepsis and severe brain injury. This highlights one of the benefits of using routinely collected data, as it allows for larger sample sizes to be utilised for the development of multivariable prediction models. For the outcome of survival, two variable selection strategies were employed: the first driven by subject-matter knowledge (i.e. using the results of the systematic review from **Chapter 2;** Model 1) and a second more traditional, data-driven approach (Model 2). Both models performed similarly on performance measures, including discrimination (AUROC 0.83 for Model 1 compared to 0.84 for Model 2), model calibration (E:O=1.00, CITL=-0.000, slope=1.000 for Model 1 compared to E:O=0.999, CITL=0.006, slope=1.016 for Model 2), Cragg & Uhler's R^2 (Model 1: 0.15 vs. Model 2: 0.15) and the Brier score (Model 1: 0.09 vs. Model 2: 0.09). Due to the similar performance, the literature-driven model was favoured over the data-driven approach on the basis of superior explainability and the principle of parsimony.

For the outcome of late-onset sepsis, predictors included in the model were gestational age at birth, mother's ethnicity, IMD decile, presence of an additional major anomaly, sex and surgical condition. This prediction model for late-onset sepsis performed well on both discrimination (AUROC 0.84), model calibration (E:O=1.000, CITL=-0.000, slope=1.000) and the Brier score (0.052). The Cragg & Uhler's R^2 was 0.097. For the multivariable prediction model for severe brain injury, the predictors included were gestational age at birth, mother's ethnicity, IMD decile, presence of an additional major anomaly, sex, surgical condition, surfactant given during resuscitation, Apgar score at 5 minutes and

antenatal steroid therapy. Similar to the model for late-onset sepsis, the model for severe brain injury also performed well on discrimination (AUROC=0.83) and model calibration (E:O=1.000, CITL=-0.000, slope=1.000). The Brier score was 0.082 and the Cragg & Uhler's R^2 was 0.15. The limitations for **Chapter 4** were the closely related to those outlined in **Chapter 3**. Although prediction models were able to be developed and internally validated for the neonatal outcomes of survival, late-onset sepsis and severe brain injury using data from the NNRD, it was not possible to examine important outcomes such as total number of operations and quality of life outcomes. Furthermore, there was a lack of long-term outcome data and predictors included in the models were limited to those that were available. Whilst it is desirable to include all data available to develop the prediction models, certain conditions with a higher incidence, such as surgical necrotising enterocolitis, may have had a greater influence on the prediction models.

7.1.4 The feasibility of utilising the HES database to explore outcomes following childhood surgery

In order to investigate long-term outcomes of children with one of the six study conditions, the HES database was explored as a potential data source. In **Chapter 5**, the feasibility of utilising HES data to investigate long-term outcomes for children with one of the six study conditions was explored. Identification of children with a study surgical condition using ICD-10 diagnostic coding alone resulted in implausible condition incidences and outcomes for certain conditions. For instance, if based on ICD-10 diagnostic coding alone, 17.2% of OA survivors (n=669) and 32.3% (n=2846) of CDH survivors did not have any operations, which is implausible given the nature of these conditions. Using additional criteria for these surgical conditions, such as the presence of a relevant OPCS-4 code within a certain

timeframe, resulted in more plausible incidences and outcomes that aligned with the findings of previous studies.

Although more granular data on operative procedures and clinically relevant markers of condition-specific severity were lacking, it was still nonetheless possible to attain markers of condition severity for each of the study conditions and to investigate outcomes deemed important from existing core outcome sets, such as survival, total number of infections and number of operations. There was a low proportion of missing data for the key predictors from the directed acyclic graph developed in **Chapter 2**, however variables derived from the maternity tails in the HES database, such as birthweight and gestational age, had a relatively high proportion of missing data.

7.1.5 The feasibility of utilising HES data to develop prediction models for long-term outcomes

In **Chapter 6**, the feasibility of developing multivariable prediction models for long-term outcomes amongst children with a paediatric surgical condition was demonstrated. Although several of the outcomes of interest were counts, namely number of infections and number of operations, methodologies and the literature pertaining to prediction modelling of count data is currently underdeveloped, particularly in the area of model assessment and evaluation. Thus, multivariable prediction models were developed using both negative binomial regression to model count data and logistic regression to model one-year outcomes (i.e. survival, three or more operations and infections within the first year of life), using a full-model approach with the same predictors: gestational age at birth, surgical condition, sex, presence of an additional major congenital anomaly, ethnicity, IMD decile and condition severity.

The prediction model using multivariable logistic regression for one-year survival performed well on discrimination (AUROC 0.82) and calibration (E:O 1.000, CITL=0.000, slope=1.000). The Cragg & Uhler's R^2 was 0.313 and the Brier score was 0.1065. Internal validation of the prediction model for one-year survival was also conducted (optimism-adjusted C-statistic 0.823; optimism-adjusted calibration: CITL 0.001, slope 0.989). The prediction model using multivariable logistic regression for the outcome of 3 or more operations within the first year of life had acceptable discrimination (AUROC 0.71) and calibration (E:O=1.000, CITL=-0.000, slope 1.000). The Cragg & Uhler's R^2 and Brier score was 0.178 and 0.203 respectively. On internal validation of the model, the optimism-adjusted c-statistic was 0.710 (95%CI 0.70-0.72) and the optimism-adjusted calibration was reasonable (E:O ratio 1.002, CITL=-0.02, slope 0.992). Finally, the prediction model using multivariable logistic regression for the outcome of infection within the first year of life performed the worst of the three models, with poor discrimination (AUROC 0.64) but good calibration (E:O=1.000, CITL=-0.000, slope=1.000). The Cragg & Uhler R^2 was 0.080 and the Brier score was 0.234. On internal validation of the model, the optimism-adjusted c-statistic was 0.635 (95%CI 0.63-0.65) and the optimism-adjusted calibration was reasonable (E:O ratio 1.000, CITL=-0.001, slope 0.976). Thus, whilst predictors of having an infection within the first year of life were identified (i.e. gestational age at birth, surgical condition, sex, presence of an additional major anomaly, ethnicity, IMD decile and condition severity), the performance of the model suggests that there are other factors, either unmeasured or not available within the HES database, that are influencing the outcome of having an infection within the first year of life. Despite the high proportion of missingness in variables from the maternity tails, the models using complete-case analysis and multiple imputation analysis

with imputed variables for gestational age were similar, suggesting that using complete-case analysis did not result in biased estimates.

7.2 Interpretation of findings

The results presented in this thesis suggest that it is feasible to utilise databases of routinely collected data to explore some outcomes following childhood surgery, though there are some notable limitations that should be carefully considered.

The results from the systematic review in **Chapter 2** highlighted the paucity of data from large-scale studies and the difficulties in aggregating data for meta-analyses due to significant heterogeneity between studies, even for the most commonly reported outcome of survival. This inability to produce meaningful estimates of outcomes underscores one of the barriers of establishing an evidence base to inform clinical decisions in the management of rare paediatric surgical conditions. This has been previously noted by Allin et al.[6] Although utilising databases of routinely collected data may help address the issue of small sample sizes and allow for the analysis of population-wide samples, using such data may present a new series of questions and limitations. Further work is required to optimise "big data", particularly in the form of routinely collected data, to investigate research questions in a robust manner.

The systematic review in **Chapter 2** also demonstrated that certain outcomes were less commonly reported, particularly quality of life and developmental outcomes. Study investigators should be encouraged to choose the most clinically relevant and important outcomes, not just those that are more readily available. Where such outcomes are absent, efforts should be made to measure and report these outcomes in a standardised fashion, in

order to generate research that is relevant and clinically meaningful. This can help reduce research wastage and contribute to answering clinical questions and aid decision making. Of the six study conditions, core outcome sets have been developed for HD and gastroschisis, though none have been developed for PUV and core outcome sets for CDH, OA and surgical NEC are still under development.[82 254 324]

To address some of the challenges in paediatric surgical research raised by the systematic review, the feasibility of using the NNRD as a data source was investigated to elucidate outcomes following childhood surgery. The NNRD is an excellent data source to investigate the outcomes of preterm infants, particularly medically relevant neonatal outcomes, such as late-onset sepsis and severe brain injury. Several studies have utilised the NNRD to investigate retinopathy of prematurity, hypoxic-ischaemic encephalopathy and early parenteral nutrition use.[247 325 326] However, the findings of this thesis suggest that the NNRD is less well equipped to explore the clinically important outcomes of neonates with a surgical condition. This is primarily due to the fact that factors and outcomes that are of clinical relevance for these surgical conditions are not routinely collected in the database, such as number of operations. Notably, there was a lack of operative data and factors relating to condition-specific severity, such as the size of defect amongst children with CDH and extent of bowel affected for children with HD and surgical NEC.

However, even in the absence of operative factors and factors relating to condition-specific severity factors, it was still possible to develop prediction models using NNRD data that performed well on discrimination and model calibration. There were several factors that were common in all three models, suggesting that there are common predictors across the six surgical conditions that are associated with outcome variation. These models highlight

the potential demographic factors that should be adjusted for and included in case-mix adjustment when comparing centres or benchmarking management practices. However, further work is required, such as external validation in another database and model updating if other important predictors are found.

Finally, as long-term outcomes following childhood surgery could not be examined using the NNRD, the HES database was explored as a potential data source for this purpose. Despite the known inaccuracies of ICD-10 diagnostic coding in the HES database, it was possible to refine the cohort using OPCS-4 codes for many of the study conditions. Furthermore, it was feasible to investigate clinically meaningful long-term outcomes, such as survival, total infections and total operations, for children with one of the six study conditions. Multivariable prediction models for long-term outcomes were developed and internally validated using common predictors, including gestational age at birth, surgical condition, sex, presence of an additional major congenital anomaly, ethnicity, IMD decile and condition severity.

7.3 Research context

The potential tools at the researcher's disposal have increased considerably in the digital age, providing novel opportunities in the field of paediatric surgical research: from the historic use of paper records that required data extraction by an investigator, to prospective cohort studies conducted by BAPS CASS, to the current environment where routinely collected data and large nation-wise databases are improving in terms of both data quality and the type of data that are being collected. This new availability of data in greater amounts than ever before also gives rise to new opportunities in prediction modelling and

artificial intelligence. This thesis demonstrated both the strengths and limitations of utilising large databases of routinely collected data for paediatric surgical research.

7.4 Strengths of this thesis

The studies that comprise this thesis represent some of the largest analyses in recent years examining the outcomes of six rare paediatric surgical conditions in England, encompassing 8,090 children from the NNRD and 18,824 children from the HES database. Utilising nationwide databases allowed for greater sample sizes and whole-population coverage, in a field of research that has been historically dominated by smaller institutional series.[327] Six different surgical conditions were explored, covering a wide range of body systems that may be encountered and managed by a general paediatric surgeon, presenting in various stages of childhood and requiring diverse management strategies. Furthermore, core predictors of outcome variation amongst this diverse surgical population were identified, many of which were common across outcomes and found to be significant predictors in both the NNRD and HES database.

Although rigorous prospective studies have been conducted by BAPSCASS for these surgical conditions, this thesis builds upon the current literature by elucidating the strengths and limitations of utilising databases of routinely collected data. The analyses in this thesis also encompass a large number of cases in the United Kingdom and span a wide timeframe. Rigorous prediction models for both short-term and long-term outcomes were developed and internally validated, following the TRIPOD guidelines.

7.5 Limitations

7.5.1 Challenges in external validation of multivariable prediction models

Before prediction models can be utilised in healthcare settings, it is crucial for these models to undergo external validation to ascertain the generalisability and utility of the model beyond the database from which it was developed. The performance of a model, when assessed in its training dataset, will invariably perform better, providing optimistic model performance results which may not be an accurate reflection of its performance in the "real world" or in a clinical setting. However, despite the importance of external validation of prediction models, it is rarely undertaken. Even when an attempt at external validation is made, investigators may randomly split the database (i.e. one segment for development, one segment for validation). This is generally viewed as an inadequate form of external validation, owing to the fact that both segments still originated from the same database and therefore will carry the same systematic database biases. Similarly, temporal splitting or splitting the database based on time epochs is not generally viewed as a sufficient form of external validation, for the same reasons.[328]

Furthermore, prediction models developed in one population will often not have the same performance in other settings, so it is crucial to externally validate models in the specific population of interest before implementing the prediction model. Riley et al. suggests that several external validation studies across differing populations are required to truly understand a model's generalisability and utility in varying settings, not just a singular external validation study, though this is very rarely undertaken.[328] Furthermore, a systematic review by Collins et al. found that even when external validation studies were performed, the majority did not report calibration, though most did investigate

discrimination.[329] Thus, this remains a clear barrier to utilising prediction models in clinical practice.

Another common barrier to performing external validation of an existing prediction model is the lack of another database or the difficulties posed in acquiring one of sufficient size. Databases of smaller sample sizes may be less useful in external validation, particularly if the medical condition of interest is rare or poorly coded in existing databases. There may be significant cost associated with acquiring data or substantial delays in obtaining access. However, even when a second database is acquired, there may be additional challenges posed, such as missing data or the issue of missing predictors, for instance, if a particular predictor is systematically not recorded or collected in the external validation database. Similarly, external validation may not be possible if the outcome of interest is not present in the external database. Although previous studies have handled this issue by omitting the missing predictor entirely when undertaking external validation in another database, this is generally viewed as an unsatisfactory solution to the issue due to the potential to introduce bias. One solution to the issue of a systematically missing predictor is to impute values for the predictor. Held et al. found that this was a superior solution to complete omission of the predictor.[330] However, there is still little clarity regarding the optimal methodology in the case of several systematically missing predictors. Imputing one predictor may be a satisfactory solution, however, if two or even three predictors are systematically missing in the database for external validation, then it may not be possible at all to utilise the database for this purpose, which highlights one of the practical challenges when attempting the external validation of prediction models.

7.5.2 Handling of missing data

The handling of missing data is a common issue that arises in the utilisation of routinely collected data, particularly for databases collected for a primary purpose other than clinical research, though it is not an issue exclusive to routinely collected data. Missing data can introduce bias and contribute to the loss of statistical power, including in the development and validation of multivariable prediction models. To address the issue of missing data in this thesis, multiple imputation was used where appropriate. As the complete-case analysis and multiple imputation analysis resulted in similar estimates, this suggests that the missing data did not significantly contribute to biased estimates in this thesis.

7.5.3 The importance of assessing the feasibility of utilising databases of routinely collected data

Though nationwide databases of routinely collected data are increasingly being used, including those utilising the NNRD and HES databases, few studies will explicitly assess the utility and limitations of using databases of routinely collected data. In order to draw meaningful conclusions and generate recommendations for clinical practice, study investigators need to critically assess the benefits and limitations of the data. One crucial consideration of using routinely collected data is the impact of the study definition for the condition, as well as the possible subgroups of the population that may be inadvertently excluded from the study. One issue commonly cited in clinical research is that stringent inclusion and exclusion criteria can have a negative impact upon the generalisability of a study's findings.[331] At worst, the study may exclude the most unwell patients, creating a blind spot in the current understanding of the disease and increase the gaps in the literature for the most vulnerable members of the disease population. This in turn, can worsen the disparities in management practices and outcomes for these patients. Furthermore, study

findings may not translate well in clinical settings, where not all patients will adhere to strict eligibility criteria.[331-333] When utilising the NNRD, a subset of neonates may be discharged from neonatal care units to standalone surgical centres early in life, for instance within the first few days of life. If these neonates do not return to neonatal care units, the outcomes of these neonates may be missing in the NNRD. Another subgroup of patients that was missing from the NNRD were those that did not present during the neonatal period. Thus, the study could only draw conclusions relating to neonatal presenting HD and PUV, for instance.

7.5.4 Potential for the development to build condition-specific models

Data from all six surgical conditions were included to develop the prediction models. However, due to the varying incidences, it is possible that certain conditions, such as surgical necrotising enterocolitis, had greater influence on the prediction model. Nonetheless, this study found common predictors that were associated across the study conditions and demonstrated it was possible to build robust prediction models based on demographic factors.

7.6 Implications for clinical practice

This thesis presents contemporary data for each of the six study conditions that would be of interest to patients and their parents, particularly incidence and outcome data. The outcome data presented can be used by health services in England to provide counselling for parents and accurate prognostication, for both short-term and long-term outcomes. Notably, outcomes are described at 1-year, 5-year and 10-year time points for survival, total infections and total operations—outcomes that have been shown to be important to patients, parents and clinicians.

Clinicians can utilise the information from the prediction models to have a better understanding of children who might be at higher risk of certain outcomes, such as infections, due to their demographic factors. For instance, using this data, health professionals can better identify parents of children who might be at higher risk of infections and therefore facilitate conversations regarding their child's risk, preventive measures, and the signs and symptoms of infection. It is crucial that parents are provided with counselling based on recent data, so that they can develop a realistic view of what to expect for their child, including an understanding of the short-term and long-term implications of their child's surgical condition. Though outcome data has historically been sparse for some of these study conditions due to their rare incidence, this thesis now presents parents and the public with up-to-date population-wide outcome data in England.

Finally, the prediction models can serve as a reminder and education tool for clinicians and parents that there may be other factors apart from management that may influence a child's outcome, including demographic and infant factors such as gestational age and socioeconomic status. Not only do the prediction models quantify the influence of certain predictors on the outcome of interest, but they can also demonstrate some of the nuances of outcome variation, including the combination of factors that influence the development of an outcome and showing that predictors may have varying degrees of associated risk.

7.7 Recommendations for further research

The findings of this thesis give rise to the following recommendations for further research:

1. This thesis only explored the following six surgical conditions: HD, gastroschisis, OA, CDH, PUV and surgical NEC. Further studies are needed to explore the utility

of routinely collected data in investigating the outcomes of other neonatal and paediatric surgical conditions.

2. The prediction models in this thesis aggregated data across six different surgical conditions. Future studies could develop condition-specific prediction models to investigate if this would improve predictive performance.
3. To aid data aggregation and be able to generate meaningful estimates of outcomes amongst children requiring surgery, there should be greater standardisation of outcome reporting, including time-points at which the outcome is measured. Furthermore, study investigators should strive to report clinically meaningful outcomes, including those identified in core outcome sets for the specific condition of interest.
4. Despite quality of life being important to both clinicians and parents, few studies report this outcome. More studies should endeavour to collect quality of life outcomes, including parent-reported quality of life data, in order to better inform clinical management decisions and improve existing guidelines.
5. Whilst the NNRD has been optimised to serve research into the medical conditions of neonates, it could better serve the surgical population by incorporating additional data fields into the routine collection process, such as more granular fields pertaining to condition-specific severity markers and operative procedures. For instance, better assimilation with existing operative records could provide valuable data for surgical neonates and influence decision making processes. However, this may present an additional burden on resources, whilst serving a relatively small population of patients in neonatal care.
6. Several prediction models for both short-term and long-term outcomes have been developed and internally validated in this thesis. Before these prediction models

can be utilised, the models should be externally validated in another database, preferably in another setting or country. There is further scope for model updating should other clinically important variables be collected in the external database. Following external validation of these prediction models, further studies could characterise the impact of instituting such prediction models in clinical or research settings.

7. Methodologies relating to the development of multivariable prediction models for binary, linear and even survival outcomes are currently well-described in healthcare settings. However, further research is required to establish appropriate methods and tools to develop prediction models for count data, including model assessment and internal validation.
8. Although the HES database contains more operative data and condition-specific severity markers than the NNRD, ICD-10 coding was often inaccurate. Data linkage to an existing registry could enhance case identification, including those who truly have the disease and excluding those who do not.
9. The introduction of a universal electronic patient record (EPR) could provide the level of clinical detail required to more extensively investigate outcomes following childhood surgery.
10. Both the NNRD and HES databases have their individual strengths and weaknesses. Data linkage of routinely collected data could help ameliorate some of these weaknesses whilst optimising the strengths of the individual databases, such as reducing missing data, more rigorous identification of cases, and allowing for a greater variety of predictors and outcomes to be explored. There is now the possibility to link health databases with other databases, such as those containing school outcomes. The next step for further research would be the development and

maintenance of a multi-modal database containing linked databases of routinely collected data, and allowing for operative data and parent-reported data to be collected, including quality of life outcomes.

7.8 Conclusion

There exist several challenges in the field of paediatric surgical research, including rare condition incidences and heterogenous outcome reporting. Utilising "big data" and databases of routinely collected data may present a potential solution to these barriers. This thesis elucidated the feasibility and utility of using databases of routinely collected data, specifically for the NNRD and HES databases, to explore outcomes following childhood surgery and identify predictors of outcome variation. Using routinely collected data, several multivariable prediction models were developed for both short-term and long-term outcomes for children with one of the six surgical conditions. Common predictors of outcome variation in this population included gestational age at birth, surgical condition, sex, presence of an additional major anomaly, ethnicity, IMD decile and condition severity. Further studies are required to externally validate these prediction models and may present an opportunity for model updating should there be additional predictors found in external databases. Data linkage and the development of multi-modal database that capture important outcomes, such as quality of life data, could help identify factors associated with outcome variation in paediatric surgery and provide robust data on which to base clinical decisions.

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Appendices

Appendix 2.1: Search Strategy

Database	Search strategy
Ovid Medline	1. Enterocolitis, Necrotizing/ or necrotising enterocolitis.mp. 2. necrotizing enterocolitis.mp. 3. Hirschsprung Disease/ or Hirschsprung*.mp. 4. aganglion*.mp. 5. HSCR.mp. 6. gastroschisis.mp. or Gastroschisis/ 7. Esophageal Atresia/ or esophag* atresia*.mp. 8. oesophag* atresia*.mp. 9. OA-TOF.mp. 10. EA-TEF.mp. 11. Hernias, Diaphragmatic, Congenital/ or congenital diaphragm* 12. Bochdalek hernia*.mp. 13. Morgagni hernia*.mp. 14. Infant, Newborn/ or neonat*.mp. 15. infant*.mp. 16. newborn*.mp. 17. diaphragm* hernia.mp. or Hernia, Diaphragmatic/ 18. 14 or 15 or 16 19. 17 and 18 20. posterior urethra* valve*.mp. 21. posterior urethra* membrane*.mp. 22. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 19 or 20 or 21 23. Treatment Outcome/ or treatment outcome*.mp. 24. Follow-Up Studies/ or follow-up stud*.mp. 25. Retrospective Studies/ or retrospective stud*.mp. 26. quality of life.mp. or “Quality of Life”/ 27. child development.mp. or Child Development/ 28. follow-up.mp. 29. long-term.mp. 30. Mortality/ or mortality.mp. 31. Death.mp. or Death/ 32. Survival/ or survival.mp. 33. Sepsis/ or sepsis.mp. or Neonatal Sepsis/ 34. re-operation.mp. 35. reoperation.mp. or Reoperation/ 36. Hospitalization/ or Patient Readmission/ or re-admission.mp. 37. readmission.mp. 38. hospitali?ation*.mp. 39. Education/ 40. education*.mp. 41. Academic Performance/ or academic.mp. 42. Educational Status/ 43. growth.mp. or Growth/ 44. Liver Diseases/ or liver disease*.mp. 45. incontinen*.mp. or Urinary Incontinence/ 46. Fecal Incontinence/ 47. enterocolitis.mp. or Enterocolitis/ 48. stress.mp or Stress, Psychological/ 49. Motor Skills/ or motor.mp. 50. Cognition/ or cogniti*.mp. 51. bowel function*.mp. 52. bowel movement*.mp.

	53. Constipation/ or constipation*.mp. 54. Surgical Stomas/ or stoma*.mp. 55. 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 56. surger*.mp. 57. operati*.mp. 58. Surgical Procedures, Operative/ or surgical procedur*.mp. 59. surgic*.mp. 60. postoperat*.mp. 61. Laparotomy/ or laparotom*.mp. 62. Laparoscopy/ or laparoscop*.mp. 63. resection.mp. 64. Enterostomy/ or enterostom*.mp. 65. Anastomosis, Surgical/ or anastomos*.mp. 66. Jejunostomy/ or jejunostom*.mp. 67. Colostomy/ or colostom*.mp. 68. Drainage/ or drainage.mp. 69. procedur*.mp. 70. repair.mp. 71. Thoracoscopy/ or thoracoscop*.mp. 72. Thoracotomy/ or thoracotom*.mp. 73. Endoscopy/ or endoscop*.mp. 74. silo.mp. 75. closure.mp. 76. Ablation techniques/ or ablation.mp. 77. incision*mp. 78. vesicostom*.mp. 79. Cystoscopy/ or cystoscop*.mp. 80. Urinary Diversion/ or diversion.mp. 81. Ureterostomy/ or ureterostom*.mp. 82. digestive system surgical procedures/ or ostomy/ or urogenital surgical procedures/ 83. 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71 or 72 or 73 or 74 or 75 or 76 or 77 or 78 or 79 or 80 or 81 or 82 84. 22 and 55 and 83 85. “Systematic Review”/ 86. Meta-Analysis/ 87. Case Reports/ 88. 85 or 86 or 87 89. 84 not 88 90. Limit 89 to yr=”2000-Current”
Embase	1. necrotising enterocolitis.mp. or necrotizing enterocolitis/ 2. necrotizing enterocolitis.mp. 3. Hirschsprung Disease/ or Hirschsprung*.mp. 4. aganglionosis/ or aganglion*.mp. 5. HSCR.mp. 6. gastroschisis.mp. or gastroschisis/ 7. esophageal atresia/ or esophag* atresia*.mp. 8. oesophag* atresia*.mp. 9. OA-TOF.mp. 10. EA-TEF.mp. 11. congenital diaphragm hernia/ or congenital diaphragm* hernia*.mp. 12. Bochdalek hernia/ or Bochdalek hernia*.mp. 13. Morgagni hernia/ or Morgagni hernia*.mp. 14. neonat*.mp. or newborn/ 15. infant*.mp. or infant/ 16. newborn.mp. 17. diaphragm hernia/ or diaphragm* hernia*.mp.

	18. 14 or 15 or 16 19. 17 and 18 20. posterior urethra* valve*.mp. 21. posterior urethra* membrane*.mp. 22. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 19 or 20 or 21 23. treatment outcome/ or treatment outcome*.mp. 24. follow-up studies/ or follow-up stud*.mp. 25. retrospective study/ or retrospective stud*.mp. 26. quality of life.mp. or "quality of life"/ 27. child development.mp. or child development/ 28. follow-up.mp. or follow up/ 29. long-term.mp. 30. mortality/ or mortality.mp. 31. death.mp. or death/ 32. survival/ or survival.mp. 33. sepsis/ or sepsis.mp. or neonatal Sepsis/ 34. reoperation/ or re-operation.mp. 35. hospital readmission/ or re-admission.mp. 36. hospitali?ation*.mp. or hospitalization/ 37. education/ or education*.mp. 38. academic achievement/ or academic.mp. 39. educational status/ 40. growth.mp. or growth/ 41. liver disease/ or liver disease*.mp. 42. incontinence/ or incontinen*.mp. 43. urine incontinence/ 44. urine incontinence/ 45. feces incontinence/ 46. enterocolitis.mp. or enterocolitis/ 47. stress.mp or emotional stress/ or stress.mp. 48. motor development/ or motor dysfunction/ or motor.mp. 49. cognition/ or cogniti*.mp. 50. bowel function*.mp. 51. bowel movement*.mp. 52. constipation/ or constipation*.mp. 53. stoma/ or stoma*.mp. 54. 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 55. surger*.mp. or surgery/ 56. operati*.mp. 57. surgical procedures, operative/ 58. surgic*.mp. or surgical technique/ 59. postoperat*.mp. 60. laparotomy/ or laparotom*.mp. 61. laparoscopy/ or laparoscopic surgery/ or laparoscop*.mp. 62. resection.mp. 63. enterostomy/ or enterostom*.mp. 64. anastomosis/ or anastomos*.mp. 65. jejunostomy/ or jejunostom*.mp. 66. colostomy/ or colostom*.mp. 67. surgical drainage/ or drainage.mp. 68. procedur*.mp. 69. repair.mp. 70. thoracoscopy/ or thoracoscop*.mp. 71. thoracotomy/ or thoracotom*.mp. 72. endoscopy/ or endoscop*.mp. 73. silo.mp. 74. closure.mp. 75. ablation.mp. or catheter ablation/ or ablation therapy/

	76. incision/ or incision*mp. 77. vesicostom*.mp. 78. cystoscopy/ or cystoscop*.mp. 79. urinary diversion/ or diversion.mp. 80. ureterostomy/ or ureterostom*.mp. 81. 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71 or 72 or 73 or 74 or 75 or 76 or 77 or 78 or 79 or 80 82. 22 and 54 and 81 83. “systematic review”/ or meta analysis/ 84. case report/ 85. conference abstract/ 86. 83 or 84 or 85 87. 84 not 86 88. Limit 87 to yr=”2000-Current”
CINAHL	S1. "necrotising enterocolitis" S2. (MH "Enterocolitis, Necrotizing") OR "necrotizing enterocolitis" S3. (MH "Hirschsprung Disease") OR "Hirschsprung*" S4. "aganglion*" S5. "HSCR" S6. (MH "Gastroschisis") S7. gastroschisis S8. (MH "Esophageal Atresia") OR "esophag* atresia*" S9. "oesophag* atresia*" S10. OA-TOF S11. EA-TEF S12. (MH "Hernia, Diaphragmatic, Congenital") OR "congenital diaphragm* hernia*" S13. Bochdalek hernia* S14. Morgagni hernia* S15. "neonat*" S16. (MH "Infant, Newborn") OR "newborn" S17. "diaphragm* hernia*" OR (MH "Hernia, Diaphragmatic") S18. 15 OR 16 S19. 17 AND 18 S20. "posterior urethra* valve*" S21. "posterior urethra* membrane*" S22. "posterior urethra* membrane*" S23. S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S19 OR S20 OR S21 OR S22 S24. S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S19 OR S20 OR S21 OR S22: Limiters – Published Date: 20000101-20211231 S25. (MH "Treatment Outcomes") OR "treatment outcome*" S26. (MH "Prospective Studies") OR "follow-up stud*" S27. "retrospective stud*" OR (MH "Retrospective Design") S28. (MH "Quality of Life") OR "quality of life" OR (MH "Psychological Well-Being") S29. (MH "Child Development") OR "child development” S30. follow up S31. long term S32. (MH "Mortality") OR "mortality” S33. (MH "Death") OR "death" S34. (MH "Survival") OR "survival" S35. (MH "Sepsis") OR "sepsis" OR (MH "Neonatal Sepsis”) S36. “re-operation” S37. reoperation S38. (MH "Readmission") OR "readmission” S39. (MH "Hospitalization") OR "hospitalization” S40. (MH "Education") OR "education*”

	S41. (MH "Growth") OR "growth" S42. (MH "Liver Diseases") OR "liver disease" S43. incontinen* S44. (MH "Incontinence") S45. (MH "Enterocolitis") OR "enterocolitis" OR (MH "Enterocolitis, Hirschsprung's-Associated") S46. (MH "Stress") OR "stress" S47. "motor" OR (MH "Motor Skills") S48. cogniti* S49. (MH "Cognition") S50. (MH "Altered Bowel Function (NANDA)") OR "bowel function*" S51. "hospitali?ation*" S52. (MH "Academic Achievement") OR (MH "Academic Performance") OR "academic" S53. (MH "Urinary Incontinence") S54. (MH "Fecal Incontinence") S55. "bowel movement*" S56. (MH "Constipation") OR "constipation" S57. "stoma*" S58. S25 OR S26 OR S27 OR S28 OR S29 OR S30 OR S31 OR S32 OR S33 OR S34 OR S35 OR S36 OR S37 OR S38 OR S39 OR S40 OR S41 OR S42 OR S43 OR S44 OR S45 OR S46 OR S47 OR S48 OR S49 OR S50 OR S51 OR S52 OR S53 OR S54 OR S55 OR S56 OR S57 S59. "surger*" S60. "operati*" S61. "surgic*" S62. "postoperat*" S63. (MH "Laparotomy") OR "laparotom*" S64. (MH "Surgery, Laparoscopic") OR "laparoscop*" S65. "resection" S66. "enterostom*" S67. (MH "Anastomosis, Surgical") OR "anastomos*" S68. (MH "Jejunostomy") OR "jejunostom*" S69. (MH "Colostomy") OR "colostom*" S70. (MH "Drainage") OR "drainage" S71. "procedur*" S72. "repair" S73. (MH "Thoracoscopy") OR "thoracoscop*" S74. (MH "Thoracotomy") OR "thoracotom*" S75. "endoscop*" S76. "silo" S77. "closure" S78. (MH "Catheter Ablation") OR (MH "Ablation Techniques") OR "ablation" S79. incision* S80. "vesicostom*" OR (MH "Cystostomy") S81. (MH "Urinary Diversion") OR "diversion" S82. (MH "Ureterostomy") OR "ureterostom*" S83. S59 OR S60 OR S61 OR S62 OR S63 OR S64 OR S65 OR S66 OR S67 OR S68 OR S69 OR S70 OR S71 OR S72 OR S73 OR S74 OR S75 OR S76 OR S77 OR S78 OR S79 OR S80 OR S81 OR S82 S84. S23 AND S58 AND S83 S85. S23 AND S58 AND S83: Limiters – Published Date: 20000101-20211231 S86. (MH "Systematic Review") S87. (MH "Meta Analysis") S88. S86 OR S87 S89. S85 NOT S88

Appendix 2.2: Newcastle-Ottawa Quality Assessment Scale

Appendix 2.2.1: Newcastle-Ottawa Quality Assessment Scale for studies on congenital diaphragmatic hernia
Legend: Orange = 0-4 stars; Yellow = 5-6 stars; Green = 7-9 stars

		Selection				Comparability		Outcome			
Study ID	Title	1 Represent-ativeness of the exposed cohort	2 Selection of the non exposed cohort	3 Ascertain-ment of exposure	4 Demonstration that outcome of interest was not present at start of study	5 Study controls for: gestational age and/or birth weight	6 Study controls for any additional factor - e.g. socio-economic status, sex	7 Assessment of outcome	8 Was follow-up long enough for outcomes to occur?	9 Adequac y of follow up of cohorts	Tota l
Abramov 2020	Comparative outcomes of right versus left congenital diaphragmatic hernia: A multicenter analysis	★	★	★	★			★	★		6
Ali 2019	Outcomes of infants with congenital diaphragmatic hernia by side of defect in the FETO era	★	★	★	★			★	★	★	7
Aydin 2019	Congenital diaphragmatic hernia: the good, the bad, and the tough	★	★	★	★	★	★	★	★	★	9
Aydin 2020	When primary repair is not enough: a comparison of synthetic patch and muscle flap closure in congenital diaphragmatic hernia?	★	★	★	★			★	★	★	7
Bairdain 2015	Nutritional outcomes in survivors of congenital diaphragmatic hernia (CDH)-factors associated with growth at one year	★	★	★	★	★	★	★	★		8
Barriere 2018	One-Year Outcome for Congenital Diaphragmatic Hernia: Results From the French National Register	★	★	★	★			★	★		6

Burgos 2017	Addressing the causes of late mortality in infants with congenital diaphragmatic hernia	★	★	★	★			★	★	★	7
Cauley 2015	Pulmonary support on day of life 30 is a strong predictor of increased 1 and 5-year morbidity in survivors of congenital diaphragmatic hernia	★	★	★	★			★	★	★	7
Chen 2019	Application of an Extracorporeal-Assisted Intracorporeal Sliding Knot-Tying Technique in Minimally Invasive Surgery in Children	★	★	★	★			★	★		6
Cioci 2020	One-year outcomes of congenital diaphragmatic hernia repair: Factors associated with recurrence and complications	★	★	★	★			★	★		6
Costerus 2016	Thoracoscopic versus open repair of CDH in cardiovascular stable neonates		★	★	★			★	★		5
Danzer 2016	Younger gestational age is associated with increased risk of adverse neurodevelopmental outcome during infancy in congenital diaphragmatic hernia	★	★	★				★	★		5
Danzer 2018	Short-Term Neurodevelopmental Outcome in Congenital Diaphragmatic Hernia: The Impact of Extracorporeal Membrane Oxygenation and Timing of Repair	★	★	★	★			★	★		6
Danzer 2018-2	Rate and risk factors associated with autism spectrum disorder in congenital diaphragmatic hernia	★	★	★	★	★	★	★	★		8
DeBie 2020	Early surgical complications after congenital diaphragmatic hernia repair by thoracotomy vs. laparotomy: A bicentric comparison		★	★	★			★	★		5
Dennett 2014	Sensorineural hearing loss in congenital diaphragmatic hernia survivors is associated with	★	★	★	★		★	★	★		7

	postnatal management and not defect size										
Garcia 2013	Lung to head ratio in infants with congenital diaphragmatic hernia does not predict long term pulmonary hypertension	★	★	★	★	★	★	★	★		8
Garriboli 2012	Trends in the treatment and outcome of congenital diaphragmatic hernia over the last decade	★		★	★			★	★	★	6
Haliburton 2015	Long-term nutritional morbidity for congenital diaphragmatic hernia survivors: Failure to thrive extends well into childhood and adolescence	★	★	★	★			★	★		5
Heiwegen 2020	Malrotation in Congenital Diaphragmatic Hernia: Is It Really a Problem?	★	★	★	★			★	★	★	7
Heiwegen 2020	Congenital diaphragmatic eventration and hernia sac compared to CDH with true defects: a retrospective cohort study	★	★	★	★			★	★		6
Jancelewicz 2013	Late surgical outcomes among congenital diaphragmatic hernia (CDH) patients: why long-term follow-up with surgeons is recommended	★	★	★	★			★	★	★	7
Janssen 2018	Factors related to long-term surgical morbidity in congenital diaphragmatic hernia survivors		★	★	★		★	★	★		6
Kadir 2017	Risk factors for postoperative mortality in congenital diaphragmatic hernia: a single-centre observational study	★	★	★	★	★	★	★	★	★	9
Lee 2018	Congenital diaphragmatic hernia: Impact of contemporary management strategies on perinatal outcomes	★	★	★	★			★	★	★	7
Liem 2011	Thoracoscopic repair for congenital diaphragmatic hernia: experience with 139 cases	★		★	★				★		4

Long 2019	One-year outcomes of infants born with congenital diaphragmatic hernia: a national population cohort study	★	★	★	★	★	★	★	★		8
Masi 2010	Sensorineural hearing loss and congenital diaphragmatic hernia	★	★	★				★	★		5
Nagata 2015	Risk factors for the recurrence of the congenital diaphragmatic hernia-report from the long-term follow-up study of Japanese CDH study group	★	★	★	★	★	★		★		7
Okuyama 2011	The Japanese experience with prenatally diagnosed congenital diaphragmatic hernia based on a multi-institutional review	★	★	★				★	★		5
Partridge 2014	Incidence and factors associated with sensorineural and conductive hearing loss among survivors of congenital diaphragmatic hernia		★	★	★			★	★		5
Pruitt 2020-3	Impact of consolidation of cases on post-operative outcomes for index pediatric surgery cases	★	★	★	★		★	★	★		7
Ruano 2015	Congenital heart anomaly in newborns with congenital diaphragmatic hernia: a single-center experience	★	★	★	★				★	★	6
Russell 2014	Musculoskeletal deformities following repair of large congenital diaphragmatic hernias	★	★	★	★				★		5
Short 2018	The "Flat Diaphragm": Does the Degree of Curvature of the Diaphragm on Postoperative X-Ray Predict Congenital Diaphragmatic Hernia Recurrence?	★	★	★	★			★	★		6
Style 2019	Fetal endoscopic tracheal occlusion reduces pulmonary hypertension in severe congenital diaphragmatic hernia		★	★	★			★	★		5
Suply 2020	Patch repair of congenital diaphragmatic hernia is not at risk of poor outcomes	★	★	★	★			★	★		6

Takayasu 2016	Musculoskeletal abnormalities in congenital diaphragmatic hernia survivors: Patterns and risk factors: Report of a Japanese multicenter follow-up survey	★		★	★			★	★	★	6
Terui 2014	Prognostic factors of gastroesophageal reflux disease in congenital diaphragmatic hernia: a multicenter study	★	★		★	★	★		★		6
Terui 2016	Growth Assessment and the Risk of Growth Retardation in Congenital Diaphragmatic Hernia: A Long-Term Follow-Up Study from the Japanese Congenital Diaphragmatic Hernia Study Group	★	★	★	★	★	★	★	★		8
Tsai 2012	Patch repair for congenital diaphragmatic hernia: is it really a problem?	★	★	★	★			★	★		6
Verla 2020	Prenatal Imaging Features and Postnatal Factors Associated with Gastrointestinal Morbidity in Congenital Diaphragmatic Hernia		★	★	★		★	★	★		6
Wang 2019	One-year outcomes for congenital diaphragmatic hernia	★	★	★	★	★	★	★	★	★	9
Ward 2017-2	Preemptive Ladd Procedure in congenital diaphragmatic hernia and Abdominal Wall defects does not reduce the risk of future volvulus	★	★	★	★		★	★	★	★	8
Weaver 2016	A Multi-Institutional Review of Thoracoscopic Congenital Diaphragmatic Hernia Repair	★	★	★	★			★	★		6
Wong 2018	Pulmonary hypertension in congenital diaphragmatic hernia patients: Prognostic markers and long-term outcomes		★	★	★			★	★		5
Wong 2019	Requirement and Duration of Tube Feed Supplementation among Congenital Diaphragmatic Hernia Patients		★	★	★			★	★	★	6

Appendix 2.2.2: Newcastle-Ottawa Quality Assessment Scale for studies on oesophageal atresia
Legend: Orange = 0-4 stars; Yellow = 5-6 stars; Green = 7-9 stars

		Selection				Comparability		Outcome			
Study ID	Title	1 Represent-ativeness of the exposed cohort	2 Selection of the non exposed cohort	3 Ascertain-ment of exposure	4 Demonstration that outcome of interest was not present at start of study	5 Study controls for: gestational age and/or birth weight	6 Study controls for any additional factor - e.g. socio-economic status, sex	7 Assessment of outcome	8 Was follow-up long enough for outcomes to occur?	9 Adequacy of follow up of cohorts	Total
Allin 2014	Outcomes at one-year post anastomosis from a national cohort of infants with oesophageal atresia	★	★	★	★	★	★		★	★	8
Ax 2021	Parent-Reported Feeding Difficulties among Children Born with Esophageal Atresia: Prevalence and Early Risk Factors	★	★	★	★		★		★	★	7
Bastard 2018	Thoracic skeletal anomalies following surgical treatment of esophageal atresia. Lessons from a national cohort	★	★	★	★			★	★		6
Baxter 2018	Structural airway abnormalities contribute to dysphagia in children with esophageal atresia and tracheoesophageal fistula	★	★	★	★	★	★	★	★	★	9
Coppens 2016	Dysphagia in children with repaired oesophageal atresia	★	★	★	★			★	★		6
Dellenmark-Blom 2018	Clinical predictors and prevalence of receiving special preschool/school	★	★	★	★	★	★		★		7

	support in children with repaired esophageal atresia										
Dellenmark-Blom 2019	The prevalence and role of coping strategies in the nutritional intake of children born with esophageal atresia: a condition-specific approach	★	★	★	★		★	★	★	★	8
Dellenmark-Blom 2020	Clinical Factors Affecting Condition-Specific Quality-of-Life Domains in Pediatric Patients after Repair of Esophageal Atresia: The Swedish-German EA-QOL Study	★	★	★	★	★	★	★	★		8
Donoso 2016	Outcome and management in infants with esophageal atresia - A single centre observational study	★	★	★	★			★	★	★	7
Donoso 2017	Risk Factors for Anastomotic Strictures after Esophageal Atresia Repair: Prophylactic Proton Pump Inhibitors Do Not Reduce the Incidence of Strictures	★		★	★	★	★	★	★		7
Elhattab 2020	Thoracoscopy Versus Thoracotomy in the Repair of Esophageal Atresia with Distal Tracheoesophageal Fistula	★	★	★	★			★	★	★	7
Fayoux 2018	Laryngotracheal anomalies associated with esophageal atresia: importance of early diagnosis			★	★			★	★		4
Flieder 2019	Generic Health-Related Quality of Life after Repair of Esophageal Atresia and Its	★		★	★	★	★	★	★		7

	Determinants within a German-Swedish Cohort										
Forster 2019	Outcomes of multi-gestational pregnancies affected by esophageal atresia - tracheoesophageal fistula	★	★	★	★			★	★		6
Francois 2019	Predictors of the Performance of Early Antireflux Surgery in Esophageal Atresia	★	★	★	★	★	★	★	★	★	9
Fung 2019	Vocal cord dysfunction following esophageal atresia and tracheoesophageal fistula (EA/TEF) repair	★	★	★	★			★	★		6
Fusco 2018	A large single-institution review of tracheoesophageal fistulae with evaluation of the use of transanastomotic feeding tubes	★	★	★	★			★	★		6
Garabedian 2015	Does prenatal diagnosis modify neonatal treatment and early outcome of children with esophageal atresia?	★	★	★	★			★	★		6
Garabedian 2015-2	Does prenatal diagnosis modify neonatal management and early outcome of children with esophageal atresia type III?. [French]	★	★	★	★			★	★		6
Hsieh 2017	Intestinal Metaplasia of the Esophagus in Children With Esophageal Atresia	★		★	★			★	★		5
Jones 2020	Association Between Administration of Antacid Medication and Anastomotic Stricture Formation After Repair of Esophageal Atresia		★	★	★	★	★	★	★		7

Jones 2020	Repair of oesophageal atresia by consultants and supervised trainees results in similar outcomes		★	★	★			★	★		5
Koivusalo 2013	Modern outcomes of oesophageal atresia: single centre experience over the last twenty years	★	★	★	★		★	★	★		7
Kovesi 2018	Vocal cord paralysis appears to be an acquired lesion in children with repaired esophageal atresia/tracheoesophageal fistula		★	★	★			★	★		5
Lal 2017	Perioperative management and outcomes of esophageal atresia and tracheoesophageal fistula		★	★	★			★	★		5
Lal 2018	Challenging surgical dogma in the management of proximal esophageal atresia with distal tracheoesophageal fistula: Outcomes from the Midwest Pediatric Surgery Consortium		★	★	★		★	★	★		6
Lawrence 2019	Relationships between hospital and surgeon operative volumes and outcomes of esophageal atresia/tracheoesophageal fistula repair	★	★	★	★	★	★	★	★		8
Mawlana 2018	Neurodevelopmental outcomes of infants with esophageal atresia and tracheoesophageal fistula			★	★			★	★		4
Nurminen 2019	Pneumonia after Repair of Esophageal Atresia-Incidence and Main Risk Factors	★	★	★	★			★	★	★	7
Oztan 2020	Outcome of Very Low and Low Birth Weight Infants with Esophageal	★	★	★	★			★	★		6

	Atresia: Results of the Turkish Esophageal Atresia Registry										
Paramalingam 2013	Operative intercostal chest drain is not required following extrapleural or transpleural esophageal atresia repair			★	★			★	★		4
Porcaro 2017	Respiratory problems in children with esophageal atresia and tracheoesophageal fistula			★	★			★	★		4
Pruitt 2020-2	Impact of consolidation of cases on post-operative outcomes for index pediatric surgery cases	★	★	★	★		★	★	★		7
Quiroz 2020	Nationwide analysis of mortality and hospital readmissions in esophageal atresia	★	★	★	★			★	★		6
Raitio 2016	Fluoroscopic balloon dilatation for anastomotic strictures in patients with esophageal atresia: A fifteen-year single centre UK experience			★	★			★	★		4
Schmedding 2020	Outcome of esophageal atresia in Germany	★	★	★	★	★	★	★	★	★	9
Schneider 2014	Results from the French National Esophageal Atresia register: one-year outcome	★	★	★	★			★	★		6
Shah 2015	Predictive factors for complications in children with esophageal atresia and tracheoesophageal fistula	★		★	★		★	★	★		6
SinghSodhi 2013	Postoperative appearances of esophageal atresia repair: retrospective study of 210 patients with review of literature ‚Äì			★	★			★	★		4

	what the radiologist should know										
Soliman 2019	Prevalence and natural history of scoliosis and associated congenital vertebral anomalies in patients operated for esophageal atresia with or without tracheoesophageal fistula	★		★	★			★	★		5
Sulkowski 2014	Morbidity and mortality in patients with esophageal atresia	★	★	★	★			★	★		6
Tambucci 2020	Eosinophilic esophagitis in esophageal atresia: Tertiary care experience of a "selective" approach for biopsy sampling	★		★	★			★	★		5
Thyoka 2014	Fluoroscopic balloon dilation of esophageal atresia anastomotic strictures in children and young adults: single-center study of 103 consecutive patients from 1999 to 2011			★	★			★	★		4
Vergouwe 2017	Longitudinal evaluation of growth in oesophageal atresia patients up to 12 years			★		★	★	★	★		5
Vergouwe 2019	Risk factors for refractory anastomotic strictures after oesophageal atresia repair: a multicentre study		★	★	★		★	★	★	★	7
Yasuda 2019	Esophagitis in Pediatric Esophageal Atresia: Acid May Not Always Be the Issue		★	★	★		★	★	★		6
Yasuda 2020	Utility of repeated therapeutic endoscopies for pediatric esophageal anastomotic strictures			★			★	★	★		4

Zhu 2018	Diagnosis and management of post-operative complications in esophageal atresia patients in China: A retrospective analysis from a single institution	★		★	★	★	★	★	★		7

Appendix 2.2.3: Newcastle-Ottawa Quality Assessment Scale for studies on gastroschisis
Legend: Orange = 0-4 stars; Yellow = 5-6 stars; Green = 7-9 stars

		Selection				Comparability		Outcome			
Study ID	Title	1 Represent-ativeness of the exposed cohort	2 Selection of the non exposed cohort	3 Ascertainment of exposure	4 Demonstration that outcome of interest was not present at start of study	5 Study controls for: gestational age and/or birth weight	6 Study controls for any additional factor - e.g. socio-economic status, sex	7 Assessment of outcome	8 Was follow-up long enough for outcomes to occur?	9 Adequacy of follow up of cohorts	Total
Abdelhafeez 2011	The incidence of symptomatic malrotation post gastroschisis repair	★		★	★			★	★		5
Abdelhafeez 2015	The risk of volvulus in abdominal wall defects	★	★	★	★			★	★		6
Anderson 2018	Epidemiology of gastroschisis: A population-based study in California from 1995 to 2012	★	★	★	★			★	★	★	7
Bradnock 2011	Gastroschisis: one year outcomes from national cohort study	★	★	★	★			★	★	★	7
Cain 2014	Perinatal outcomes and hospital costs in gastroschisis based on gestational age at delivery	★	★	★	★	★		★	★	★	8
Chen 2019	Low and decreased prevalence of congenital abdominal wall defect in Taiwan	★	★	★	★			★	★	★	7
DeBie 2020	Long-term core outcomes of patients with simple gastroschisis	★		★	★			★	★	★	6

Long 2011	Antenatal diagnosis of bowel dilatation in gastroschisis is predictive of poor postnatal outcome	★	★	★	★			★	★		6
Minutillo 2013	Growth and developmental outcomes of infants with gastroschisis at one year of age: a retrospective study	★	★	★	★	★	★	★	★		8
Schmedding 2020	Decentralized surgery of abdominal wall defects in Germany		★	★	★			★	★	★	6
Ward 2017	Preemptive Ladd Procedure in congenital diaphragmatic hernia and Abdominal Wall defects does not reduce the risk of future volvulus	★	★	★	★		★	★	★	★	8

Appendix 2.2.4: Newcastle-Ottawa Quality Assessment Scale for studies on surgical necrotising enterocolitis
Legend: Orange = 0-4 stars; Yellow = 5-6 stars; Green = 7-9 stars

		Selection				Comparability		Outcome			
Study ID	Title	1 Represent-ativeness of the exposed cohort	2 Selection of the non exposed cohort	3 Ascertainment of exposure	4 Demonstration that outcome of interest was not present at start of study	5 Study controls for: gestational age and/or birth weight	6 Study controls for any additional factor - e.g. socio-economic status, sex	7 Assessment of outcome	8 Was follow-up long enough for outcomes to occur?	9 Adequacy of follow up of cohorts	Total
Allin 2018	One-year outcomes following surgery for necrotising enterocolitis: a UK-wide cohort study	★	★	★	★	★	★	★	★	★	9
Calvert 2020	Necrotising enterocolitis-A 15-year outcome report from a UK specialist centre	★	★	★	★	★	★	★	★		8
Cole 2008	Very low birth weight preterm infants with surgical short bowel syndrome: incidence, morbidity and mortality, and growth outcomes at 18 to 22 months	★	★	★	★	★	★	★	★		8
Elfvin 2015	Low birthweight, gestational age, need for surgical intervention and gram-negative bacteraemia predict intestinal failure following necrotising enterocolitis	★	★	★	★			★	★	★	7
Fredrikss on 2019	Survival rates for surgically treated necrotising enterocolitis have improved over the last four decades	★	★	★	★	★		★	★		7
Fullerton 2018	Severe neurodevelopmental disability and healthcare needs among survivors of medical and surgical necrotizing enterocolitis: A prospective cohort study	★	★	★	★			★	★		6

Hong 2018	Growth morbidity in extremely low birth weight survivors of necrotizing enterocolitis at discharge and two-year follow-up	★	★	★	★	★	★	★	★		8
Shah 2012	Hospital and neurodevelopmental outcomes of extremely low-birth-weight infants with necrotizing enterocolitis and spontaneous intestinal perforation	★	★	★	★	★	★	★	★		8
Sung 2019	The Impact of Surgical Intervention on Neurodevelopmental Outcomes in Very Low Birth Weight Infants: a Nationwide Cohort Study in Korea	★	★	★	★	★	★	★	★		8
Wadhawan 2014	Neurodevelopmental outcomes of extremely low birth weight infants with spontaneous intestinal perforation or surgical necrotizing enterocolitis	★	★	★	★	★	★	★	★		8

Appendix 2.2.5: Newcastle-Ottawa Quality Assessment Scale for studies on Hirschsprung's disease
Legend: Orange = 0-4 stars; Yellow = 5-6 stars; Green = 7-9 stars

		Selection				Comparability		Outcome			
Study ID	Title	1 Represent-ativeness of the exposed cohort	2 Selection of the non exposed cohort	3 Ascertainment of exposure	4 Demonstration that outcome of interest was not present at start of study	5 Study controls for: gestational age and/or birth weight	6 Study controls for any additional factor - e.g. socio-economic status, sex	7 Assessment of outcome	8 Was follow-up long enough for outcomes to occur?	9 Adequacy of follow up of cohorts	Total
Allin 2020	Outcomes at five to eight years of age for children with Hirschsprung's disease	★	★	★	★				★	★	5
Anderson 2018	Epidemiology of Hirschsprung disease in California from 1995 to 2013	★	★	★				★	★	★	6
Apfeld 2020	Relationships Between Hospital and Surgeon Operative Volumes and Surgical Outcomes in Hirschsprungs Disease		★	★	★		★	★	★		6
Bing 2017	Transanal pullthrough Soave and Swenson techniques for pediatric patients with Hirschsprung disease	★	★	★	★			★	★	★	7
Bischoff 2017	Damaged anal canal as a cause of fecal incontinence after surgical repair for Hirschsprung disease - a preventable and under-reported complication		★	★		★	★	★	★	★	7
Dahal 2011	Long-term outcome of children after single-stage transanal endorectal pull-	★	★	★	★			★	★		6

	through for Hirschsprung's disease										
Elhalaby 2004	Transanal one-stage endorectal pull-through for Hirschsprung's disease: a multicenter study	★	★	★	★			★	★	★	7
Giuliani 2020	Outcomes of Primary versus Multiple-Staged Repair in Hirschsprung's Disease in England	★	★	★	★	★	★	★	★		8
Huang 2018	Prevalence, Risk Factors, and Prognosis of Postoperative Complications after Surgery for Hirschsprung Disease	★	★	★	★		★	★	★		7
Jiao 2018	A Long-Term Follow-Up of a New Surgery Method: Laparoscope-Assisted Heart-Shaped Anastomosis for Hirschsprung's Disease	★	★	★	★			★	★		6
Khazdouz 2015	Clinical outcome and bowel function after surgical treatment in Hirschsprung's disease	★	★	★	★			★	★		6
Kwendakwema 2016	Enterocolitis and bowel function in children with Hirschsprung disease and trisomy 21	★	★	★	★			★	★		6
Li 2006	A new modification of transanal Soave pull-through procedure for Hirschsprung's disease	★	★	★	★				★		5
Liem 2008	One-stage operation for Hirschsprung's disease: experience with 192 cases	★	★	★	★			★	★		6
Lu 2017	Single-stage transanal endorectal pull-through procedure for correction of Hirschsprung disease in neonates and nonneonates: A multicenter study		★	★				★	★		4

Meng 2020	Long-term outcomes of single-incision laparoscopic technique in Soave procedure compared with heart-shaped anastomosis for Hirschsprung disease	★	★	★	★			★	★		6
Miyano 2018	Hirschsprung's disease in the laparoscopic transanal pull-through era: implications of age at surgery and technical aspects	★	★	★					★		4
Nguyen 2009	Early and late outcomes of primary laparoscopic endorectal colon pull-through leaving a short rectal seromuscular sleeve for Hirschsprung disease	★		★	★				★	★	5
Parahita 2018	Comparison of Hirschsprung-associated enterocolitis following Soave and Duhamel procedures	★	★	★				★	★	★	6
Pruitt 2020	Impact of consolidation of cases on post-operative outcomes for index pediatric surgery cases	★	★	★	★		★	★	★		7
Pruitt 2020 (2)	Hirschsprung-associated enterocolitis in children treated at US children's hospitals		★	★			★	★	★		5
Quiroz 2020	Pull-through procedure in children with Hirschsprung disease: A nationwide analysis on postoperative outcomes		★	★	★			★	★		5
Sulkowski 2014	Single-stage versus multi-stage pull-through for Hirschsprung's disease: practice trends and outcomes in infants	★	★	★	★	★	★	★	★	★	9

Sun 2015	[Complication analysis of endorectal pull-through radical operation for Hirschsprung disease]	★	★	★	★				★	★	6
Taghavi 2020	Contemporary management of Hirschsprung disease in New Zealand	★		★	★			★	★		5
Tang 2012	10 years of experience with laparoscopic-assisted endorectal Soave pull-through procedure for Hirschsprung's disease in China		★	★				★	★		4
Taylor 2020	Comparison of Hirschsprung Disease Characteristics between Those with a History of Postoperative Enterocolitis and Those without: Results from the Pediatric Colorectal and Pelvic Learning Consortium	★	★	★			★	★	★	★	7
Yang 2012	Transanal endorectal pull-through for Hirschsprung's disease using long cuff dissection and short V-shaped partially resected cuff anastomosis: early and late outcomes		★	★				★	★		4
Zhang 2014	Transanal rectal mucosectomy and partial internal anal sphincterectomy for Hirschsprung's disease			★				★	★	★	4
Zhang 2020	Primary laparoscopic endorectal pull-through procedure with or without a postoperative rectal tube for Hirschsprung disease: a multicenter perspective study	Risk-of-bias assessment using the Cochrane Risk of Bias 2 tool was used for randomised controlled Overall risk-of-bias judgement: Some concerns - The study is judged to raise **some concerns** in at least one domain for this result, but not to be at high risk of bias for any domain.									

Zheng 2018	Transanal endorectal stepwise gradient muscular cuff cutting pull-through method: Technique refinements and comparison with laparoscopy-assisted procedures		★	★					★	★	4
Zhu 2019	Optimal time for single-stage pull-through colectomy in infants with short-segment Hirschsprung disease	★	★	★					★		4
Zhuansun 2020	Long-term outcomes of laparoscope-assisted heart-shaped anastomosis for children with Hirschsprung disease: A 10-year review study	★	★	★					★		4

Appendix 2.2.6: Newcastle-Ottawa Quality Assessment Scale for studies on posterior urethral valves
Legend: Orange = 0-4 stars; Yellow = 5-6 stars; Green = 7-9 stars

		Selection				Comparability		Outcome			
Study ID	Title	1 Represent-ativeness of the exposed cohort	2 Selection of the non exposed cohort	3 Ascertainment of exposure	4 Demonstration that outcome of interest was not present at start of study	5 Study controls for: gestational age and/or birth weight	6 Study controls for any additional factor - e.g. socio-economic status, sex	7 Assessment of outcome	8 Was follow-up long enough for outcomes to occur?	9 Adequacy of follow up of cohorts	Total
Akhtar 2014	Outcomes of posterior urethral valves in boys	★	★	★	★			★	★		6
Amirzargar 2020	Risk Factors Associated with Chronic Kidney Disease In Infants With Posterior Urethral Valve: A Single Center Study of 110 Patients Managed By Valve Ablation And Bladder Neck Incision	★	★	★	★			★	★	★	7
Ansari 2010	Risk factors for progression to end-stage renal disease in children with posterior urethral valves	★	★	★	★		★	★	★		7
Ansari 2018	Bladder contractility index in posterior urethral valve: A new marker for early prediction of progression to renal failure	★	★	★	★	★	★	★	★		8
Bhadoo 2014	Posterior urethral valve: Prognostic factors and renal outcome	★	★	★	★			★	★		6
Bilgutay 2016	Posterior urethral valves: Risk factors for progression to renal failure	★	★	★	★		★	★	★		7

Chatterje e 2020	Insight into posterior urethral valve from our experience: Paradigm appended to abate renal failure	★		★	★			★	★		5
Menon 2010	Posterior urethral valves: morphological normalization of posterior urethra after fulguration is a significant factor in prognosis		★	★	★			★	★		5
Sarhan 2017	Posterior urethral valves: Impact of low birth weight and preterm delivery on the final renal outcome		★	★	★		★	★	★		6
Tourchi 2014	The management of vesicoureteral reflux in the setting of posterior urethral valve with emphasis on bladder function and renal outcome: a single center cohort study		★	★	★			★	★		5

Appendix 3.1

Appendix 3.1.1: Code list of major congenital anomalies from the NNRD-AI

ID	Name	Non-Cardiac	Cardiac
15930	(unknown or unspecified cause) spina bifida with hydrocephalus	x	
10008	Absence of bladder	x	
10066	Adult polycystic kidney disease type I	x	
15890	Anencephaly	x	
15893	Anencephaly and similar malformations	x	
16496	Aplasia of diaphragmatic hernia	x	
16196	Atresia of oesophagus with tracheo-oesophageal fistula (TOF)	x	
16195	Atresia of oesophagus without fistula	x	
16083	Atresia of pulmonary artery		x
10097	Atrio-ventricular septal defect (AVSD)		x
16039	Atrioventricular septal defect (AVSD)		x
16035	Atrium single		x
10099	Autosomal dominant polycystic kidney in childhood	x	
10100	Autosomal recessive polycystic kidney - infantile	x	
10123	Bilateral renal agenesis	x	
15926	Cervical spina bifida with hydrocephalus	x	
15931	Cervical spina bifida without hydrocephalus	x	
16079	Coarctation of aorta		x
10227	Coarctation of the aorta	x	x
16024	Common arterial trunk (Truncus malformation)		x
16223	Cong abscence atresia / stenosis of large intestine part unspec	x	
16220	Cong absence atresia / stenosis anus with fistula	x	
16221	Cong absence atresia / stenosis anus without fistula	x	
16218	Cong absence atresia / stenosis of rectum with fistula	x	
16219	Cong absence atresia / stenosis rectum without fistula	x	
16032	Cong malforms of cardiac chambers and connections unspec		x
16222	Congen absence atresia / stenosis parts of large intestine	x	
16360	Congenital absence of bladder and urethra	x	
10236	Congenital absence of urethra	x	
16212	Congenital absence, atresia and stenosis of duodenum	x	
16215	Congenital absence, atresia and stenosis of ileum	x	
16224	Congenital absence, atresia and stenosis of large intestine	x	
16217	Congenital absence, atresia and stenosis of small intestine	x	

10240	Congenital anal stenosis	x	
10246	Congenital diaphragmatic hernia	x	
16495	Congenital diaphragmatic hernia	x	
16056	Congenital insufficiency of aortic valve		x
16061	Congenital malformation of aortic and mitral valves unspec		x
16053	Congenital malformation of tricuspid valve (unknown or unspecified cause)		x
16062	Congenital malformations of aortic and mitral valves		x
16033	Congenital malformations of cardiac chambers and connections		x
16054	Congenital malformations of pulmonary and tricuspid valves		x
16057	Congenital mitral stenosis (MS)		x
16357	Congenital posterior urethral valves (PUV)	x	
16047	Congenital pulmonary valve insufficiency		x
16046	Congenital pulmonary valve stenosis		x
16198	Congenital stenosis and stricture of oesophagus	x	
16055	Congenital stenosis of aortic valve (AS)		x
10273	Congenital stenosis of the oesophagus	x	
16197	Congenital tracheo-oesophageal fistula without atresia (TOF)	x	
16049	Congenital tricuspid atresia / stenosis		x
15891	Craniorachischisis	x	
16029	Discordant atrioventricular connection		x
16028	Double inlet ventricle (DILV)		x
16026	Double outlet left ventricle (DOLV)		x
10356	Double outlet right ventricle (DORV)		x
16025	Double outlet right ventricle (DORV)		x
16593	Down's syndrome	x	
16592	Down's syndrome (unknown or unspecified cause)	x	
16213	Duodenal atresia / stenosis	x	
10358	Duodenal atresia / stenosis / web (specify)	x	
16050	Ebstein's anomaly		x
10367	Ectopia vesicae	x	
16597	Edwards' syndrome (unknown or unspecified cause)	x	
16602	Edwards' syndrome and Patau's syndrome	x	
15899	Encephalocele	x	
15898	Encephalocele (unknown or unspecified cause)	x	
15897	Encephalocele of other sites	x	
16497	Eventration of diaphragmatic hernia	x	
10395	Exomphalos	x	
16498	Exomphalos Malrotation	x	
16356	Exstrophy of urinary bladder	x	
15894	Frontal encephalocele	x	

16499	Gastroschisis	x	
10490	Hernia into the cord	NA	
10493	High anorectal anomaly with fistula (specify)	x	
10494	High anorectal anomaly with rectocloacal fistula	x	
10495	High anorectal anomaly with rectocutaneous fistula	x	
10496	High anorectal anomaly with rectourethral fistula	x	
10497	High anorectal anomaly with rectovesical fistula	x	
10498	High anorectal anomaly with rectovulval fistula	x	
10499	High anorectal anomaly without fistula	x	
16080	Hypoplasia of aortic arch		x
16059	Hypoplastic left heart syndrome (HLH)		x
16051	Hypoplastic right heart syndrome		x
16216	Ileal atresia / stenosis	x	
10541	Ileal atresia / stenosis (specify)	x	
15892	Iniencephaly	x	
16030	Isomerism of atrial appendages		x
16214	Jejunal atresia / stenosis	x	
10605	Jejunal atresia / stenosis (specify)	x	
10636	Low anorectal anomaly with anocutaneous fistula	x	
10637	Low anorectal anomaly with anovestibular fistula	x	
10638	Low anorectal anomaly with fistula (other specify)	x	
10639	Low anorectal anomaly without fistula	x	
15928	Lumbar spina bifida with hydrocephalus	x	
15933	Lumbar spina bifida without hydrocephalus	x	
16082	Malformation of aorta		x
16058	Mitral atresia		x
10704	Myelomeningocele (specify site)	x	
15895	Nasofrontal encephalocele	x	
15896	Occipital encephalocele	x	
10740	Oesophageal atresia with distal tracheo-oesophageal fistula	x	
10741	Oesophageal atresia without distal fistula	x	
16199	Oesophageal web	x	
16031	Other cong malforms of cardiac chambers and connections		x
16060	Other congenital malformations of aortic and mitral valves		x
16086	Other congenital malformations of great arteries		x
16048	Other congenital malformations of pulmonary valve		x
16052	Other congenital malformations of tricuspid valve		x
16601	Patau's syndrome (unknown or unspecified cause)	x	
16328	Polycystic kidney, adult type	x	
16327	Polycystic kidney, infantile type	x	
10854	Posterior urethral valves (PUV)	x	

16324	Potter's syndrome	x	
16045	Pulmonary valve atresia		x
16318	Renal agenesis, bilateral	x	
15929	Sacral spina bifida with hydrocephalus	x	
15934	Sacral spina bifida without hydrocephalus	x	
10986	Spina bifida	x	
15936	Spina bifida	x	
15935	Spina bifida (unknown or unspecified cause)	x	
16081	Stenosis of aorta (AS)		x
16084	Stenosis of pulmonary artery (PS)		x
11043	Tetralogy of Fallot		x
16040	Tetralogy of Fallot		x
16475	Thanatophoric short stature	x	
15927	Thoracic spina bifida with hydrocephalus	x	
15932	Thoracic spina bifida without hydrocephalus	x	
16092	Total anomalous pulmonary venous connection (TAPVD)		x
11057	Total anomylous pulmonary venous drainage (TAPVD)		x
16027	Transposition great arteries (TGA)		x
11070	Transposition of the great vessels (TGA)		x
16087	Transposition of the great vessels (TGA)		x
16598	Trisomy 13, meiotic nondisjunction	x	
16599	Trisomy 13, mosaicism (mitotic nondisjunction)	x	
16600	Trisomy 13, translocation	x	
16594	Trisomy 18, meiotic nondisjunction	x	
16595	Trisomy 18, mosaicism (mitotic nondisjunction)	x	
16596	Trisomy 18, translocation	x	
16589	Trisomy 21, meiotic nondisjunction	x	
16590	Trisomy 21, mosaicism (mitotic nondisjunction)	x	
16591	Trisomy 21, translocation	x	
16036	Ventricle single		x

Appendix 3.1.2 Code lists developed by Harnden et al.

Appendix A: Category 1 definition
Category 1. An antenatal or postnatal diagnosis of a condition which is not compatible with long term survival.
Meets definition if any of the following are present in diagnosis table OR PrincipalDiagnosisAtDischarge OR DiagnosesDay:

Code	Condition
15890	Anencephaly
15891	Craniorachischisis
16475	Thanatophoric short stature
16594	Trisomy 18, meiotic nondisjunction
16595	Trisomy 18, mosaicism (mitotic nondisjunction)
16597	Edwards syndrome (unknown or unspecified cause)
16598	Trisomy 13, meiotic nondisjunction
16599	Trisomy 13, mosaicism (mitotic nondisjunction)
16601	Patau's syndrome (unknown or unspecified cause)
16602	Edwards syndrome and Pataus syndrome
16610	Triploidy and polyploidy
10123	Bilateral renal agenesis
16318	Renal agenesis, bilateral
500250	Tracheal agenesis or atresia
1010778	Laryngeal Atresia
15893	Anencephaly and similar malformations
16145	Alveolar Capillary Dysplasia

Appendix B: Category 2 definition
Category 2. An antenatal or postnatal diagnosis of a condition which carries a high risk of significant morbidity or death.

Meets definition if any of the following are present in diagnosis table OR PrincipalDiagnosisAtDischarge OR DiagnosesDay:

10008	Absence of bladder
10236	Congenital absence of urethra
10246	Congenital diaphragmatic hernia
15180	Werdnig-Hoffman - SMA type 1
15181	Spinal Muscular Atrophy
15199	Muscular dystrophy
15200	Myotonic Dystrophy
15201	Myotonic disorder
15202	Congenital myopathy
15203	Mitochondrial myopathy
15730	Hydrops fetalis (non isoimmune haemolytic disease)
15841	Hydrops fetalis (non-haemolytic)
15892	Iniencephaly
15911	Lissencephaly
15918	Holoprosencephaly
15922	Congenital cerebral cysts
15923	Other specified congenital malformations of brain
16028	Double inlet ventricle (DILV)
16036	Ventricle single
16049	Congenital tricuspid atresia / stenosis
16051	Hypoplastic right heart syndrome
16058	Mitral atresia
16059	Hypoplastic left heart syndrome (HLH)
16108	Aneurysm of Vein of Galen
16324	Potter's syndrome
16327	Polycystic kidney, infantile type
16360	Congenital absence of bladder and urethra
16495	Congenital diaphragmatic hernia
16496	Aplasia of diaphragm
16510	Harlequin fetus
16515	Epidermolysis bullosa letalis
16577	Zelweggers syndrome
16583	Conjoined twins
200606	Myotonic dystrophy requiring endotracheal intubation and assisted ventilation
200606	Myotonic dystrophy requiring endotracheal intubation and assisted ventilation
16143	Pulmonary Hypoplasia
10892	Pulmonary hypoplasia

OR

16045 Pulmonary valve atresia	Only if the following NOT present: 11133 Ventricular septal defect (VSD) 16037 Ventricular septal defect (VSD)

Appendix 4.1

The association between the predictors and late-onset sepsis did not vary significantly between cohorts, except for the presence of an additional major congenital anomaly, which was not a significant predictor of the outcome of late-onset sepsis for the 2012-2016 cohort (aOR 1.35 95%CI 0.81-2.22). The pseudo R2, area-under-ROC and calibration belt plot was calculated for each of the resulting models for the three cohorts, demonstrating that the restricting cohorts by birth year did not materially change the performance of the model for late-onset sepsis.

Appendix 4.1.1: Neonates coded as having late-onset sepsis by birth year

Key
frequency *row percentage*

	LateOnsetSepsis		
Birth year	0	1	Total
2012	950	52	1,002
	94.81	5.19	100.00
2013	885	38	923
	95.88	4.12	100.00
2014	926	53	979
	94.59	5.41	100.00
2015	881	43	924
	95.35	4.65	100.00
2016	840	51	891
	94.28	5.72	100.00
2017	847	75	922
	91.87	8.13	100.00
2018	740	59	799
	92.62	7.38	100.00
2019	798	74	872
	91.51	8.49	100.00
2020	722	56	778
	92.80	7.20	100.00
Total	7,589	501	8,090
	93.81	6.19	100.00

Pearson chi2(8) = 30.8942 Pr = 0.000

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Appendix 4.1.2 Association between selected neonatal characteristics and late-onset sepsis amongst neonates by cohort

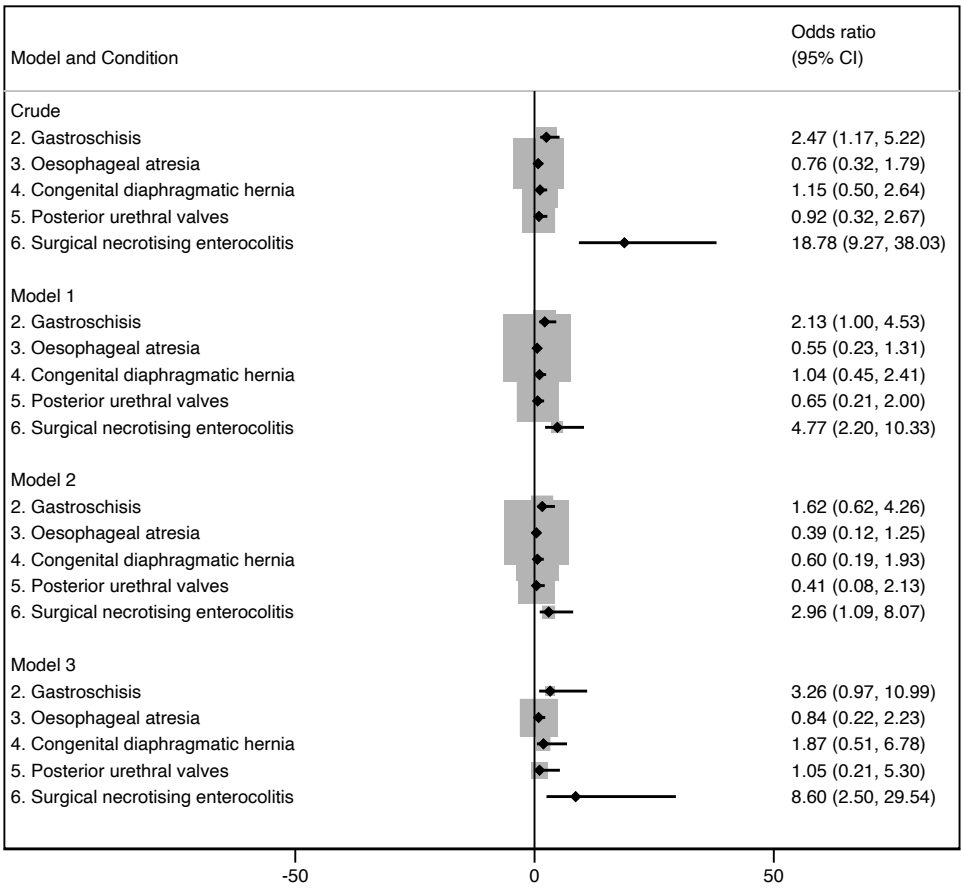
	Crude odds ratio (95%CI)	p-value	Whole cohort: Adjusted odds ratio (95%CI)	p-value	2012-2016 cohort: Adjusted odds ratio (95% CI)	p-value	2017-2020 cohort: Adjusted odds ratio (95% CI)	p-value
Gestational age at birth (weeks)	0.80 (0.78-0.81)	<0.01	0.87 (0.84-0.90)	<0.01	0.86 (0.82-0.90)	<0.01	0.88 (0.84-0.92)	<0.01
Surgical Condition		<0.01		<0.01		<0.01		<0.01
Hirschsprung's Disease	REF		REF		REF		REF	
Gastroschisis	2.47 (1.17-5.22)		2.13 (1.00-4.53)		1.62 (0.62-4.26)		3.26 (0.97-10.99)	
Oesophageal Atresia	0.76 (0.32-1.79)		0.55 (0.23-1.31)		0.39 (0.12-1.25)		0.84 (0.22-2.23)	
Congenital Diaphragmatic Hernia	1.15 (0.50-2.64)		1.04 (0.45-2.41)		0.60 (0.19-1.93)		1.87 (0.51-6.78)	
Posterior Urethral Valves	0.92 (0.32-2.67)		0.65 (0.21-2.00)		0.41 (0.08-2.13)		1.05 (0.21-5.30)	
Surgical Necrotising Enterocolitis	18.78 (9.27-38.03)		4.77 (2.20-10.33)		2.96 (1.09-8.07)		8.60 (2.50-29.54)	
Sex								
Male	1.07 (0.89-1.29)	0.45	1.19 (0.97-1.45)	0.11	1.18 (0.89-1.58)	0.26	1.21 (0.90-1.61)	0.20
Female	REF		REF		REF		REF	
Additional major congenital anomaly								
No additional major congenital anomaly	REF		REF		REF		REF	
Additional major congenital anomaly	0.80 (0.59-1.10)	0.17	1.47 (1.05-2.06)	0.02	1.35 (0.81-2.22)	0.25	1.61 (1.01-2.57)	0.05
Mother's ethnicity		0.004		0.14		0.45		0.30
White	REF		REF		REF		REF	
Mixed	2.08 (1.13-3.83)		1.60 (0.81-3.17)		1.26 (0.46-3.44)		2.10 (0.80-5.47)	

	Crude odds ratio (95%CI)	p-value	Whole cohort: Adjusted odds ratio (95%CI)	p-value	2012-2016 cohort: Adjusted odds ratio (95% CI)	p-value	2017-2020 cohort: Adjusted odds ratio (95% CI)	p-value
Asian or Asian British	1.54 (1.17-2.03)		1.32 (0.97-1.79)		1.45 (0.95-2.21)		1.21 (0.77-1.89)	
Black or Black British	1.41 (0.98-2.02)		0.74 (0.50-1.10)		0.83 (0.50-1.39)		0.71 (0.39-1.31)	
Other Ethnic Groups	1.16 (0.60-2.23)		0.99 (0.49-1.99)		0.67 (0.20-2.26)		1.28 (0.52-3.11)	
Missing	0.98 (0.76-1.26)		1.005 (0.77-1.32)		1.07 (0.69-1.66)		0.85 (0.59-1.20)	
IMD Decile		0.27		0.31		0.63		0.22
IMD Decile 1	REF		REF		REF		REF	
IMD Decile 2	0.79 (0.57-1.10)		0.74 (0.52-1.05)		0.71 (0.43-1.17)		0.75 (0.45-1.24)	
IMD Decile 3	1.09 (0.79-1.48)		1.16 (0.83-1.62)		0.95 (0.59-1.55)		1.38 (0.85-2.24)	
IMD Decile 4	0.91 (0.64-1.28)		0.99 (0.68-1.43)		0.89 (0.54-1.48)		1.15 (0.67-1.99)	
IMD Decile 5	1.01 (0.72-1.43)		1.06 (0.73-1.53)		0.68 (0.38-1.22)		1.44 (0.87-2.37)	
IMD Decile 6	0.63 (0.42-0.97)		0.70 (0.44-1.09)		0.75 (0.40-1.38)		0.64 (0.33-1.24)	
IMD Decile 7	0.80 (0.54-1.18)		0.80 (0.52-1.23)		0.61 (0.33-1.15)		1.07 (0.60-1.93)	
IMD Decile 8	0.89 (0.60-1.34)		0.97 (0.63-1.49)		1.11 (0.62-1.98)		0.82 (0.42-1.60)	
IMD Decile 9	0.76 (0.49-1.18)		0.96 (0.60-1.54)		0.97 (0.50-1.86)		0.97 (0.49-1.91)	
IMD Decile 10	0.72 (0.46-1.13)		0.77 (0.48-1.26)		0.60 (0.29-1.25)		0.98 (0.51-1.92)	

Data are presented as median (IQR) for continuous measures, and n (row %) for categorical measures. Wald test used to calculate p-values. Adjusted for gestational age (weeks), mother's ethnicity, IMD decile, additional major congenital anomaly, sex and surgical condition.

Appendix 4.1.3: Forest plot demonstrating the relationship between surgical condition and late-onset sepsis by cohort

Model 1: Whole cohort. Adjusted for gestational age (weeks), mother's ethnicity, IMD decile, additional major congenital anomaly, sex and surgical condition.
Model 2: Cohort from 2012-2016. Same adjustment as Model 1.
Model 3: Cohort from 2017-2020. Same adjustment as Model 1.



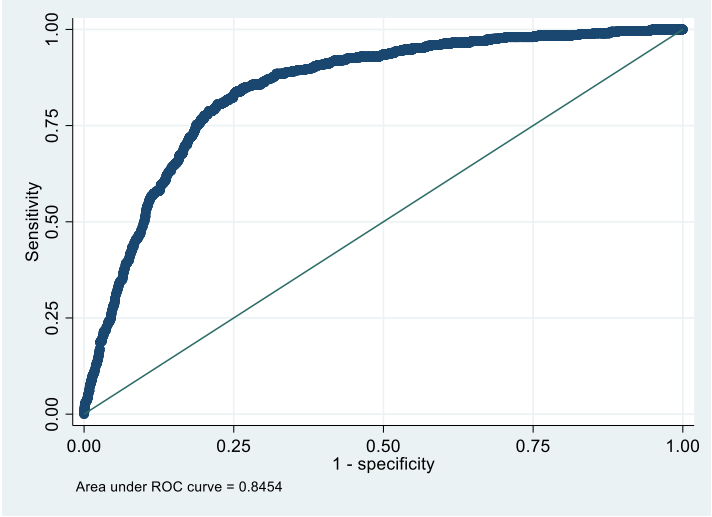
Appendix 4.1.4 Pseudo R2 for each model

All three models are adjusted for gestational age (weeks), mother's ethnicity, IMD decile, additional major congenital anomaly, sex and surgical condition.

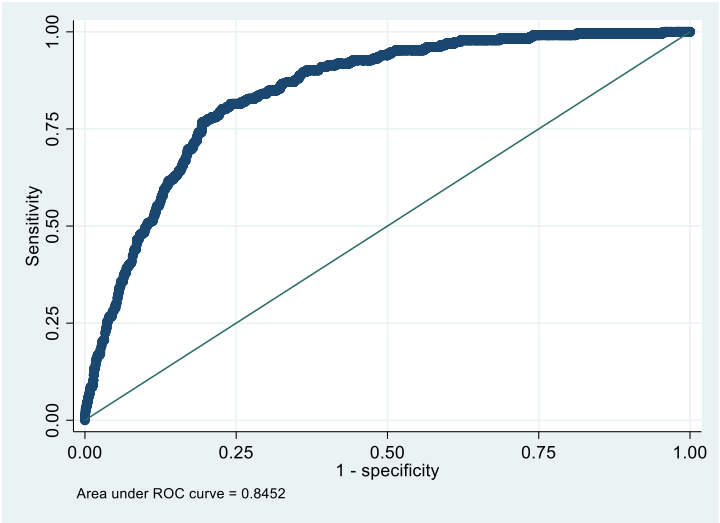
Cohort	**Pseudo R2**
Model 1: Whole cohort	0.2189
Model 2: Cohort from 2012-2016	0.2189
Model 3: Cohort from 2017-2020	0.2377

Appendix 4.1.5: Model area-under-ROC

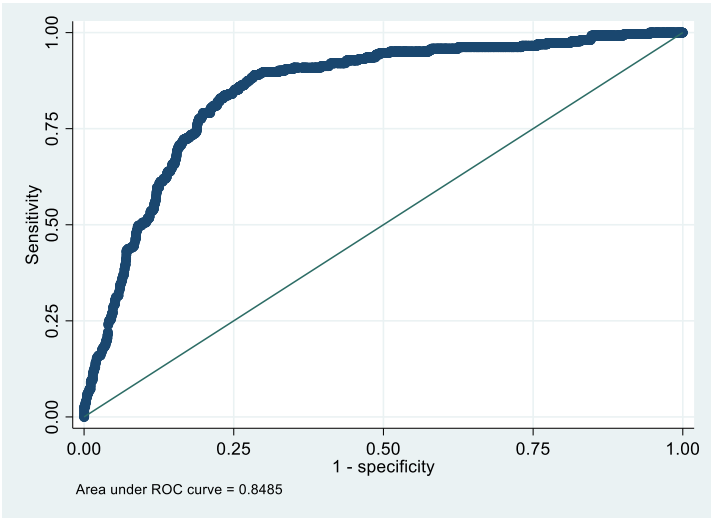
Model 1:



Model 2:

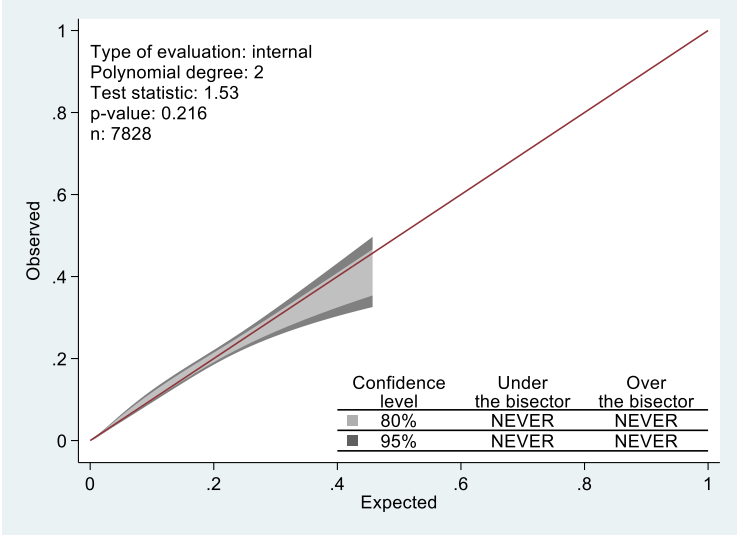


Model 3:

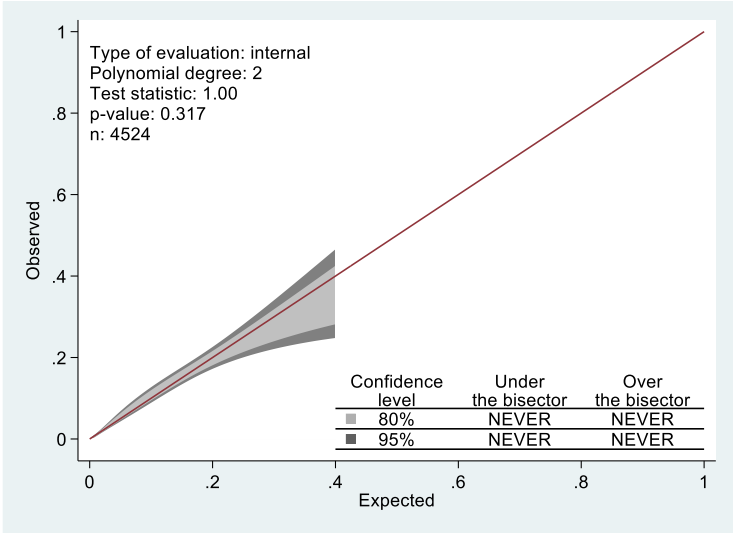


Appendix 4.1.6: Calibration belt for each model

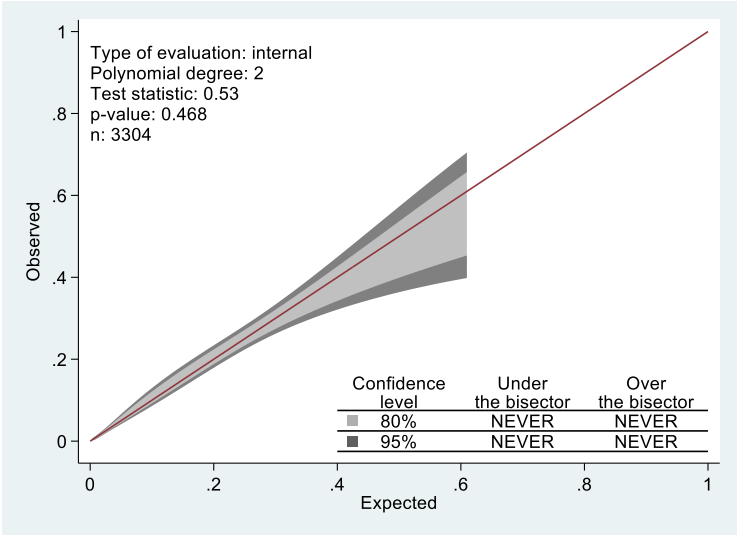
Model 1:



Model 2:

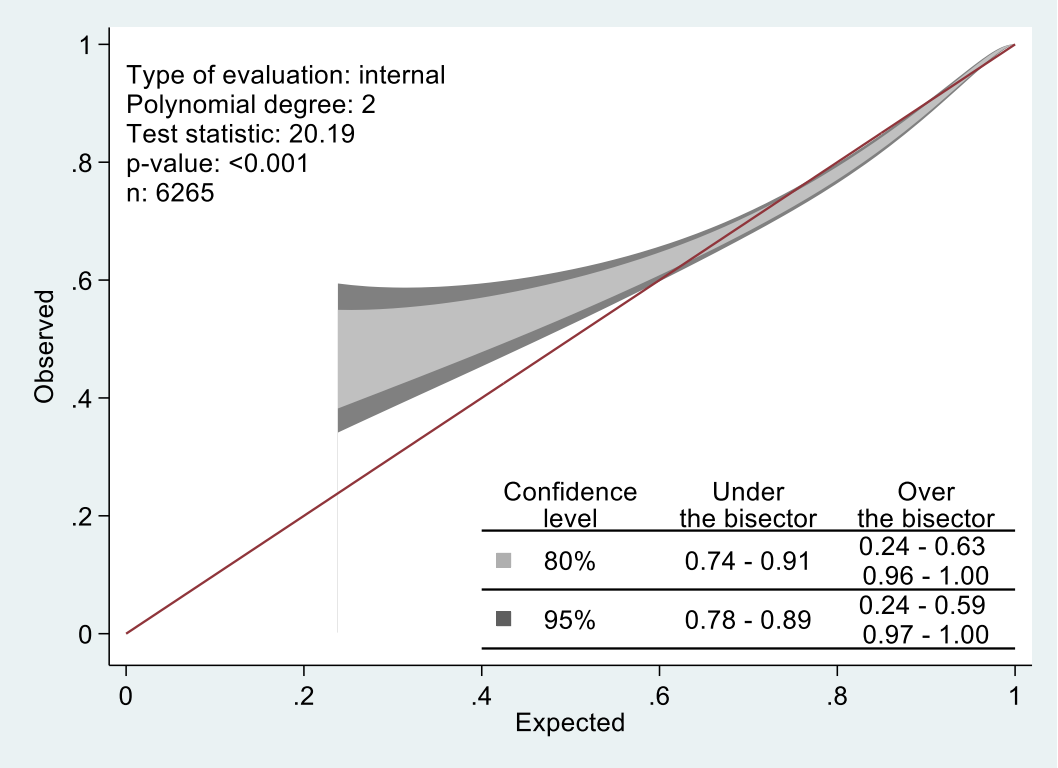


Model 3:

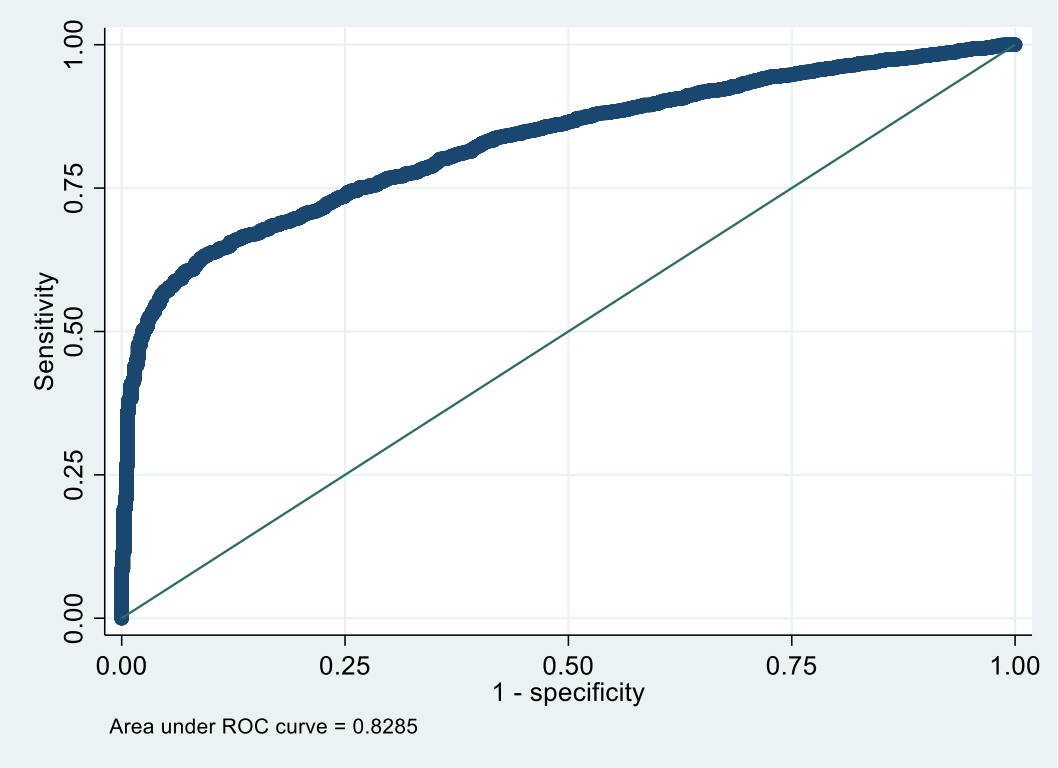


Appendix 4.2

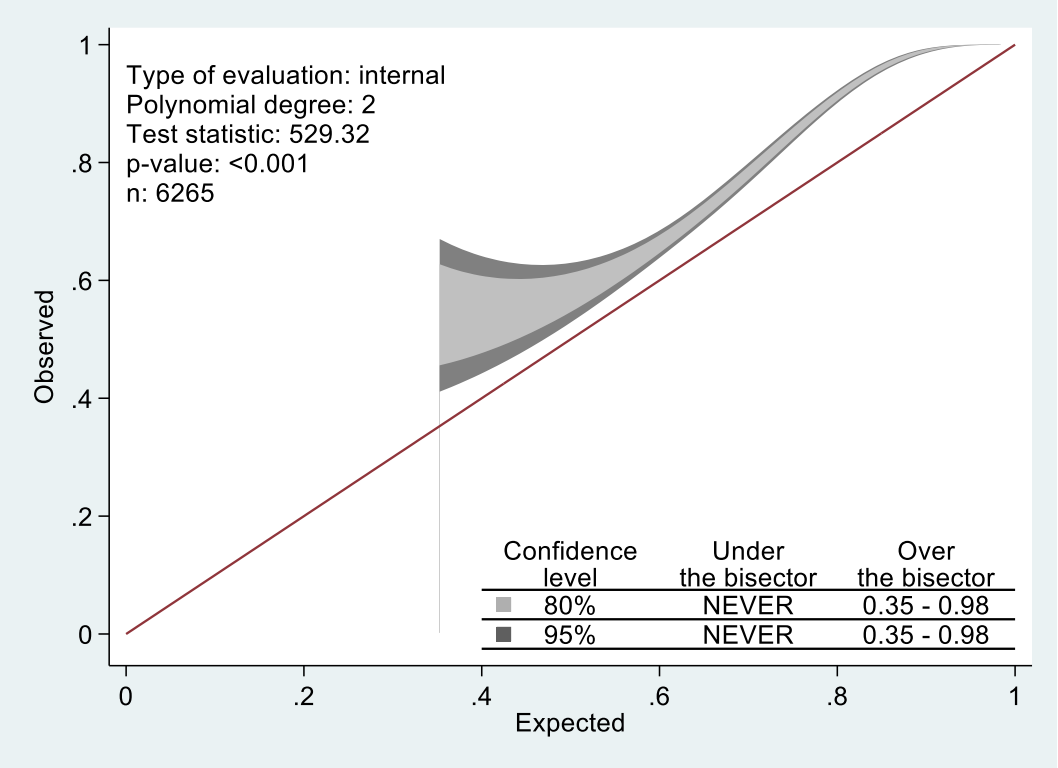
Appendix 4.2.1: Calibration belt plot for penalised logistic regression model



Appendix 4.2.2: Aura under ROV curve for probit model



Appendix 4.2.3: Calibration belt plot for probit model



Appendix 5.1 Cohort based on ICD-10 diagnostic alone

Selected characteristics of the cohort defined by ICD-10 diagnostic codes alone is outlined in **Table 5.1.1**. Based on the presence of a qualifying ICD diagnostic code alone, 32.3% (n=2846) of CDH survivors and 17.2% of OA survivors (n=669) had no operations, which is implausible given the nature of these conditions (**Table 5.1.2**).

Appendix Table 5.1.1 Selected characteristics of children born and admitted to an NHS hospital from January 2005 – November 2022 with one of the six study conditions, based on the presence of a qualifying ICD diagnosis

	Hirschsprung's Disease N=3,629	Gastroschisis N=4,086	Oesophageal Atresia N=4,343	Congenital Diaphragmatic Hernia N=3,800	Posterior Urethral Valves N=2,709	Necrotising Enterocolitis* N=19,532	Total N=38,099
Birthweight (grams)	3325.0 (2900.0-3680.0)	2370.0 (2010.0-2724.0)	2623.5 (2000.0-3140.0)	2970.0 (2445.0-3375.0)	3310.0 (2890.0-3667.5)	1085.0 (778.0-1742.0)	2040.0 (1020.0-3010.0)
Gestational age (in weeks)	39.0 (38.0-40.0)	36.0 (35.0-37.0)	37.0 (35.0-39.0)	38.0 (36.0-39.0)	38.0 (37.0-40.0)	28.0 (26.0-32.0)	34.0 (28.0-38.0)
Sex							
Male	2,606 (71.8%)	2,110 (51.6%)	2,511 (57.8%)	2,230 (58.7%)	2,678 (98.9%)	10,997 (56.3%)	23,132 (60.7%)
Female	1,023 (28.2%)	1,969 (48.2%)	1,829 (42.1%)	1,564 (41.2%)	29 (1.1%)	8,523 (43.6%)	14,937 (39.2%)
Indeterminate	0 (0.0%)	5 (0.1%)	1 (0.0%)	3 (0.1%)	0 (0.0%)	5 (0.0%)	14 (0.0%)
Missing	0 (0.0%)	2 (0.0%)	2 (0.0%)	3 (0.1%)	2 (0.1%)	7 (0.0%)	16 (0.0%)
Secondary study condition							
Hirschsprung's Disease	0 (0.0%)	7 (0.2%)	3 (0.1%)	5 (0.1%)	6 (0.2%)	0 (0.0%)	21 (0.1%)
Gastroschisis	0 (0.0%)	0 (0.0%)	4 (0.1%)	21 (0.6%)	2 (0.1%)	0 (0.0%)	27 (0.1%)
Oesophageal Atresia	0 (0.0%)	0 (0.0%)	0 (0.0%)	32 (0.8%)	0 (0.0%)	0 (0.0%)	32 (0.1%)
Posterior Urethral Valves	0 (0.0%)	0 (0.0%)	6 (0.1%)	4 (0.1%)	0 (0.0%)	0 (0.0%)	10 (0.0%)
Necrotising Enterocolitis	202 (5.6%)	328 (8.0%)	113 (2.6%)	60 (1.6%)	16 (0.6%)	0 (0.0%)	719 (1.9%)
Missing	3,427 (94.4%)	3,751 (91.8%)	4,217 (97.1%)	3,678 (96.8%)	2,685 (99.1%)	19,532 (100.0%)	37,290 (97.9%)
Additional major congenital anomaly							

	Hirschsprung's Disease	Gastroschisis	Oesophageal Atresia	Congenital Diaphragmatic Hernia	Posterior Urethral Valves	Necrotising Enterocolitis*	Total
No additional major congenital anomaly	2,752 (75.8%)	3,144 (76.9%)	1,621 (37.3%)	2,184 (57.5%)	2,181 (80.5%)	9,670 (49.5%)	21,552 (56.6%)
Additional major congenital anomaly	877 (24.2%)	942 (23.1%)	2,722 (62.7%)	1,616 (42.5%)	528 (19.5%)	9,862 (50.5%)	16,547 (43.4%)
Ethnicity							
White	2,646 (72.9%)	3,632 (88.9%)	3,283 (75.6%)	2,658 (69.9%)	1,742 (64.3%)	13,512 (69.2%)	27,473 (72.1%)
Mixed	146 (4.0%)	160 (3.9%)	122 (2.8%)	128 (3.4%)	128 (4.7%)	961 (4.9%)	1,645 (4.3%)
Asian or Asian British	299 (8.2%)	65 (1.6%)	348 (8.0%)	523 (13.8%)	464 (17.1%)	2,133 (10.9%)	3,832 (10.1%)
Black or Black British	183 (5.0%)	56 (1.4%)	112 (2.6%)	130 (3.4%)	173 (6.4%)	1,681 (8.6%)	2,335 (6.1%)
Other	169 (4.7%)	45 (1.1%)	191 (4.4%)	120 (3.2%)	85 (3.1%)	445 (2.3%)	1,055 (2.8%)
Missing	186 (5.1%)	128 (3.1%)	287 (6.6%)	241 (6.3%)	117 (4.3%)	800 (4.1%)	1,759 (4.6%)
IMD rank	12474.0 (5452.0-21569.0)	10237.0 (4549.5-18113.0)	13498.0 (6125.5-22600.0)	12547.0 (5444.0-21282.0)	13015.0 (6063.0-22279.0)	11002.3 (4810.0-19922.0)	11584.0 (5105.0-20427.0)
IMD decile							
1	510 (14.1%)	697 (17.1%)	544 (12.5%)	567 (14.9%)	344 (12.7%)	3,241 (16.6%)	5,903 (15.5%)
2	453 (12.5%)	588 (14.4%)	442 (10.2%)	443 (11.7%)	333 (12.3%)	2,899 (14.8%)	5,158 (13.5%)
3	394 (10.9%)	536 (13.1%)	439 (10.1%)	419 (11.0%)	316 (11.7%)	2,394 (12.3%)	4,498 (11.8%)
4	326 (9.0%)	432 (10.6%)	402 (9.3%)	384 (10.1%)	283 (10.4%)	2,049 (10.5%)	3,876 (10.2%)
5	308 (8.5%)	373 (9.1%)	380 (8.7%)	350 (9.2%)	248 (9.2%)	1,787 (9.1%)	3,446 (9.0%)
6	304 (8.4%)	331 (8.1%)	316 (7.3%)	311 (8.2%)	227 (8.4%)	1,455 (7.4%)	2,944 (7.7%)
7	258 (7.1%)	264 (6.5%)	321 (7.4%)	295 (7.8%)	210 (7.8%)	1,429 (7.3%)	2,777 (7.3%)
8	272 (7.5%)	202 (4.9%)	320 (7.4%)	238 (6.3%)	207 (7.6%)	1,275 (6.5%)	2,514 (6.6%)
9	230 (6.3%)	192 (4.7%)	308 (7.1%)	262 (6.9%)	181 (6.7%)	1,081 (5.5%)	2,254 (5.9%)
10	190 (5.2%)	135 (3.3%)	260 (6.0%)	230 (6.1%)	186 (6.9%)	940 (4.8%)	1,941 (5.1%)
Missing	384 (10.6%)	336 (8.2%)	611 (14.1%)	301 (7.9%)	174 (6.4%)	982 (5.0%)	2,788 (7.3%)

Data are presented as median (IQR) for continuous measures, and n (%) for categorical measures.

*Necrotising enterocolitis includes both medical and surgical necrotising enterocolitis.

Appendix Table 5.1.2 Proportion of children who survived and were coded as having no operations

	Hirschsprung's Disease	Gastroschisis	Oesophageal Atresia	Congenital Diaphragmatic Hernia	Posterior Urethral Valves	Necrotising Enterocolitis	Total
	N=3,540	N=3,922	N=3,896	N=2,846	N=2,611	N=15,382	N=32,197
No operations	340 (9.6%)	1341 (34.2%)	669 (17.2%)	920 (32.3%)	225 (8.6%)	6093 (39.6%)	9588 (29.8%)

Data are presented as n (%).

Appendix 5.2: Developing the code list for additional major congenital anomaly by mapping ICD-10 codes onto Badgernet diagnostic codes

Clevermed ID	Condition name	ICD code
15930	(unknown or unspecified cause) spina bifida with hydrocephalus	Q05
10008	Absence of bladder	Q64.5
10066	Adult polycystic kidney disease type I	Q61.2
15890	Anencephaly	Q00.0
15893	Anencephaly and similar malformations	Q00
16496	Aplasia of diaphragmatic hernia	None found
16196	Atresia of oesophagus with tracheo-oesophageal fistula (TOF)	Q39.1
16195	Atresia of oesophagus without fistula	Q39.0
16083	Atresia of pulmonary artery	Q25.5
10097	Atrio-ventricular septal defect (AVSD)	Q21.2
16039	Atrioventricular septal defect (AVSD)	Q21.2
16035	Atrium single	Q21.2
10099	Autosomal dominant polycystic kidney in childhood	None found
10100	Autosomal recessive polycystic kidney - infantile	Q61.1
		Q61.3
10123	Bilateral renal agenesis	Q60.1
15926	Cervical spina bifida with hydrocephalus	Q05
15931	Cervical spina bifida without hydrocephalus	Q05
16079	Coarctation of aorta	Q25.1
10227	Coarctation of the aorta	Q25.1
16024	Common arterial trunk (Truncus malformation)	Q20.0
16223	Cong abscence atresia / stenosis of large intestine part unspec	Q42
16220	Cong absence atresia / stenosis anus with fistula	Q42
16221	Cong absence atresia / stenosis anus without fistula	Q42
16218	Cong absence atresia / stenosis of rectum with fistula	Q42
16219	Cong absence atresia / stenosis rectum without fistula	Q42
16032	Cong malforms of cardiac chambers and connections unspec	Q20
16222	Congen absence atresia / stenosis parts of large intestine	Q42
16360	Congenital absence of bladder and urethra	Q64.5
10236	Congenital absence of urethra	Q64.5
16212	Congenital absence, atresia and stenosis of duodenum	Q41
16215	Congenital absence, atresia and stenosis of ileum	Q41
16224	Congenital absence, atresia and stenosis of large intestine	Q41
16217	Congenital absence, atresia and stenosis of small intestine	Q41
10240	Congenital anal stenosis	Q42
10246	Congenital diaphragmatic hernia	Q79.0
16495	Congenital diaphragmatic hernia	Q79.0
16056	Congenital insufficiency of aortic valve	Q23

16061	Congenital malformation of aortic and mitral valves unspec	Q23
16053	Congenital malformation of tricuspid valve (unknown or unspecified cause)	Q22
16062	Congenital malformations of aortic and mitral valves	Q23
16033	Congenital malformations of cardiac chambers and connections	Q20
16054	Congenital malformations of pulmonary and tricuspid valves	Q22
16057	Congenital mitral stenosis (MS)	Q23.2
16357	Congenital posterior urethral valves (PUV)	Q64.2
16047	Congenital pulmonary valve insufficiency	Q22
16046	Congenital pulmonary valve stenosis	Q22
16198	Congenital stenosis and stricture of oesophagus	Q39.3
16055	Congenital stenosis of aortic valve (AS)	Q23
10273	Congenital stenosis of the oesophagus	Q39.3
16197	Congenital tracheo-oesophageal fistula without atresia (TOF)	Q39.2
16049	Congenital tricuspid atresia / stenosis	Q22
15891	Craniorachischisis	Q00.1
16029	Discordant atrioventricular connection	Q20
16028	Double inlet ventricle (DILV)	Q20
16026	Double outlet left ventricle (DOLV)	Q20
10356	Double outlet right ventricle (DORV)	Q20
16025	Double outlet right ventricle (DORV)	Q20
16593	Down's syndrome	Q90
16592	Down's syndrome (unknown or unspecified cause)	Q90
16213	Duodenal atresia / stenosis	Q41
10358	Duodenal atresia / stenosis / web (specify)	Q41
16050	Ebstein's anomaly	Q22.5
10367	Ectopia vesicae	Q64.1
16597	Edwards' syndrome (unknown or unspecified cause)	Q91
16602	Edwards' syndrome and Patau's syndrome	Q91
15899	Encephalocele	Q01
15898	Encephalocele (unknown or unspecified cause)	Q01
15897	Encephalocele of other sites	Q01
16497	Eventration of diaphragmatic hernia	Q79.1
10395	Exomphalos	Q79.2
16498	Exomphalos Malrotation	None found
16356	Exstrophy of urinary bladder	Q64.1
15894	Frontal encephalocele	Q79.2
16499	Gastroschisis	Q79.3
10490	Hernia into the cord	None found
10493	High anorectal anomaly with fistula (specify)	See ARM diagnoses below
10494	High anorectal anomaly with rectocloacal fistula	See ARM diagnoses below

10495	High anorectal anomaly with rectocutaneous fistula	See ARM diagnoses below
10496	High anorectal anomaly with rectourethral fistula	See ARM diagnoses below
10497	High anorectal anomaly with rectovesical fistula	See ARM diagnoses below
10498	High anorectal anomaly with rectovulval fistula	See ARM diagnoses below
10499	High anorectal anomaly without fistula	See ARM diagnoses below
16080	Hypoplasia of aortic arch	None found
16059	Hypoplastic left heart syndrome (HLH)	Q23
16051	Hypoplastic right heart syndrome	Q22
16216	Ileal atresia / stenosis	Q41
10541	Ileal atresia / stenosis (specify)	Q41
15892	Iniencephaly	Q00
16030	Isomerism of atrial appendages	Q20
16214	Jejunal atresia / stenosis	Q41
10605	Jejunal atresia / stenosis (specify)	Q41
10636	Low anorectal anomaly with anocutaneous fistula	See ARM diagnoses below
10637	Low anorectal anomaly with anovestibular fistula	See ARM diagnoses below
10638	Low anorectal anomaly with fistula (other specify)	See ARM diagnoses below
10639	Low anorectal anomaly without fistula	See ARM diagnoses below
15928	Lumbar spina bifida with hydrocephalus	Q05
15933	Lumbar spina bifida without hydrocephalus	Q05
16082	Malformation of aorta	Q25.4
16058	Mitral atresia	Q23
10704	Myelomeningocele (specify site)	Q05
15895	Nasofrontal encephalocele	Q01
15896	Occipital encephalocele	Q01
10740	Oesophageal atresia with distal tracheo-oesophageal fistula	Q39.1
10741	Oesophageal atresia without distal fistula	Q39.0
16199	Oesophageal web	Q39.4
16031	Other cong malforms of cardiac chambers and connections	Q20
16060	Other congenital malformations of aortic and mitral valves	Q23
16086	Other congenital malformations of great arteries	Q25.7
16048	Other congenital malformations of pulmonary valve	Q22
16052	Other congenital malformations of tricuspid valve	Q22
16601	Patau's syndrome (unknown or unspecified cause)	Q91
16328	Polycystic kidney, adult type	Q61.2
16327	Polycystic kidney, infantile type	Q61.1
10854	Posterior urethral valves (PUV)	Q64.2
16324	Potter's syndrome	Q60.6

16045	Pulmonary valve atresia (Only if the following NOT present: 11133 Ventricular septal defect (VSD), 16037 Ventricular septal defect (VSD))	
16318	Renal agenesis, bilateral	Q60.1
15929	Sacral spina bifida with hydrocephalus	Q05
15934	Sacral spina bifida without hydrocephalus	Q05
10986	Spina bifida	Q05
15936	Spina bifida	Q05
15935	Spina bifida (unknown or unspecified cause)	Q05
16081	Stenosis of aorta (AS)	Q25.3
16084	Stenosis of pulmonary artery (PS)	Q25.6
11043	Tetralogy of Fallot	Q21.3
16040	Tetralogy of Fallot	Q21.3
16475	Thanatophoric short stature	Q77.1
15927	Thoracic spina bifida with hydrocephalus	Q05
15932	Thoracic spina bifida without hydrocephalus	Q05
16092	Total anomalous pulmonary venous connection (TAPVD)	Q26.2
11057	Total anomylous pulmonary venous drainage (TAPVD)	None found
16027	Transposition great arteries (TGA)	Q20
11070	Transposition of the great vessels (TGA)	Q20
16087	Transposition of the great vessels (TGA)	Q20
16598	Trisomy 13, meiotic nondisjunction	Q91
16599	Trisomy 13, mosaicism (mitotic nondisjunction)	Q91
16600	Trisomy 13, translocation	Q91
16594	Trisomy 18, meiotic nondisjunction	Q91
16595	Trisomy 18, mosaicism (mitotic nondisjunction)	Q91
16596	Trisomy 18, translocation	Q91
16589	Trisomy 21, meiotic nondisjunction	Q90
16590	Trisomy 21, mosaicism (mitotic nondisjunction)	Q90
16591	Trisomy 21, translocation	Q90
16036	Ventricle single	Q20
Codes for anorectal malformation		
Anorectal malformation (ARM)	Congenital absence, atresia and stenosis of rectum with fistula	Q42.0
	Congenital absence, atresia and stenosis of rectum without fistula	Q42.1
	Congenital absence, atresia and stenosis of anus with fistula	Q42.2
	Congenital absence, atresia and stenosis of anus without fistula	Q42.3
	Ectopic anus	Q43.5
	Congenital fistula of rectum and anus	Q43.6
	Persistent cloaca	Q43.7
	Congenital rectovaginal fistula Excl.: cloaca (Q43.7)	Q52.2
	Rectal fistula	K60.4
	Anorectal fistula	K60.5

	Stenosis of anus and rectum	K62.4
	Vesicointestinal fistula	N32.1
	Urethral fistula	N36.0
	Fistula of vagina to large intestine	N82.3
	Other female intestinal-genital tract fistulae	N82.4
Additional diagnoses from Harnden et al. that was not included in the NNRD AI		
16610	Triploidy and polyploidy	Q92.7
500250	Tracheal agenesis or atresia	Q32.1
1010778	Laryngeal atresia	Q31.8
16145	Alveolar Capillary Dysplasia	J84.8
15180	Werdnig-Hoffman - SMA type 1	G12
15181	Spinal Muscular Atrophy	G12
15199	Muscular dystrophy	G71.0
15200	Myotonic Dystrophy	G71.1
15201	Myotonic disorder	G71.1
15202	Congenital myopathy	G71.2
15203	Mitochondrial myopathy	G71.3
15730	Hydrops fetalis (non isoimmune haemolytic disease)	P56.9
15841	Hydrops fetalis (non-haemolytic)	P83.2
15911	Lissencephaly	Q04.3
15918	Holoprosencephaly	Q04.2
15922	Congenital cerebral cysts	Q04.6
15923	Other specified congenital malformations of brain	Q04.8
16108	Aneurysm of Vein of Galen	None found
16510	Harlequin fetus	Q80.4
16515	Epidermolysis bullosa letalis	Q81.1
16577	Zelweggers syndrome	Q87.8
16583	Conjoined twins	Q89.4
200606	Myotonic dystrophy requiring endotracheal intubation and assisted ventilation	G71.0
16143	Pulmonary Hypoplasia	Q33.6
10892	Pulmonary hypoplasia	Q33.6

5.3 Appendix OC: Categorisation of OPCS-4 codes by grade (major vs. minor) and surgical condition

OPCS-4=Office of Population Censuses and Surveys Classification of Interventions and Procedures Version 4; HD=Hirschsprung's disease; GS=gastroschisis; OA=oesophageal atresia; CDH=congenital diaphragmatic hernia; PUV=posterior urethral valves; NEC=necrotising enterocolitis

OPCS-4 code and description	Major	Minor	HD	GS	OA	CDH	PUV	NEC
E29.7: Cordectomy of vocal cord NEC	1				1			
E31.1: Laryngotracheal reconstruction using cartilage graft	1				1			
E31.2: Laryngotracheoplasty NEC	1				1			
E31.3: Division of stenosis of larynx and insertion of prosthesis into larynx	1				1			
E31.4: Implantation of artificial voice box into larynx	1				1			
E31.5: Attention to artificial voice box in larynx	1				1			
E31.8: Other specified reconstruction of larynx	1				1			
E31.9: Unspecified reconstruction of larynx	1				1			
E33.1: External arytenoidectomy	1				1			
E33.2: Cordopexy of vocal cord	1				1			
E33.5: Vocal cord medialisation using implant	1				1			
E33.6: Vocal cord medialisation using biological material	1				1			
E35.7: Endoscopic vocal cord medialisation	1				1			
E39.1: Open excision of lesion of trachea	1				1	1		
E39.8: Other specified partial excision of trachea	1				1	1		
E39.9: Unspecified partial excision of trachea	1				1	1		
E40.1: Reconstruction of trachea and anastomosis HFQ	1				1	1		
E40.2: Reconstruction of trachea using graft	1				1	1		
E40.3: Reconstruction of trachea NEC	1				1	1		
E40.8: Other specified plastic operations on trachea	1				1	1		
E40.9: Unspecified plastic operations on trachea	1				1	1		
E41.1: Open insertion of tubal prosthesis in trachea	1				1	1		

OPCS-4 code and description	Major	Minor	HD	GS	OA	CDH	PUV	NEC
E41.2: Open renewal of tubal prosthesis in trachea	1				1	1		
E41.3: Open removal of tubal prosthesis from trachea	1				1	1		
E41.4: Tracheo-oesophageal puncture with insertion of speech prosthesis	1				1	1		
E41.8: Other specified open placement of prosthesis in trachea	1				1	1		
E41.9: Unspecified open placement of prosthesis in trachea	1				1	1		
E42.1: Permanent tracheostomy	1				1	1		
E42.2: Cricothyroidostomy	1				1	1		
E42.3: Temporary tracheostomy	1				1	1		
E42.4: Revision of tracheostomy	1				1	1		
E42.5: Closure of tracheostomy	1				1	1		
E42.6: Replacement of tracheostomy tube		1			1	1		
E42.7: Removal of tracheostomy tube		1			1	1		
E42.8: Other specified exteriorisation of trachea	1				1	1		
E42.9: Unspecified exteriorisation of trachea	1				1	1		
E43.3: Tracheopexy	1				1	1		
E44.1: Excision of carina	1				1	1		
E44.2: Reconstruction of carina	1				1	1		
E44.3: Open biopsy of lesion of carina	1				1	1		
E44.8: Other specified open operations on carina	1				1	1		
E44.9: Unspecified open operations on carina	1				1	1		
E46.1: Sleeve resection of bronchus and anastomosis HFQ	1				1	1		
E46.2: Excision of cyst of bronchus	1				1	1		
E46.3: Excision of lesion of bronchus NEC	1				1	1		
E46.8: Other specified partial extirpation of bronchus	1				1	1		
E46.9: Unspecified partial extirpation of bronchus	1				1	1		
E47.2: Closure of fistula of bronchus	1				1	1		
E47.3: Repair of bronchus NEC	1				1	1		

OPCS-4 code and description	Major	Minor	HD	GS	OA	CDH	PUV	NEC
E47.8: Other specified other open operations on bronchus	1				1	1		
E47.9: Unspecified other open operations on bronchus	1				1	1		
E48.8: Other specified therapeutic fibreoptic endoscopic operations on lower respiratory tract		1			1	1		
E48.9: Unspecified therapeutic fibreoptic endoscopic operations on lower respiratory tract		1			1	1		
E49.8: Other specified diagnostic fibreoptic endoscopic examination of lower respiratory tract		1			1	1		
E49.9: Unspecified diagnostic fibreoptic endoscopic examination of lower respiratory tract		1			1	1		
E50.8: Other specified therapeutic endoscopic operations on lower respiratory tract using rigid bronchoscope		1			1	1		
E50.9: Unspecified therapeutic endoscopic operations on lower respiratory tract using rigid bronchoscope		1			1	1		
E51.8: Other specified diagnostic endoscopic examination of lower respiratory tract using rigid bronchoscope		1			1	1		
E51.9: Unspecified diagnostic endoscopic examination of lower respiratory tract using rigid bronchoscope		1			1	1		
E52.8: Other specified other operations on bronchus		1			1	1		
E52.9: Unspecified other operations on bronchus		1			1	1		
E53.1: Double lung transplant	1					1		
E53.2: Single lung transplant	1					1		
E53.3: Single lobe lung transplant	1					1		
E53.8: Other specified transplantation of lung	1					1		
E53.9: Unspecified transplantation of lung	1					1		
E59.4: Drainage of lung	1				1	1		
E61.3: Open drainage of mediastinum	1				1	1		
E61.4: Mediastinotomy NEC	1				1	1		
E61.5: Exploration of mediastinum NEC	1				1	1		

OPCS-4 code and description	Major	Minor	HD	GS	OA	CDH	PUV	NEC
E61.8: Other specified open operations on mediastinum	1				1	1		
E61.9: Unspecified open operations on mediastinum	1				1	1		
E62.8: Other specified therapeutic endoscopic operations on mediastinum		1			1	1		
E62.9: Unspecified therapeutic endoscopic operations on mediastinum		1			1	1		
E63.2: Endobronchial ultrasound examination of mediastinum		1			1	1		
E63.3: Endo-oesophageal ultrasound examination of mediastinum		1			1	1		
E63.4: Endoscopic ultrasound examination of mediastinum and biopsy of lesion of mediastinum		1			1	1		
E63.8: Other specified diagnostic endoscopic examination of mediastinum		1			1	1		
E63.9: Unspecified diagnostic endoscopic examination of mediastinum		1			1	1		
E67.8: Other specified other therapeutic fibreoptic endoscopic operations on lower respiratory tract		1			1	1		
E67.9: Unspecified other therapeutic fibreoptic endoscopic operations on lower respiratory tract		1			1	1		
G01.1: Oesophagogastrectomy and anastomosis of oesophagus to stomach	1				1			
G01.2: Oesophagogastrectomy and anastomosis of oesophagus to transposed jejunum	1				1			
G01.3: Oesophagogastrectomy and anastomosis of oesophagus to jejunum NEC	1				1			
G01.8: Other specified excision of oesophagus and stomach	1				1			
G01.9: Unspecified excision of oesophagus and stomach	1				1			
G02.1: Total oesophagectomy and anastomosis of pharynx to stomach	1				1			

OPCS-4 code and description	Major	Minor	HD	GS	OA	CDH	PUV	NEC
G02.2: Total oesophagectomy and interposition of microvascularly attached jejunum	1				1			
G02.3: Total oesophagectomy and interposition of jejunum NEC	1				1			
G02.4: Total oesophagectomy and interposition of microvascularly attached colon	1				1			
G02.5: Total oesophagectomy and interposition of colon NEC	1				1			
G02.8: Other specified total excision of oesophagus	1				1			
G02.9: Unspecified total excision of oesophagus	1				1			
G03.1: Partial oesophagectomy and end to end anastomosis of oesophagus	1				1			
G03.2: Partial oesophagectomy and interposition of microvascularly attached jejunum	1				1			
G03.3: Partial oesophagectomy and anastomosis of oesophagus to transposed jejunum	1				1			
G03.4: Partial oesophagectomy and anastomosis of oesophagus to jejunum NEC	1				1			
G03.5: Partial oesophagectomy and interposition of microvascularly attached colon	1				1			
G03.6: Partial oesophagectomy and interposition of colon NEC	1				1			
G03.8: Other specified partial excision of oesophagus	1				1			
G03.9: Unspecified partial excision of oesophagus	1				1			
G04.1: Excision of lesion of oesophagus	1				1			
G04.2: Open laser destruction of lesion of oesophagus	1				1			
G04.3: Open destruction of lesion of oesophagus NEC	1				1			
G04.8: Other specified open extirpation of lesion of oesophagus	1				1			
G04.9: Unspecified open extirpation of lesion of oesophagus	1				1			
G05.1: Bypass of oesophagus by anastomosis of oesophagus to oesophagus	1				1			

OPCS-4 code and description	Major	Minor	HD	GS	OA	CDH	PUV	NEC
G05.2: Bypass of oesophagus by anastomosis of oesophagus to stomach	1				1			
G05.3: Bypass of oesophagus by interposition of microvascularly attached jejunum	1				1			
G05.4: Bypass of oesophagus by interposition of jejunum NEC	1				1			
G05.5: Bypass of oesophagus by interposition of microvascularly attached colon	1				1			
G05.6: Bypass of oesophagus by interposition of colon NEC	1				1			
G05.8: Other specified bypass of oesophagus	1				1			
G05.9: Unspecified bypass of oesophagus	1				1			
G06.1: Revision of interposition anastomosis of oesophagus	1				1			
G06.2: Revision of anastomosis of oesophagus NEC	1				1			
G06.3: Removal of bypass of oesophagus	1				1			
G06.4: Closure of bypass of oesophagus NEC	1				1			
G06.8: Other specified attention to connection of oesophagus	1				1			
G06.9: Unspecified attention to connection of oesophagus	1				1			
G06.0: Conversion from previous direct anastomosis of oesophagus	1				1			
G07.1: Closure of tracheo-oesophageal fistula	1				1			
G07.2: Closure of fistula of oesophagus NEC	1				1			
G07.3: Correction of congenital atresia of oesophagus	1				1			
G07.4: Repair of rupture of oesophagus	1				1			
G07.8: Other specified repair of oesophagus	1				1			
G07.9: Unspecified repair of oesophagus	1				1			
G08.1: Exteriorisation of pouch of oesophagus	1				1			
G08.2: External fistulisation of oesophagus NEC	1				1			
G08.3: Tube oesophagostomy	1				1			
G08.8: Other specified artificial opening into oesophagus	1				1			

OPCS-4 code and description	Major	Minor	HD	GS	OA	CDH	PUV	NEC
G08.9: Unspecified artificial opening into oesophagus	1				1			
G09.1: Cardiomyotomy	1				1			
G09.2: Oesophagomyotomy NEC	1				1			
G09.3: Division of web of oesophagus	1				1			
G09.4: Drainage of oesophagus	1				1			
G09.8: Other specified incision of oesophagus	1				1			
G09.9: Unspecified incision of oesophagus	1				1			
G11.1: Insertion of tubal prosthesis into oesophagus through stomach	1				1			
G11.2: Open insertion of tubal prosthesis into oesophagus NEC	1				1			
G11.3: Open revision of tubal prosthesis in oesophagus	1				1			
G11.4: Open removal of tubal prosthesis from oesophagus	1				1			
G11.8: Other specified open placement of prosthesis in oesophagus	1				1			
G11.9: Unspecified open placement of prosthesis in oesophagus	1				1			
G12.1: Fibreoptic endoscopic mucosal resection of lesion of oesophagus	1				1			
G12.8: Other specified other fibreoptic endoscopic extirpation of lesion of oesophagus	1				1			
G12.9: Unspecified other fibreoptic endoscopic extirpation of lesion of oesophagus	1				1			
G13.1: Open biopsy of lesion of oesophagus	1				1			
G13.2: Open removal of foreign body from oesophagus	1				1			
G13.8: Other specified other open operations on oesophagus	1				1			
G13.9: Unspecified other open operations on oesophagus		1			1			
G14.1: Fibreoptic endoscopic snare resection of lesion of oesophagus		1			1			
G14.2: Fibreoptic endoscopic laser destruction of lesion of oesophagus		1			1			

OPCS-4 code and description	Major	Minor	HD	GS	OA	CDH	PUV	NEC
G14.3: Fibreoptic endoscopic cauterisation of lesion of oesophagus		1			1			
G14.4: Fibreoptic endoscopic injection sclerotherapy to varices of oesophagus		1			1			
G14.5: Fibreoptic endoscopic destruction of lesion of oesophagus NEC		1			1			
G14.6: Fibreoptic endoscopic submucosal resection of lesion of oesophagus		1			1			
G14.7: Fibreoptic endoscopic photodynamic therapy of lesion of oesophagus		1			1			
G14.8: Other specified fibreoptic endoscopic extirpation of lesion of oesophagus		1			1			
G14.9: Unspecified fibreoptic endoscopic extirpation of lesion of oesophagus		1			1			
G15.1: Fibreoptic endoscopic removal of foreign body from oesophagus		1			1			
G15.2: Fibreoptic endoscopic balloon dilation of oesophagus		1			1			
G15.3: Fibreoptic endoscopic dilation of oesophagus NEC		1			1			
G15.4: Fibreoptic endoscopic insertion of tubal prosthesis into oesophagus		1			1			
G15.5: Fibreoptic endoscopic dilation of web of oesophagus		1			1			
G15.6: Fibreoptic endoscopic insertion of expanding metal stent into oesophagus NEC		1			1			
G15.7: Fibreoptic endoscopic insertion of expanding covered metal stent into oesophagus		1			1			
G15.8: Other specified other therapeutic fibreoptic endoscopic operations on oesophagus		1			1			
G15.9: Unspecified other therapeutic fibreoptic endoscopic operations on oesophagus		1			1			

OPCS-4 code and description	Major	Minor	HD	GS	OA	CDH	PUV	NEC
G16.1: Diagnostic fibreoptic endoscopic examination of oesophagus and biopsy of lesion of oesophagus		1			1			
G16.2: Diagnostic fibreoptic endoscopic ultrasound examination of oesophagus		1			1			
G16.3: Diagnostic fibreoptic insertion of Bravo pH capsule into oesophagus		1			1			
G16.8: Other specified diagnostic fibreoptic endoscopic examination of oesophagus		1			1			
G16.9: Unspecified diagnostic fibreoptic endoscopic examination of oesophagus		1			1			
G17.1: Endoscopic snare resection of lesion of oesophagus using rigid oesophagoscope		1			1			
G17.2: Endoscopic laser destruction of lesion of oesophagus using rigid oesophagoscope		1			1			
G17.3: Endoscopic cauterisation of lesion of oesophagus using rigid oesophagoscope		1			1			
G17.8: Other specified endoscopic extirpation of lesion of oesophagus using rigid oesophagoscope		1			1			
G17.9: Unspecified endoscopic extirpation of lesion of oesophagus using rigid oesophagoscope		1			1			
G18.1: Endoscopic removal of foreign body from oesophagus using rigid oesophagoscope		1			1			
G18.2: Endoscopic balloon dilation of oesophagus using rigid oesophagoscope		1			1			
G18.3: Endoscopic dilation of oesophagus using rigid oesophagoscope NEC		1			1			
G18.4: Endoscopic insertion of tubal prosthesis into oesophagus using rigid oesophagoscope		1			1			
G18.5: Dilation of web of oesophagus using rigid oesophagoscope		1			1			

OPCS-4 code and description	Major	Minor	HD	GS	OA	CDH	PUV	NEC
G18.8: Other specified other therapeutic endoscopic operations on oesophagus using rigid oesophagoscope		1			1			
G18.9: Unspecified other therapeutic endoscopic operations on oesophagus using rigid oesophagoscope		1			1			
G19.1: Diagnostic endoscopic examination of oesophagus and biopsy of lesion of oesophagus using rigid oesophagoscope		1			1			
G19.2: Diagnostic endoscopic insertion of Bravo pH capsule using rigid oesophagoscope		1			1			
G19.8: Other specified diagnostic endoscopic examination of oesophagus using rigid oesophagoscope		1			1			
G19.9: Unspecified diagnostic endoscopic examination of oesophagus using rigid oesophagoscope		1			1			
G20.1: Fibreoptic endoscopic coagulation of bleeding lesion of oesophagus NEC		1			1			
G20.2: Fibreoptic endoscopic coagulation of bleeding lesion of oesophagus using haemostatic spray		1			1			
G20.8: Other specified therapeutic fibreoptic endoscopic operations on oesophagus		1			1			
G20.9: Unspecified therapeutic fibreoptic endoscopic operations on oesophagus		1			1			
G21.1: Intubation of oesophagus for pH manometry		1			1			
G21.2: Intubation of oesophagus for pressure manometry		1			1			
G21.4: Intubation of oesophagus NEC		1			1			
G21.5: Insertion of stent into oesophagus NEC		1			1			
G21.6: Cytology of oesophagus using ingestible sponge		1			1			
G21.8: Other specified other operations on oesophagus		1			1			
G21.9: Unspecified other operations on oesophagus		1			1			
G23.1: Repair of oesophageal hiatus using thoracic approach	1				1	1		

OPCS-4 code and description	Major	Minor	HD	GS	OA	CDH	PUV	NEC
G23.2: Repair of diaphragmatic hernia using thoracic approach NEC	1					1		
G23.3: Repair of oesophageal hiatus using abdominal approach	1				1	1		
G23.4: Repair of diaphragmatic hernia using abdominal approach NEC	1					1		
G23.8: Other specified repair of diaphragmatic hernia	1					1		
G23.9: Unspecified repair of diaphragmatic hernia	1					1		
G24.1: Antireflux fundoplication using thoracic approach	1			1	1	1		1
G24.2: Antireflux operation using thoracic approach NEC	1			1	1	1		1
G24.3: Antireflux fundoplication using abdominal approach	1			1	1	1		1
G24.4: Antireflux gastropexy	1			1	1	1		1
G24.5: Gastroplasty and antireflux procedure HFQ	1			1	1	1		1
G24.6: Insertion of Angelchick prosthesis	1			1	1	1		1
G24.8: Other specified antireflux operations	1			1	1	1		1
G24.9: Unspecified antireflux operations	1			1	1	1		1
G25.1: Revision of fundoplication of stomach	1			1	1	1		1
G25.2: Adjustment to Angelchick prosthesis	1			1	1	1		1
G25.3: Removal of Angelchick prosthesis	1			1	1	1		1
G25.8: Other specified revision of antireflux operations	1			1	1	1		1
G25.9: Unspecified revision of antireflux operations	1			1	1	1		1
G34.1: Creation of permanent gastrostomy	1		1	1	1	1		1
G34.2: Creation of temporary gastrostomy	1		1	1	1	1		1
G34.3: Reconstruction of gastrostomy	1		1	1	1	1		1
G34.4: Closure of gastrostomy	1		1	1	1	1		1
G34.5: Attention to gastrostomy tube	1		1	1	1	1		1
G34.8: Other specified artificial opening into stomach	1		1	1	1	1		1
G34.9: Unspecified artificial opening into stomach	1		1	1	1	1		1
G36.1: Gastropexy NEC	1			1	1	1		1

OPCS-4 code and description	Major	Minor	HD	GS	OA	CDH	PUV	NEC
G36.2: Closure of perforation of stomach NEC	1			1	1	1		1
G36.3: Closure of abnormal opening of stomach NEC	1			1	1	1		1
G36.8: Other specified other repair of stomach	1			1	1	1		1
G36.9: Unspecified other repair of stomach	1			1	1	1		1
G38.3: Open insertion of feeding tube into stomach	1		1	1	1	1		1
G38.6: Reduction of volvulus of stomach	1		1	1	1	1		1
G41.2: Repair of perforation of pylorus	1		1	1	1	1		1
G44.1: Fibreoptic endoscopic insertion of prosthesis into upper gastrointestinal tract		1			1			
G44.2: Fibreoptic endoscopic removal of foreign body from upper gastrointestinal tract		1			1			
G44.3: Fibreoptic endoscopic dilation of upper gastrointestinal tract NEC		1			1			
G44.4: Fibreoptic endoscopic reduction of intussusception of gastroenterostomy		1	1	1	1	1		1
G44.5: Fibreoptic endoscopic percutaneous insertion of gastrostomy		1	1	1	1	1		1
G44.6: Fibreoptic endoscopic pressure controlled balloon dilation of lower oesophageal sphincter		1			1	1		
G44.7: Fibreoptic endoscopic removal of gastrostomy tube		1	1	1	1	1		1
G44.8: Other specified other therapeutic fibreoptic endoscopic operations on upper gastrointestinal tract		1	1	1	1	1		1
G44.9: Unspecified other therapeutic fibreoptic endoscopic operations on upper gastrointestinal tract		1	1	1	1	1		1
G45.2: Fibreoptic endoscopic ultrasound examination of upper gastrointestinal tract		1	1	1	1	1		1
G45.4: Fibreoptic endoscopic examination of upper gastrointestinal tract and staining of gastric mucosa		1	1	1	1	1		1

OPCS-4 code and description	Major	Minor	HD	GS	OA	CDH	PUV	NEC
G45.8: Other specified diagnostic fibreoptic endoscopic examination of upper gastrointestinal tract		1	1	1	1	1		1
G45.9: Unspecified diagnostic fibreoptic endoscopic examination of upper gastrointestinal tract		1	1	1	1	1		1
G46.1: Fibreoptic endoscopic endoluminal plication of gastro-oesophageal junction		1	1	1	1	1		1
G46.2: Fibreoptic endoscopic coagulation of bleeding lesion of upper gastrointestinal tract NEC		1	1	1	1	1		1
G46.3: Fibreoptic endoscopic coagulation of bleeding lesion of upper gastrointestinal tract using haemostatic spray		1	1	1	1	1		1
G46.8: Other specified therapeutic fibreoptic endoscopic operations on upper gastrointestinal tract		1	1	1	1	1		1
G46.9: Unspecified therapeutic fibreoptic endoscopic operations on upper gastrointestinal tract		1	1	1	1	1		1
G47.1: Intubation of stomach for pH manometry		1			1			
G47.2: Intubation of stomach for pressure manometry		1			1			
G47.8: Other specified intubation of stomach		1			1			
G47.9: Unspecified intubation of stomach		1			1			
G49.2: Total excision of duodenum				1	1	1		1
G49.3: Partial excision of duodenum				1	1	1		1
G49.8: Other specified excision of duodenum				1	1	1		1
G49.9: Unspecified excision of duodenum				1	1	1		1
G50.1: Excision of lesion of duodenum				1	1	1		1
G50.2: Open destruction of lesion of duodenum				1	1	1		1
G51.1: Bypass of duodenum by anastomosis of stomach to jejunum				1	1	1		1
G51.2: Bypass of duodenum by anastomosis of duodenum to duodenum				1	1	1		1

OPCS-4 code and description	Major	Minor	HD	GS	OA	CDH	PUV	NEC
G51.3: Bypass of duodenum by anastomosis of duodenum to jejunum				1	1	1		1
G51.4: Bypass of duodenum by anastomosis of duodenum to colon				1	1	1		1
G51.8: Other specified bypass of duodenum				1	1	1		1
G51.9: Unspecified bypass of duodenum				1	1	1		1
G53.2: Closure of perforation of duodenum NEC	1			1	1	1		1
G53.5: Incision of duodenum NEC	1			1	1	1		1
G53.6: Correction of malrotation of duodenum	1			1	1	1		1
G53.8: Other specified other open operations on duodenum	1			1	1	1		1
G53.9: Unspecified other open operations on duodenum	1			1	1	1		1
G54.2: Endoscopic dilation of duodenum		1		1	1	1		1
G54.3: Endoscopic insertion of tubal prosthesis into duodenum		1		1	1	1		1
G54.8: Other specified therapeutic endoscopic operations on duodenum		1		1	1	1		1
G54.9: Unspecified therapeutic endoscopic operations on duodenum		1		1	1	1		1
G55.1: Diagnostic endoscopic examination of duodenum and biopsy of lesion of duodenum		1		1	1	1		1
G55.8: Other specified diagnostic endoscopic examination of duodenum		1		1	1	1		1
G55.9: Unspecified diagnostic endoscopic examination of duodenum		1		1	1	1		1
G57.8: Other specified other operations on duodenum	1			1	1	1		1
G57.9: Unspecified other operations on duodenum	1			1	1	1		1
G58.1: Total jejunectomy and anastomosis of stomach to ileum	1		1	1		1		1
G58.2: Total jejunectomy and anastomosis of duodenum to ileum	1		1	1		1		1
G58.3: Total jejunectomy and anastomosis of duodenum to colon	1		1	1		1		1
G58.4: Partial jejunectomy and anastomosis of jejunum to ileum	1		1	1		1		1

OPCS-4 code and description	Major	Minor	HD	GS	OA	CDH	PUV	NEC
G58.5: Partial jejunectomy and anastomosis of duodenum to colon	1		1	1		1		1
G58.8: Other specified excision of jejunum	1		1	1		1		1
G58.9: Unspecified excision of jejunum	1		1	1		1		1
G60.1: Creation of jejunostomy	1		1	1		1		1
G60.2: Refashioning of jejunostomy	1		1	1		1		1
G60.3: Closure of jejunostomy	1		1	1		1		1
G60.4: Attention to jejunostomy tube	1		1	1		1		1
G60.8: Other specified artificial opening into jejunum	1		1	1		1		1
G60.9: Unspecified artificial opening into jejunum	1		1	1		1		1
G61.1: Bypass of jejunum by anastomosis of jejunum to jejunum	1		1	1		1		1
G61.2: Bypass of jejunum by anastomosis of jejunum to ileum	1		1	1		1		1
G61.3: Bypass of jejunum by anastomosis of jejunum to colon	1		1	1		1		1
G61.8: Other specified bypass of jejunum	1		1	1		1		1
G61.9: Unspecified bypass of jejunum	1		1	1		1		1
G62.1: Open jejunoscopy	1		1	1		1		1
G62.8: Other specified open endoscopic operations on jejunum	1		1	1		1		1
G62.9: Unspecified open endoscopic operations on jejunum	1		1	1		1		1
G63.1: Open biopsy of lesion of jejunum	1		1					
G63.2: Incision of jejunum	1		1	1		1		1
G63.3: Closure of perforation of jejunum	1		1	1		1		1
G63.4: Open intubation of jejunum	1		1	1		1		1
G63.8: Other specified other open operations on jejunum	1		1	1		1		1
G63.9: Unspecified other open operations on jejunum	1		1	1		1		1
G64.2: Endoscopic dilation of jejunum		1	1	1		1		1
G64.3: Endoscopic insertion of tubal prosthesis into jejunum		1	1	1		1		1
G64.8: Other specified therapeutic endoscopic operations on jejunum		1	1	1		1		1
G64.9: Unspecified therapeutic endoscopic operations on jejunum		1	1	1		1		1

OPCS-4 code and description	Major	Minor	HD	GS	OA	CDH	PUV	NEC
G65.1: Diagnostic endoscopic examination of jejunum and biopsy of lesion of jejunum		1	1	1		1		1
G65.8: Other specified diagnostic endoscopic examination of jejunum		1	1	1		1		1
G65.9: Unspecified diagnostic endoscopic examination of jejunum		1	1	1		1		1
G67.1: Intubation of jejunum for decompression of intestine		1	1	1		1		1
G67.2: Intubation of jejunum for measurement of intestinal function		1	1	1		1		1
G67.3: Passage of Crosby capsule into jejunum for biopsy of mucosa of jejunum		1	1					
G67.4: Intubation of jejunum NEC		1	1	1		1		1
G67.8: Other specified other operations on jejunum	1		1	1		1		1
G67.9: Unspecified other operations on jejunum	1		1	1		1		1
G68.1: Allotransplantation of ileum	1		1	1		1		1
G68.8: Other specified transplantation of ileum	1		1	1		1		1
G68.9: Unspecified transplantation of ileum	1		1	1		1		1
G69.1: Ileectomy and anastomosis of stomach to ileum	1		1	1		1		1
G69.2: Ileectomy and anastomosis of duodenum to ileum	1		1	1		1		1
G69.3: Ileectomy and anastomosis of ileum to ileum	1		1	1		1		1
G69.4: Ileectomy and anastomosis of ileum to colon	1		1	1		1		1
G69.8: Other specified excision of ileum	1		1	1		1		1
G69.9: Unspecified excision of ileum	1		1	1		1		1
G71.1: Bypass of ileum by anastomosis of jejunum to ileum	1		1	1		1		1
G71.2: Bypass of ileum by anastomosis of ileum to ileum	1		1	1		1		1
G71.3: Bypass of ileum by anastomosis of ileum to caecum	1		1	1		1		1
G71.4: Bypass of ileum by anastomosis of ileum to transverse colon	1		1	1		1		1
G71.5: Bypass of ileum by anastomosis of ileum to colon NEC	1		1	1		1		1
G71.8: Other specified bypass of ileum	1		1	1		1		1

OPCS-4 code and description	Major	Minor	HD	GS	OA	CDH	PUV	NEC
G71.9: Unspecified bypass of ileum	1		1	1		1		1
G72.1: Anastomosis of ileum to caecum	1		1	1		1		1
G72.2: Anastomosis of ileum to transverse colon	1		1	1		1		1
G72.3: Anastomosis of ileum to colon NEC	1		1	1		1		1
G72.4: Anastomosis of ileum to rectum	1		1	1		1		1
G72.5: Anastomosis of ileum to anus and creation of pouch HFQ	1		1	1		1		1
G72.8: Other specified other connection of ileum	1		1	1		1		1
G72.9: Unspecified other connection of ileum	1		1	1		1		1
G73.1: Revision of anastomosis of ileum	1		1	1		1		1
G73.2: Closure of anastomosis of ileum	1		1	1		1		1
G73.3: Resection of ileostomy	1		1	1		1		1
G73.4: Resection of ileocolic anastomosis	1		1	1		1		1
G73.8: Other specified attention to connection of ileum	1		1	1		1		1
G73.9: Unspecified attention to connection of ileum	1		1	1		1		1
G74.1: Creation of continent ileostomy	1		1	1		1		1
G74.2: Creation of temporary ileostomy	1		1	1		1		1
G74.3: Creation of defunctioning ileostomy	1		1	1		1		1
G74.8: Other specified creation of artificial opening into ileum	1		1	1		1		1
G74.9: Unspecified creation of artificial opening into ileum	1		1	1		1		1
G75.1: Refashioning of ileostomy	1		1	1		1		1
G75.2: Repair of prolapse of ileostomy	1		1	1		1		1
G75.3: Closure of ileostomy	1		1	1		1		1
G75.4: Dilation of ileostomy	1		1	1		1		1
G75.5: Reduction of prolapse of ileostomy	1		1	1		1		1
G75.6: Resiting of ileostomy	1		1	1		1		1
G75.8: Other specified attention to artificial opening into ileum	1		1	1		1		1
G75.9: Unspecified attention to artificial opening into ileum	1		1	1		1		1
G76.2: Open relief of strangulation of ileum	1		1	1		1		1

OPCS-4 code and description	Major	Minor	HD	GS	OA	CDH	PUV	NEC
G76.3: Open relief of obstruction of ileum NEC	1		1	1		1		1
G76.4: Plication of ileum	1		1	1		1		1
G76.8: Other specified intra-abdominal manipulation of ileum	1		1	1		1		1
G76.9: Unspecified intra-abdominal manipulation of ileum	1		1	1		1		1
G78.1: Open biopsy of lesion of ileum	1		1	1		1		1
G78.2: Strictureplasty of ileum	1		1	1		1		1
G78.4: Closure of perforation of ileum	1		1	1		1		1
G78.5: Exclusion of segment of ileum	1		1	1		1		1
G78.6: Open intubation of ileum	1		1	1		1		1
G78.8: Other specified other open operations on ileum	1		1	1		1		1
G78.9: Unspecified other open operations on ileum	1		1	1		1		1
G79.2: Endoscopic dilation of ileum		1	1	1		1		1
G79.3: Endoscopic insertion of tubal prosthesis into ileum		1	1	1		1		1
G79.8: Other specified therapeutic endoscopic operations on ileum		1	1	1		1		1
G79.9: Unspecified therapeutic endoscopic operations on ileum		1	1	1		1		1
G80.1: Diagnostic endoscopic examination of ileum and biopsy of lesion of ileum		1	1	1		1		1
G80.3: Diagnostic endoscopic balloon examination of ileum		1	1	1		1		1
G80.8: Other specified diagnostic endoscopic examination of ileum		1	1	1		1		1
G80.9: Unspecified diagnostic endoscopic examination of ileum		1	1	1		1		1
G82.2: Intubation of ileum for decompression of intestine		1	1	1		1		1
G82.3: Intubation of ileum for studies on function HFQ		1	1	1		1		1
G82.4: Intubation of ileum NEC		1	1	1		1		1
G82.8: Other specified other operations on ileum		1	1	1		1		1
G82.9: Unspecified other operations on ileum		1	1	1		1		1
H03.3: Exteriorisation of appendix	1		1	1		1		1
H04.1: Panproctocolectomy and ileostomy	1		1	1		1		1

OPCS-4 code and description	Major	Minor	HD	GS	OA	CDH	PUV	NEC
H04.2: Panproctocolectomy and anastomosis of ileum to anus and creation of pouch HFQ	1		1	1		1		1
H04.3: Panproctocolectomy and anastomosis of ileum to anus NEC	1		1	1		1		1
H04.8: Other specified total excision of colon and rectum	1		1	1		1		1
H04.9: Unspecified total excision of colon and rectum	1		1	1		1		1
H05.1: Total colectomy and anastomosis of ileum to rectum	1		1	1		1		1
H05.2: Total colectomy and ileostomy and creation of rectal fistula HFQ	1		1	1		1		1
H05.3: Total colectomy and ileostomy NEC	1		1	1		1		1
H05.8: Other specified total excision of colon	1		1	1		1		1
H05.9: Unspecified total excision of colon	1		1	1		1		1
H06.1: Extended right hemicolectomy and end to end anastomosis	1		1	1		1		1
H06.2: Extended right hemicolectomy and anastomosis of ileum to colon	1		1	1		1		1
H06.3: Extended right hemicolectomy and anastomosis NEC	1		1	1		1		1
H06.4: Extended right hemicolectomy and ileostomy HFQ	1		1	1		1		1
H06.5: Extended right hemicolectomy and end to side anastomosis	1		1	1		1		1
H06.8: Other specified extended excision of right hemicolon	1		1	1		1		1
H06.9: Unspecified extended excision of right hemicolon	1		1	1		1		1
H07.1: Right hemicolectomy and end to end anastomosis of ileum to colon	1		1	1		1		1
H07.2: Right hemicolectomy and side to side anastomosis of ileum to transverse colon	1		1	1		1		1
H07.3: Right hemicolectomy and anastomosis NEC	1		1	1		1		1
H07.4: Right hemicolectomy and ileostomy HFQ	1		1	1		1		1
H07.5: Right hemicolectomy and end to side anastomosis	1		1	1		1		1
H07.8: Other specified other excision of right hemicolon	1		1	1		1		1

OPCS-4 code and description	Major	Minor	HD	GS	OA	CDH	PUV	NEC
H07.9: Unspecified other excision of right hemicolon	1		1	1		1		1
H08.1: Transverse colectomy and end to end anastomosis	1		1	1		1		1
H08.2: Transverse colectomy and anastomosis of ileum to colon	1		1	1		1		1
H08.3: Transverse colectomy and anastomosis NEC	1		1	1		1		1
H08.4: Transverse colectomy and ileostomy HFQ	1		1	1		1		1
H08.5: Transverse colectomy and exteriorisation of bowel NEC	1		1	1		1		1
H08.6: Transverse colectomy and end to side anastomosis	1		1	1		1		1
H08.8: Other specified excision of transverse colon	1		1	1		1		1
H08.9: Unspecified excision of transverse colon	1		1	1		1		1
H09.1: Left hemicolectomy and end to end anastomosis of colon to rectum	1		1	1		1		1
H09.2: Left hemicolectomy and end to end anastomosis of colon to colon	1		1	1		1		1
H09.3: Left hemicolectomy and anastomosis NEC	1		1	1		1		1
H09.4: Left hemicolectomy and ileostomy HFQ	1		1	1		1		1
H09.5: Left hemicolectomy and exteriorisation of bowel NEC	1		1	1		1		1
H09.6: Left hemicolectomy and end to side anastomosis	1		1	1		1		1
H09.8: Other specified excision of left hemicolon	1		1	1		1		1
H09.9: Unspecified excision of left hemicolon	1		1	1		1		1
H10.1: Sigmoid colectomy and end to end anastomosis of ileum to rectum	1		1	1		1		1
H10.2: Sigmoid colectomy and anastomosis of colon to rectum	1		1	1		1		1
H10.3: Sigmoid colectomy and anastomosis NEC	1		1	1		1		1
H10.4: Sigmoid colectomy and ileostomy HFQ	1		1	1		1		1
H10.5: Sigmoid colectomy and exteriorisation of bowel NEC	1		1	1		1		1
H10.6: Sigmoid colectomy and end to side anastomosis	1		1	1		1		1
H10.8: Other specified excision of sigmoid colon	1		1	1		1		1
H10.9: Unspecified excision of sigmoid colon	1		1	1		1		1

OPCS-4 code and description	Major	Minor	HD	GS	OA	CDH	PUV	NEC
H11.1: Colectomy and end to end anastomosis of colon to colon NEC	1		1	1		1		1
H11.2: Colectomy and side to side anastomosis of ileum to colon NEC	1		1	1		1		1
H11.3: Colectomy and anastomosis NEC	1		1	1		1		1
H11.4: Colectomy and ileostomy NEC	1		1	1		1		1
H11.5: Colectomy and exteriorisation of bowel NEC	1		1	1		1		1
H11.6: Colectomy and end to side anastomosis NEC	1		1	1		1		1
H11.8: Other specified other excision of colon	1		1	1		1		1
H11.9: Unspecified other excision of colon	1		1	1		1		1
H13.1: Bypass of colon by anastomosis of ileum to colon	1		1	1		1		1
H13.2: Bypass of colon by anastomosis of caecum to sigmoid colon	1		1	1		1		1
H13.3: Bypass of colon by anastomosis of transverse colon to sigmoid colon	1		1	1		1		1
H13.4: Bypass of colon by anastomosis of transverse colon to rectum	1		1	1		1		1
H13.5: Bypass of colon by anastomosis of colon to rectum NEC	1		1	1		1		1
H13.8: Other specified bypass of colon	1		1	1		1		1
H13.9: Unspecified bypass of colon	1		1	1		1		1
H14.1: Tube caecostomy	1		1	1		1		1
H14.2: Refashioning of caecostomy	1		1	1		1		1
H14.3: Closure of caecostomy	1		1	1		1		1
H14.4: Appendicocaecostomy	1		1	1		1		1
H14.8: Other specified exteriorisation of caecum	1		1	1		1		1
H14.9: Unspecified exteriorisation of caecum	1		1	1		1		1
H15.1: Loop colostomy	1		1	1		1		1
H15.2: End colostomy	1		1	1		1		1

OPCS-4 code and description	Major	Minor	HD	GS	OA	CDH	PUV	NEC
H15.3: Refashioning of colostomy	1		1	1		1		1
H15.4: Closure of colostomy	1		1	1		1		1
H15.5: Dilation of colostomy	1		1	1		1		1
H15.6: Reduction of prolapse of colostomy	1		1	1		1		1
H15.7: Percutaneous endoscopic sigmoid colostomy	1		1	1		1		1
H15.8: Other specified other exteriorisation of colon	1		1	1		1		1
H15.9: Unspecified other exteriorisation of colon	1		1	1		1		1
H16.1: Drainage of colon		1	1	1		1		1
H16.2: Caecotomy	1		1	1		1		1
H16.3: Colotomy	1		1	1	1	1		1
H16.8: Other specified incision of colon	1		1	1	1	1		1
H16.9: Unspecified incision of colon	1		1	1	1	1		1
H17.2: Open reduction of volvulus of caecum	1		1	1	1	1		1
H17.3: Open reduction of volvulus of sigmoid colon	1		1	1	1	1		1
H17.4: Open reduction of volvulus of colon NEC	1		1	1	1	1		1
H17.5: Open relief of strangulation of colon	1		1	1	1	1		1
H17.6: Open relief of obstruction of colon NEC	1		1	1	1	1		1
H17.8: Other specified intra-abdominal manipulation of colon	1		1	1	1	1		1
H17.9: Unspecified intra-abdominal manipulation of colon	1		1	1	1	1		1
H18.1: Open colonoscopy	1		1	1	1	1		1
H18.8: Other specified open endoscopic operations on colon	1		1	1	1	1		1
H18.9: Unspecified open endoscopic operations on colon	1		1	1	1	1		1
H19.1: Open biopsy of lesion of colon	1		1					
H19.2: Fixation of colon	1		1	1	1	1		1
H19.3: Enterorrhaphy of colon	1		1	1	1	1		1
H19.8: Other specified other open operations on colon	1		1	1	1	1		1
H19.9: Unspecified other open operations on colon	1		1	1	1	1		1
H21.1: Fibreoptic endoscopic dilation of colon		1	1	1	1	1		1

OPCS-4 code and description	Major	Minor	HD	GS	OA	CDH	PUV	NEC
H21.2: Fibreoptic endoscopic coagulation of blood vessel of colon		1	1	1	1	1		1
H21.4: Fibreoptic endoscopic insertion of expanding metal stent into colon		1	1	1	1	1		1
H21.5: Fibreoptic endoscopic decompression of colon		1	1	1	1	1		1
H21.6: Fibreoptic endoscopic insertion of tubal prosthesis into colon		1	1	1	1	1		1
H21.8: Other specified other therapeutic endoscopic operations on colon		1	1	1	1	1		1
H21.9: Unspecified other therapeutic endoscopic operations on colon		1	1	1	1	1		1
H22.1: Diagnostic fibreoptic endoscopic examination of colon and biopsy of lesion of colon		1	1	1	1	1		1
H22.8: Other specified diagnostic endoscopic examination of colon		1	1	1	1	1		1
H22.9: Unspecified diagnostic endoscopic examination of colon		1	1	1	1	1		1
H24.1: Endoscopic dilation of lower bowel using fibreoptic sigmoidoscope		1	1	1	1	1		1
H24.2: Endoscopic coagulation of blood vessel of lower bowel using fibreoptic sigmoidoscope		1	1	1	1	1		1
H24.3: Endoscopic insertion of tubal prosthesis into lower bowel using fibreoptic sigmoidoscope		1	1	1	1	1		1
H24.4: Endoscopic insertion of expanding metal stent into lower bowel using fibreoptic sigmoidoscope		1	1	1	1	1		1
H24.5: Endoscopic decompression of lower bowel using fibreoptic sigmoidoscope		1	1	1	1	1		1
H24.8: Other specified other therapeutic endoscopic operations on lower bowel using fibreoptic sigmoidoscope		1	1	1	1	1		1
H24.9: Unspecified other therapeutic endoscopic operations on lower bowel using fibreoptic sigmoidoscope		1	1	1	1	1		1

OPCS-4 code and description	Major	Minor	HD	GS	OA	CDH	PUV	NEC
H25.1: Diagnostic endoscopic examination of lower bowel and biopsy of lesion of lower bowel using fibreoptic sigmoidoscope		1	1	1	1	1		1
H25.2: Diagnostic endoscopic examination of lower bowel and sampling for bacterial overgrowth using fibreoptic sigmoidoscope		1	1	1	1	1		1
H25.8: Other specified diagnostic endoscopic examination of lower bowel using fibreoptic sigmoidoscope		1	1	1	1	1		1
H25.9: Unspecified diagnostic endoscopic examination of lower bowel using fibreoptic sigmoidoscope		1	1	1	1	1		1
H27.1: Endoscopic dilation of sigmoid colon using rigid sigmoidoscope		1		?				?
H27.3: Endoscopic insertion of tubal prosthesis into sigmoid colon using rigid sigmoidoscope		1	1	1	1	1		1
H27.4: Endoscopic insertion of expanding metal stent into sigmoid colon using rigid sigmoidoscope		1	1	1	1	1		1
H27.5: Endoscopic decompression of sigmoid colon using rigid sigmoidoscope		1	1	1	1	1		1
H27.8: Other specified other therapeutic endoscopic operations on sigmoid colon using rigid sigmoidoscope		1	1	1	1	1		1
H27.9: Unspecified other therapeutic endoscopic operations on sigmoid colon using rigid sigmoidoscope		1	1	1	1	1		1
H28.1: Diagnostic endoscopic examination of sigmoid colon and biopsy of lesion of sigmoid colon using rigid sigmoidoscope		1	1	1	1	1		1
H28.8: Other specified diagnostic endoscopic examination of sigmoid colon using rigid sigmoidoscope		1	1	1	1	1		1
H28.9: Unspecified diagnostic endoscopic examination of sigmoid colon using rigid sigmoidoscope		1	1	1	1	1		1
H29.1: Subtotal excision of colon and rectum and creation of colonic pouch and anastomosis of colon to anus	1		1	1	1	1		1

OPCS-4 code and description	Major	Minor	HD	GS	OA	CDH	PUV	NEC
H29.2: Subtotal excision of colon and rectum and creation of colonic pouch NEC	1		1	1	1	1		1
H29.3: Subtotal excision of colon and creation of colonic pouch and anastomosis of colon to rectum	1		1	1	1	1		1
H29.4: Subtotal excision of colon and creation of colonic pouch NEC	1		1	1	1	1		1
H29.5: Subtotal excision of colon and anastomosis of colon to ileum	1		1	1	1	1		1
H29.8: Other specified subtotal excision of colon	1		1	1	1	1		1
H29.9: Unspecified subtotal excision of colon	1		1	1	1	1		1
H30.2: Intubation of colon for pressure manometry		1	1	1	1	1		1
H30.3: Passage of flatus tube to reduce volvulus of sigmoid colon		1	1	1	1	1		1
H30.4: Intubation of colon NEC		1	1	1	1	1		1
H30.5: Irrigation of colon		1	1	1	1	1		1
H30.8: Other specified other operations on colon		1	1	1	1	1		1
H30.9: Unspecified other operations on colon		1	1	1	1	1		1
H31.3: Image guided balloon dilation of colorectal stricture		1	1	1	1	1		1
H31.4: Image guided insertion of colorectal stent		1	1	1	1	1		1
H31.5: Image guided removal of colorectal stent		1	1	1	1	1		1
H31.8: Other specified image guided colorectal therapeutic operations		1	1	1	1	1		1
H31.9: Unspecified image guided colorectal therapeutic operations		1	1	1	1	1		1
H32.1: Resiting of colostomy	1		1	1	1	1		1
H32.8: Other specified exteriorisation of colon	1		1	1	1	1		1
H32.9: Unspecified exteriorisation of colon	1		1	1	1	1		1
H33.1: Abdominoperineal excision of rectum and end colostomy	1		1	1				1
H33.2: Proctectomy and anastomosis of colon to anus	1		1	1				1

OPCS-4 code and description	Major	Minor	HD	GS	OA	CDH	PUV	NEC
H33.3: Anterior resection of rectum and anastomosis of colon to rectum using staples	1		1	1				1
H33.4: Anterior resection of rectum and anastomosis NEC	1		1	1				1
H33.5: Rectosigmoidectomy and closure of rectal stump and exteriorisation of bowel	1		1	1				1
H33.6: Anterior resection of rectum and exteriorisation of bowel	1		1	1				1
H33.7: Perineal resection of rectum HFQ	1		1	1				1
H33.8: Other specified excision of rectum	1		1	1				1
H33.9: Unspecified excision of rectum	1		1	1				1
H34.1: Open excision of lesion of rectum	1		1	1				1
H35.1: Anterior fixation of rectum NEC	1		1	1				1
H35.2: Posterior fixation of rectum using prosthetic material	1		1	1				1
H35.3: Posterior fixation of rectum NEC	1		1	1				1
H35.4: Fixation of rectum using fascia lata	1		1	1				1
H35.5: Anterior fixation of rectum using prosthetic material	1		1	1				1
H35.8: Other specified fixation of rectum for prolapse	1		1	1				1
H35.9: Unspecified fixation of rectum for prolapse	1		1	1				1
H36.1: Abdominal repair of levator ani muscles	1		1	1				1
H36.8: Other specified other abdominal operations for prolapse of rectum	1		1	1				1
H36.9: Unspecified other abdominal operations for prolapse of rectum	1		1	1				1
H40.4: Trans-sphincteric anastomosis of colon to anus	1		1	1				1
H40.8: Other specified operations on rectum through anal sphincter	1		1	1				1
H40.9: Unspecified operations on rectum through anal sphincter	1		1	1				1
H41.1: Rectosigmoidectomy and peranal anastomosis	1		1	1				1
H41.2: Peranal excision of lesion of rectum	1		1	1				1

OPCS-4 code and description	Major	Minor	HD	GS	OA	CDH	PUV	NEC
H41.4: Peranal mucosal proctectomy and endoanal anastomosis	1		1	1				1
H41.8: Other specified other operations on rectum through anus	1		1	1				1
H41.9: Unspecified other operations on rectum through anus	1		1	1				1
H42.1: Insertion of encircling suture around perianal sphincter	1		1	1				1
H42.2: Perineal plication of levator ani muscles and anal sphincters	1		1					
H42.3: Insertion of supralevator sling	1		1					
H42.4: Removal of encircling suture from around perianal sphincter	1		1					
H42.5: Excision of mucosal prolapse of rectum NEC	1		1					
H42.6: Perineal repair of prolapse of rectum NEC	1		1					
H42.7: Rubber band ligation of prolapsed rectal mucosa	1		1					
H42.8: Other specified perineal operations for prolapse of rectum	1		1					
H42.9: Unspecified perineal operations for prolapse of rectum	1		1					
H44.2: Manual reduction of prolapse of rectum		1	1	1				1
H44.3: Manual evacuation of impacted faeces from rectum		1	1	1				1
H44.4: Examination of rectum under anaesthetic		1	1	1				1
H44.8: Other specified manipulation of rectum		1		1				1
H44.9: Unspecified manipulation of rectum		1		1				1
H46.3: Intubation of rectum for pressure manometry		1		1				1
H46.4: Intubation of rectum NEC		1		1				1
H46.8: Other specified other operations on rectum		1		1				1
H46.9: Unspecified other operations on rectum		1		1				1
H47.1: Excision of sphincter of anus	1			1				1
H47.8: Other specified excision of anus	1			1				1
H47.9: Unspecified excision of anus	1			1				1
H50.1: Posterior repair of anal sphincter	1		1	1		1		1
H50.2: Anterior repair of anal sphincter	1		1	1		1		1
H50.3: Cutback of covered anus	1		1	1		1		1

OPCS-4 code and description	Major	Minor	HD	GS	OA	CDH	PUV	NEC
H50.4: Reanastomosis of rectum to anal canal for correction of congenital atresia of rectum NEC	1		1	1		1		1
H50.5: Reanastomosis of rectum to anal canal and creation of anal sphincter	1		1	1		1		1
H50.8: Other specified repair of anus	1		1	1		1		1
H50.9: Unspecified repair of anus	1		1	1		1		1
H54.1: Anorectal stretch	1		1	1		1		1
H54.8: Other specified dilation of anal sphincter	1		1	1		1		1
H54.9: Unspecified dilation of anal sphincter	1		1	1		1		1
H55.8: Other specified other operations on perianal region	1		1	1		1		1
H55.9: Unspecified other operations on perianal region	1		1	1		1		1
H56.1: Biopsy of lesion of anus		1	1					
H56.8: Other specified other operations on anus		1	1	1		1		1
H56.9: Unspecified other operations on anus		1	1	1		1		1
H57.1: Placement of artificial anal sphincter NEC	1		1	1		1		1
H57.2: Maintenance of artificial anal sphincter NEC	1		1	1		1		1
H57.3: Removal of artificial anal sphincter NEC	1		1	1		1		1
H57.4: Creation of graciloplasty sphincter	1		1	1		1		1
H57.5: Placement of dynamic graciloplasty sphincter	1		1	1		1		1
H57.6: Maintenance of dynamic graciloplasty sphincter	1		1	1		1		1
H57.7: Removal of dynamic graciloplasty sphincter	1		1	1		1		1
H57.8: Other specified other operations on the anal sphincter to control continence	1		1	1		1		1
H57.9: Unspecified other operations on the anal sphincter to control continence	1		1	1		1		1
H58.1: Drainage of ischiorectal abscess		1	1	1		1		1
H58.2: Drainage of perianal abscess		1	1	1		1		1
H58.3: Drainage of perirectal abscess		1	1	1		1		1

OPCS-4 code and description	Major	Minor	HD	GS	OA	CDH	PUV	NEC
H58.8: Other specified drainage through perineal region		1	1	1		1		1
H58.9: Unspecified drainage through perineal region		1	1	1		1		1
H62.2: Mobilisation of bowel NEC	1		1	1		1		1
H62.3: Dilation of bowel NEC	1		1	1		1		1
H62.4: Intubation of bowel NEC		1	1	1		1		1
H62.5: Irrigation of bowel NEC		1	1	1		1		1
H62.6: Proctoscopy		1	1	1		1		1
H62.7: Endoanal ultrasound examination of lower bowel		1	1	1		1		1
H62.8: Other specified other operations on bowel	1		1					
H62.9: Unspecified other operations on bowel	1		1	1		1		1
H66.1: Excision of ileoanal pouch	1		1	1		1		1
H66.2: Revision of ileoanal pouch	1		1	1		1		1
H66.8: Other specified therapeutic operations on ileoanal pouch	1		1	1		1		1
H66.9: Unspecified therapeutic operations on ileoanal pouch	1		1	1		1		1
H68.1: Diagnostic endoscopic examination of colonic pouch and biopsy of colonic pouch using colonoscope		1	1	1		1		1
H68.2: Diagnostic endoscopic examination of colonic pouch using colonoscope NEC		1	1	1		1		1
H68.3: Diagnostic endoscopic examination of ileoanal pouch and biopsy of ileoanal pouch using colonoscope		1	1	1		1		1
H68.4: Diagnostic endoscopic examination of ileoanal pouch using colonoscope NEC		1	1	1		1		1
H68.8: Other specified diagnostic endoscopic examination of enteric pouch using colonoscope		1	1	1		1		1
H68.9: Unspecified diagnostic endoscopic examination of enteric pouch using colonoscope		1	1	1		1		1
H69.1: Diagnostic endoscopic examination of colonic pouch and biopsy of colonic pouch using fibreoptic sigmoidoscope		1	1	1		1		1

OPCS-4 code and description	Major	Minor	HD	GS	OA	CDH	PUV	NEC
H69.2: Diagnostic endoscopic examination of colonic pouch using fibreoptic sigmoidoscope NEC		1	1	1		1		1
H69.3: Diagnostic endoscopic examination of ileoanal pouch and biopsy of ileoanal pouch using fibreoptic sigmoidoscope		1	1	1		1		1
H69.4: Diagnostic endoscopic examination of ileoanal pouch using fibreoptic sigmoidoscope NEC		1	1	1		1		1
H69.8: Other specified diagnostic endoscopic examination of enteric pouch using fibreoptic sigmoidoscope		1	1	1		1		1
H69.9: Unspecified diagnostic endoscopic examination of enteric pouch using fibreoptic sigmoidoscope		1	1	1		1		1
H70.1: Diagnostic endoscopic examination of colonic pouch and biopsy of colonic pouch using rigid sigmoidoscope		1	1	1		1		1
H70.2: Diagnostic endoscopic examination of colonic pouch using rigid sigmoidoscope NEC		1	1	1		1		1
H70.3: Diagnostic endoscopic examination of ileoanal pouch and biopsy of ileoanal pouch using rigid sigmoidoscope		1	1	1		1		1
H70.4: Diagnostic endoscopic examination of ileoanal pouch using rigid sigmoidoscope NEC		1	1	1		1		1
H70.8: Other specified diagnostic endoscopic examination of enteric pouch using rigid sigmoidoscope		1	1	1		1		1
H70.9: Unspecified diagnostic endoscopic examination of enteric pouch using rigid sigmoidoscope		1	1	1		1		1
H71.1: Fibreoptic endoscopic balloon dilation of colonic pouch NEC		1	1	1		1		1
H71.8: Other specified therapeutic endoscopic operations on enteric pouch		1	1	1		1		1
H71.9: Unspecified therapeutic endoscopic operations on enteric pouch		1	1	1		1		1
H72.1: Excision of lesion of anus using high resolution anoscope		1	1	1		1		1

OPCS-4 code and description	Major	Minor	HD	GS	OA	CDH	PUV	NEC
H72.2: Destruction of lesion of anus using high resolution anoscope		1	1	1		1		1
H72.8: Other specified therapeutic operations on anus using high resolution anoscope		1	1	1		1		1
H72.9: Unspecified therapeutic operations on anus using high resolution anoscope		1	1	1		1		1
H73.1: Diagnostic examination of anus and biopsy of anus using high resolution anoscope		1	1	1		1		1
H73.8: Other specified diagnostic operations on anus using high resolution anoscope		1	1	1		1		1
H73.9: Unspecified diagnostic operations on anus using high resolution anoscope		1	1	1		1		1
J01.1: Orthotopic transplantation of liver NEC	1		1	1		1		1
J01.2: Heterotopic transplantation of liver	1		1	1		1		1
J01.3: Replacement of previous liver transplant	1		1	1		1		1
J01.4: Transplantation of liver cells	1		1	1		1		1
J01.5: Orthotopic transplantation of whole liver	1		1	1		1		1
J01.8: Other specified transplantation of liver	1		1	1		1		1
J01.9: Unspecified transplantation of liver	1		1	1		1		1
J02.1: Right hemihepatectomy NEC	1		1	1		1		1
J02.2: Left hemihepatectomy NEC	1		1	1		1		1
J02.3: Resection of segment of liver	1		1	1		1		1
J02.4: Wedge excision of liver	1		1	1		1		1
J02.5: Marsupialisation of lesion of liver	1		1	1		1		1
J02.6: Extended right hemihepatectomy	1		1	1		1		1
J02.7: Extended left hemihepatectomy	1		1	1		1		1
J02.8: Other specified partial excision of liver	1		1	1		1		1
J02.9: Unspecified partial excision of liver	1		1	1		1		1

OPCS-4 code and description	Major	Minor	HD	GS	OA	CDH	PUV	NEC
J04.1: Removal of lacerated fragment of liver	1		1	1		1		1
J04.2: Repair of laceration of liver	1		1	1		1		1
J04.3: Packing of laceration of liver	1		1	1		1		1
J04.8: Other specified repair of liver	1		1	1		1		1
J04.9: Unspecified repair of liver	1		1	1		1		1
J05.8: Other specified incision of liver	1		1	1		1		1
J05.9: Unspecified incision of liver	1		1	1		1		1
L91.1: Open insertion of central venous catheter		1	1	1	1	1	1	1
L91.2: Insertion of central venous catheter NEC		1	1	1	1	1	1	1
L91.3: Attention to central venous catheter NEC		1	1	1	1	1	1	1
L91.4: Removal of central venous catheter		1	1	1	1	1	1	1
L91.5: Insertion of tunnelled venous catheter		1	1	1	1	1	1	1
L92.1: Fibrin sheath stripping of access catheter		1	1	1	1	1	1	1
L92.2: Wire brushing of access catheter		1	1	1	1	1	1	1
L92.3: Thrombolysis of access catheter		1	1	1	1	1	1	1
L92.8: Other specified unblocking of access catheter		1	1	1	1	1	1	1
L92.9: Unspecified unblocking of access catheter		1	1	1	1	1	1	1
L99.7: Percutaneous transluminal peripheral insertion of central catheter		1	1	1	1	1	1	1
M01.1: Autotransplantation of kidney	1						1	
M01.2: Allotransplantation of kidney from live donor	1						1	
M01.3: Allotransplantation of kidney from cadaver NEC	1						1	
M01.4: Allotransplantation of kidney from cadaver heart beating	1						1	
M01.5: Allotransplantation of kidney from cadaver heart non-beating	1						1	
M01.8: Other specified transplantation of kidney	1						1	
M01.9: Unspecified transplantation of kidney	1						1	
M02.1: Nephrectomy and excision of perirenal tissue	1						1	

OPCS-4 code and description	Major	Minor	HD	GS	OA	CDH	PUV	NEC
M02.2: Nephroureterectomy NEC	1						1	
M02.3: Bilateral nephrectomy	1						1	
M02.5: Nephrectomy NEC	1						1	
M02.6: Excision of rejected transplanted kidney	1						1	
M02.7: Excision of transplanted kidney NEC	1						1	
M02.8: Other specified total excision of kidney	1						1	
M02.9: Unspecified total excision of kidney	1						1	
M03.8: Other specified partial excision of kidney	1						1	
M03.9: Unspecified partial excision of kidney	1						1	
M05.4: Plication of kidney	1						1	
M05.5: Repair of laceration of kidney	1						1	
M05.8: Other specified open repair of kidney	1						1	
M05.9: Unspecified open repair of kidney	1						1	
M06.2: Drainage of kidney NEC	1						1	
M06.3: Closure of nephrostomy	1						1	
M06.8: Other specified incision of kidney	1						1	
M06.9: Unspecified incision of kidney	1						1	
M07.8: Other specified therapeutic ureteroscopic operations on kidney		1					1	
M07.9: Unspecified therapeutic ureteroscopic operations on kidney		1					1	
M08.3: Exploration of kidney	1						1	
M08.4: Exploration of transplanted kidney	1						1	
M08.8: Other specified other open operations on kidney	1						1	
M08.9: Unspecified other open operations on kidney	1						1	
M10.8: Other specified other therapeutic endoscopic operations on kidney		1					1	
M10.9: Unspecified other therapeutic endoscopic operations on kidney		1					1	

OPCS-4 code and description	Major	Minor	HD	GS	OA	CDH	PUV	NEC
M12.1: Percutaneous pyeloureterodynamics		1					1	
M12.8: Other specified percutaneous studies of upper urinary tract		1					1	
M12.9: Unspecified percutaneous studies of upper urinary tract		1					1	
M13.2: Percutaneous drainage of kidney		1					1	
M13.3: Percutaneous aspiration of kidney NEC		1					1	
M13.4: Percutaneous injection of therapeutic substance into kidney		1					1	
M13.5: Percutaneous injection of radiocontrast substance into kidney		1					1	
M13.6: Percutaneous insertion of nephrostomy tube		1					1	
M13.7: Percutaneous radiofrequency ablation of lesion of kidney		1					1	
M13.8: Other specified percutaneous puncture of kidney		1					1	
M13.9: Unspecified percutaneous puncture of kidney		1					1	
M15.1: Nephrostomography		1					1	
M15.8: Other specified operations on kidney along nephrostomy tube track		1					1	
M15.9: Unspecified operations on kidney along nephrostomy tube track		1					1	
M16.1: Irrigation of kidney		1					1	
M16.2: Maintenance of drainage tube of kidney		1					1	
M16.5: Removal of nephrostomy tube		1					1	
M16.8: Other specified other operations on kidney		1					1	
M16.9: Unspecified other operations on kidney		1					1	
M18.1: Total ureterectomy	1		1				1	
M18.2: Excision of segment of ureter	1		1				1	
M18.3: Secondary ureterectomy	1		1				1	
M18.4: Excision of duplex ureter	1		1				1	
M18.8: Other specified excision of ureter	1		1				1	

OPCS-4 code and description	Major	Minor	HD	GS	OA	CDH	PUV	NEC
M18.9: Unspecified excision of ureter	1		1				1	
M19.1: Construction of ileal conduit	1		1				1	
M19.2: Creation of urinary diversion to intestine NEC	1		1				1	
M19.3: Revision of urinary diversion	1		1				1	
M19.4: Cutaneous ureterostomy NEC	1		1				1	
M19.5: Revision of ureterostomy stoma	1		1				1	
M19.6: Percutaneous tunnelled kidney to bladder bypass using prosthesis	1		1				1	
M19.7: Construction of orthotopic bladder substitute using intestine	1		1				1	
M19.8: Other specified urinary diversion	1		1				1	
M19.9: Unspecified urinary diversion	1		1				1	
M20.1: Bilateral replantation of ureter	1		1				1	
M20.2: Unilateral replantation of ureter	1		1				1	
M20.3: Replantation of ureter after urinary diversion	1		1				1	
M20.8: Other specified replantation of ureter	1		1				1	
M20.9: Unspecified replantation of ureter	1		1				1	
M21.1: Direct anastomosis of ureter to bladder	1		1				1	
M21.2: Anastomosis of ureter to bladder using flap of bladder	1		1				1	
M21.3: Ileal replacement of ureter	1		1				1	
M21.4: Colonic replacement of ureter	1		1				1	
M21.5: Revision of anastomosis of ureter NEC	1		1				1	
M21.6: Ureteroureterostomy	1		1				1	
M21.8: Other specified other connection of ureter	1		1				1	
M21.9: Unspecified other connection of ureter	1		1				1	
M22.1: Suture of ureter		1	1				1	
M22.2: Removal of ligature from ureter		1	1				1	
M22.8: Other specified repair of ureter	1		1				1	
M22.9: Unspecified repair of ureter	1		1				1	

OPCS-4 code and description	Major	Minor	HD	GS	OA	CDH	PUV	NEC
M23.8: Other specified incision of ureter	1		1				1	
M23.9: Unspecified incision of ureter	1		1				1	
M24.1: Construction of continent catheterisable intestinal pouch NEC	1		1				1	
M24.2: Construction of continent catheterisable intestinal pouch with continent cystostomy NEC	1		1				1	
M24.3: Construction of continent catheterisable intestinal pouch with continent cystostomy using appendix	1		1				1	
M24.4: Construction of continent catheterisable intestinal pouch with continent cystostomy using ileum	1		1				1	
M24.5: Creation of continent cystostomy NEC	1		1				1	
M24.6: Creation of continent cystostomy using appendix	1		1				1	
M24.7: Creation of continent cystostomy using ileum	1		1				1	
M24.8: Other specified other urinary diversion	1		1				1	
M24.9: Unspecified other urinary diversion	1		1				1	
M25.3: Ureterolysis	1		1				1	
M25.5: Open exploration of ureter	1		1				1	
M25.8: Other specified other open operations on ureter	1		1				1	
M25.9: Unspecified other open operations on ureter	1		1				1	
M26.4: Nephroscopic insertion of tubal prosthesis into ureter		1	1				1	
M26.8: Other specified therapeutic nephroscopic operations on ureter		1	1				1	
M26.9: Unspecified therapeutic nephroscopic operations on ureter		1	1				1	
M27.4: Ureteroscopic insertion of ureteric stent		1	1				1	
M27.5: Ureteroscopic removal of ureteric stent		1	1				1	
M27.6: Ureteroscopic endoluminal balloon rupture of stenosis of ureter		1	1				1	
M27.7: Ureteroscopic dilation of ureter		1	1				1	

OPCS-4 code and description	Major	Minor	HD	GS	OA	CDH	PUV	NEC
M29.2: Endoscopic insertion of tubal prosthesis into ureter NEC		1	1				1	
M29.3: Endoscopic removal of tubal prosthesis from ureter		1	1				1	
M29.4: Endoscopic dilation of ureter		1	1				1	
M29.5: Endoscopic renewal of tubal prosthesis into ureter		1	1				1	
M29.8: Other specified other therapeutic endoscopic operations on ureter		1	1				1	
M29.9: Unspecified other therapeutic endoscopic operations on ureter		1	1				1	
M30.1: Endoscopic retrograde pyelography		1	1				1	
M30.2: Endoscopic catheterisation of ureter		1	1				1	
M30.3: Endoscopic ureteric urine sampling		1	1				1	
M30.4: Nephroscopic ureteroscopy		1	1				1	
M30.5: Diagnostic endoscopic examination of ureter and biopsy of lesion of ureter NEC		1	1				1	
M30.6: Diagnostic endoscopic examination of ureter and biopsy of lesion of ureter using rigid ureteroscope		1	1				1	
M30.8: Other specified diagnostic endoscopic examination of ureter		1	1				1	
M30.9: Unspecified diagnostic endoscopic examination of ureter		1	1				1	
M32.1: Endoscopic extirpation of lesion of ureteric orifice		1	1				1	
M32.2: Endoscopic meatotomy of ureteric orifice		1	1				1	
M32.3: Endoscopic injection of inert substance around ureteric orifice		1	1				1	
M32.4: Endoscopic dilation of ureteric orifice		1	1				1	
M32.5: Endoscopic incision of ureterocele		1	1				1	
M32.6: Endoscopic transurethral resection of ureteric orifice		1	1				1	
M32.8: Other specified operations on ureteric orifice		1	1				1	
M32.9: Unspecified operations on ureteric orifice		1	1				1	

OPCS-4 code and description	Major	Minor	HD	GS	OA	CDH	PUV	NEC
M33.1: Percutaneous insertion of metallic stent into ureter		1	1				1	
M33.2: Percutaneous insertion of plastic stent into ureter		1	1				1	
M33.3: Percutaneous replacement of metallic stent into ureter		1	1				1	
M33.4: Percutaneous replacement of plastic stent into ureter		1	1				1	
M33.5: Percutaneous insertion of ureteric stent into ureter NEC		1	1				1	
M33.6: Percutaneous removal of ureteric stent from ureter NEC		1	1				1	
M33.8: Other specified percutaneous ureteric stent procedures		1	1				1	
M33.9: Unspecified percutaneous ureteric stent procedures		1	1				1	
M34.3: Cystectomy NEC	1		1				1	
M34.4: Simple cystectomy	1		1				1	
M34.8: Other specified total excision of bladder	1		1				1	
M34.9: Unspecified total excision of bladder	1		1				1	
M35.1: Diverticulectomy of bladder	1		1				1	
M35.8: Other specified partial excision of bladder	1		1				1	
M35.9: Unspecified partial excision of bladder	1		1				1	
M36.1: Caecocystoplasty	1		1				1	
M36.2: Ileocystoplasty	1		1				1	
M36.3: Colocystoplasty	1		1				1	
M36.8: Other specified enlargement of bladder	1		1				1	
M36.9: Unspecified enlargement of bladder	1		1				1	
M37.1: Cystourethroplasty	1		1				1	
M37.2: Repair of vesicocolic fistula	1		1				1	
M37.3: Repair of rupture of bladder	1		1				1	
M37.8: Other specified other repair of bladder	1		1				1	
M37.9: Unspecified other repair of bladder	1		1				1	
M38.1: Perineal urethrostomy and drainage of bladder		1	1				1	
M38.2: Cystostomy and insertion of suprapubic tube into bladder		1	1				1	
M38.3: Cystostomy NEC		1	1				1	

OPCS-4 code and description	Major	Minor	HD	GS	OA	CDH	PUV	NEC
M38.8: Other specified open drainage of bladder		1	1				1	
M38.9: Unspecified open drainage of bladder		1	1				1	
M39.8: Other specified other open operations on contents of bladder	1		1				1	
M39.9: Unspecified other open operations on contents of bladder	1		1				1	
M41.3: Open transection of bladder	1		1				1	
M41.5: Exploration of bladder		1	1				1	
M41.6: Detrusor myotomy	1		1				1	
M41.8: Other specified other open operations on bladder	1		1				1	
M41.9: Unspecified other open operations on bladder	1		1				1	
M42.1: Endoscopic resection of lesion of bladder		1	1				1	
M42.2: Endoscopic cauterisation of lesion of bladder		1	1				1	
M42.3: Endoscopic destruction of lesion of bladder NEC		1	1				1	
M42.8: Other specified endoscopic extirpation of lesion of bladder		1	1				1	
M42.9: Unspecified endoscopic extirpation of lesion of bladder		1	1				1	
M44.4: Endoscopic removal of blood clot from bladder		1	1				1	
M44.5: Endoscopic removal of mesh from bladder		1	1				1	
M44.8: Other specified other therapeutic endoscopic operations on bladder		1	1				1	
M44.9: Unspecified other therapeutic endoscopic operations on bladder		1	1				1	
M45.5: Diagnostic endoscopic examination of bladder using rigid cystoscope		1	1				1	
M45.8: Other specified diagnostic endoscopic examination of bladder		1	1				1	
M45.9: Unspecified diagnostic endoscopic examination of bladder		1	1				1	
M47.1: Urethral irrigation of bladder		1	1				1	
M47.2: Change of urethral catheter into bladder		1	1				1	

OPCS-4 code and description	Major	Minor	HD	GS	OA	CDH	PUV	NEC
M47.3: Removal of urethral catheter from bladder		1	1				1	
M47.4: Urodynamic studies using catheter		1	1				1	
M47.5: Maintenance of urethral catheter in bladder		1	1				1	
M47.8: Other specified urethral catheterisation of bladder		1	1				1	
M47.9: Unspecified urethral catheterisation of bladder		1	1				1	
M48.1: Suprapubic aspiration of bladder		1	1				1	
M48.2: Urodynamic studies using suprapubic tube		1	1				1	
M48.8: Other specified operations on bladder		1	1				1	
M48.9: Unspecified operations on bladder		1	1				1	
M49.1: Closure of cystostomy	1		1				1	
M49.2: Change of suprapubic tube into bladder		1	1				1	
M49.3: Removal of suprapubic tube from bladder		1	1				1	
M49.4: Introduction of therapeutic substance into bladder		1	1				1	
M49.5: Injection of therapeutic substance into bladder wall		1	1				1	
M49.6: Micturating cystography		1	1				1	
M49.7: High intensity focused ultrasound of bladder		1	1				1	
M49.8: Other specified other operations on bladder	1		1				1	
M49.9: Unspecified other operations on bladder	1		1				1	
M60.1: Insertion of male retropubic continence device NEC	1		1				1	
M60.2: Removal of male retropubic device NEC	1		1				1	
M60.3: Removal of artificial urinary sphincter from outlet of male bladder	1		1				1	
M60.4: Attention to artificial urinary sphincter in outlet of male bladder	1		1				1	
M60.5: Total removal of transobturator sling	1		1				1	
M60.6: Partial removal of transobturator sling	1		1				1	
M60.8: Other specified open operations on outlet of male bladder	1		1				1	
M60.9: Unspecified open operations on outlet of male bladder	1		1				1	

OPCS-4 code and description	Major	Minor	HD	GS	OA	CDH	PUV	NEC
M64.1: Open resection of outlet of male bladder	1		1				1	
M64.2: Implantation of artificial urinary sphincter into outlet of male bladder	1		1				1	
M64.3: Insertion of prosthetic collar around outlet of male bladder	1		1				1	
M64.4: Maintenance of prosthetic collar around outlet of male bladder	1		1				1	
M64.5: Removal of prosthetic collar from around outlet of male bladder	1		1				1	
M64.6: Reconstruction of neck of male bladder NEC	1		1				1	
M64.7: Introduction of transobturator sling	1		1				1	
M64.8: Other specified other open operations on outlet of male bladder	1		1				1	
M64.9: Unspecified other open operations on outlet of male bladder	1		1				1	
M65.8: Other specified endoscopic resection of outlet of male bladder		1	1				1	
M65.9: Unspecified endoscopic resection of outlet of male bladder		1	1				1	
M66.1: Endoscopic sphincterotomy of external sphincter of male bladder		1	1				1	
M66.2: Endoscopic incision of outlet of male bladder NEC		1	1				1	
M66.3: Endoscopic injection of inert substance into outlet of male bladder		1	1				1	
M66.4: Endoscopic removal of inert substance from outlet of male bladder		1	1				1	
M66.8: Other specified other therapeutic endoscopic operations on outlet of male bladder		1	1				1	
M66.9: Unspecified other therapeutic endoscopic operations on outlet of male bladder		1	1				1	
M70.8: Other specified other operations on outlet of male bladder		1	1				1	

OPCS-4 code and description	Major	Minor	HD	GS	OA	CDH	PUV	NEC
M70.9: Unspecified other operations on outlet of male bladder		1	1				1	
M72.1: Partial urethrectomy	1		1				1	
M72.2: Urethrectomy NEC	1		1				1	
M72.3: Excision of lesion of urethra NEC	1		1				1	
M72.4: Secondary urethrectomy	1		1				1	
M72.8: Other specified excision of urethra	1		1				1	
M72.9: Unspecified excision of urethra	1		1				1	
M73.3: Closure of fistula of urethra	1		1				1	
M73.4: Reconstruction of urethra	1		1				1	
M73.5: Pull through of urethra	1		1				1	
M73.6: Urethroplasty NEC	1		1				1	
M73.7: Repair of rupture of urethra NEC	1		1				1	
M73.8: Other specified repair of urethra	1		1				1	
M73.9: Unspecified repair of urethra	1		1				1	
M75.2: Insertion of prosthesis for compression of bulb of male urethra	1		1				1	
M75.3: External urethrotomy	1		1				1	
M75.8: Other specified other open operations on urethra	1		1				1	
M75.9: Unspecified other open operations on urethra	1		1				1	
M76.1: Endoscopic extirpation of lesion of urethra		1	1				1	
M76.3: Optical urethrotomy		1	1				1	
M76.4: Endoscopic dilation of urethra		1	1				1	
M76.5: Endoscopic destruction of urethral valves		1	1				1	
M76.6: Endoscopic insertion of urethral stent		1	1				1	
M76.7: Endoscopic removal of urethral stent		1	1				1	
M76.8: Other specified therapeutic endoscopic operations on urethra		1	1				1	
M76.9: Unspecified therapeutic endoscopic operations on urethra		1	1				1	

OPCS-4 code and description	Major	Minor	HD	GS	OA	CDH	PUV	NEC
M77.1: Diagnostic endoscopic examination of urethra and biopsy of lesion of urethra		1	1				1	
M77.8: Other specified diagnostic endoscopic examination of urethra		1	1				1	
M77.9: Unspecified diagnostic endoscopic examination of urethra		1	1				1	
M78.1: Endoscopic removal of mesh from urethra		1	1				1	
M78.8: Other specified other therapeutic endoscopic operations on urethra		1	1				1	
M78.9: Unspecified other therapeutic endoscopic operations on urethra		1	1				1	
M79.1: Bouginage of urethra		1	1				1	
M79.2: Dilation of urethra NEC		1	1				1	
M79.3: Calibration of urethra		1	1				1	
M79.4: Internal urethrotomy NEC		1	1				1	
M79.5: Urethrography ascending and descending		1	1				1	
M79.6: Urethrography ascending NEC		1	1				1	
M79.7: Urethrography descending NEC		1	1				1	
M79.8: Other specified other operations on urethra		1	1				1	
M79.9: Unspecified other operations on urethra		1	1				1	
M81.1: Extirpation of lesion of meatus of urethra		1	1				1	
M81.2: Meatoplasty of urethra		1	1				1	
M81.3: External meatotomy of urethral orifice		1	1				1	
M81.4: Dilation of meatus of urethra		1	1				1	
M81.8: Other specified operations on urethral orifice		1	1				1	
M81.9: Unspecified operations on urethral orifice		1	1				1	
M83.1: Drainage of paravesical abscess		1	1				1	
M83.2: Exploration of retropubic space		1	1				1	
M83.8: Other specified other operations on urinary tract		1	1				1	

OPCS-4 code and description	Major	Minor	HD	GS	OA	CDH	PUV	NEC
M83.9: Unspecified other operations on urinary tract		1	1				1	
M85.1: Endoscopic examination of intestinal conduit		1	1				1	
M85.8: Other specified diagnostic endoscopic examination of urinary diversion		1	1				1	
M85.9: Unspecified diagnostic endoscopic examination of urinary diversion		1	1				1	
M86.8: Other specified therapeutic endoscopic operations on urinary diversion		1	1				1	
M86.9: Unspecified therapeutic endoscopic operations on urinary diversion		1	1				1	
N08.1: Bilateral microvascular transfer of testes to scrotum		1		1				
N08.2: One stage bilateral orchidopexy NEC		1		1				
N08.3: First stage bilateral orchidopexy		1		1				
N08.4: Second stage bilateral orchidopexy		1		1				
N08.8: Other specified bilateral placement of testes in scrotum		1		1				
N08.9: Unspecified bilateral placement of testes in scrotum		1		1				
N09.1: Microvascular transfer of testis to scrotum NEC		1		1				
N09.2: One stage orchidopexy NEC		1		1				
N09.3: First stage orchidopexy NEC		1		1				
N09.4: Second stage orchidopexy NEC		1		1				
N09.8: Other specified other placement of testis in scrotum		1		1				
N09.9: Unspecified other placement of testis in scrotum		1		1				
N24.2: Operations on skin of male perineum NEC		1	1					
N24.3: Excision of male periurethral tissue NEC		1	1					
N24.4: Incision of male periurethral tissue		1	1					
N24.8: Other specified operations on male perineum		1	1					
N24.9: Unspecified operations on male perineum		1	1					
P13.6: Operations on female periurethral tissue NEC		1	1					

OPCS-4 code and description	Major	Minor	HD	GS	OA	CDH	PUV	NEC
P13.8: Other specified other operations on female perineum		1	1					
P13.9: Unspecified other operations on female perineum		1	1					
P29.1: Freeing of adhesions of vagina		1	1	1	1	1		1
P31.2: Drainage of pouch of Douglas		1	1	1	1	1	1	1
Q20.1: Freeing of adhesions of uterus	1		1	1	1	1		1
Q30.1: Reconstruction of fallopian tube	1		1	1	1	1		1
Q30.2: Replantation of fallopian tube	1		1	1	1	1		1
Q30.3: Anastomosis of fallopian tube NEC	1		1	1	1	1		1
Q30.4: Salpingostomy	1		1	1	1	1		1
Q30.5: Suture of fallopian tube	1		1	1	1	1		1
Q30.8: Other specified other repair of fallopian tube	1		1	1	1	1		1
Q30.9: Unspecified other repair of fallopian tube	1		1	1	1	1		1
Q34.1: Open freeing of adhesions of fallopian tube	1		1	1	1	1		1
Q38.1: Endoscopic freeing of adhesions of fallopian tube		1	1	1	1	1		1
Q45.8: Other specified repair of ovary	1		1	1	1	1		1
Q45.9: Unspecified repair of ovary	1		1	1	1	1		1
Q47.2: Open freeing of adhesions of ovary	1		1	1	1	1		1
Q49.2: Endoscopic freeing of adhesions of ovary		1	1	1	1	1		1
R01.2: Fetoscopic insertion of tracheal plug	1					1		
R01.3: Fetoscopic removal of tracheal plug	1					1		
R04.1: Percutaneous insertion of fetal vesicoamniotic shunt	1						1	
R04.5: Percutaneous insertion of fetal bladder drain	1						1	
R04.6: Percutaneous insertion of fetal tracheal plug	1						1	
R11.1: Percutaneous removal of fetal tracheal plug	1					1		
S02.1: Abdominoplasty	1			1				
S02.8: Other specified plastic excision of skin of abdominal wall	1			1				
S02.9: Unspecified plastic excision of skin of abdominal wall	1			1				
T01.1: Thoracoplasty	1				1	1		

OPCS-4 code and description	Major	Minor	HD	GS	OA	CDH	PUV	NEC
T01.8: Other specified partial excision of chest wall	1				1	1		
T01.9: Unspecified partial excision of chest wall	1				1	1		
T02.1: Correction of pectus deformity of chest wall	1				1	1		
T02.2: Insertion of silicone implant for correction of pectus excavatum	1				1	1		
T02.3: Insertion of prosthesis into chest wall NEC	1				1	1		
T02.4: Removal of prosthesis from chest wall	1				1	1		
T02.8: Other specified reconstruction of chest wall	1				1	1		
T02.9: Unspecified reconstruction of chest wall	1				1	1		
T03.1: Exploratory median sternotomy	1				1	1		
T03.2: Reopening of chest and re-exploration of intrathoracic operation site and surgical arrest of postoperative bleeding	1				1	1		
T03.3: Reopening of chest and re-exploration of intrathoracic operation site NEC	1				1	1		
T03.4: Reopening of chest NEC	1				1	1		
T03.8: Other specified opening of chest	1				1	1		
T03.9: Unspecified opening of chest	1				1	1		
T05.1: Suture of chest wall	1				1	1		
T05.2: Resuture of previous incision of chest wall	1				1	1		
T05.3: Repair of chest wall NEC	1				1	1		
T05.4: Removal of wire from chest wall	1				1	1		
T05.8: Other specified other operations on chest wall		1			1	1		
T05.9: Unspecified other operations on chest wall		1			1	1		
T07.1: Decortication of pleura	1				1	1		
T07.2: Open excision of lesion of pleura	1				1	1		
T07.8: Other specified open excision of pleura	1				1	1		
T07.9: Unspecified open excision of pleura	1				1	1		
T08.1: Resection of rib and open drainage of pleural cavity	1				1	1		

OPCS-4 code and description	Major	Minor	HD	GS	OA	CDH	PUV	NEC
T08.2: Closure of open drainage of pleural cavity	1				1	1		
T08.3: Fenestration of pleura	1				1	1		
T08.4: Closure of fenestration of pleura	1				1	1		
T08.8: Other specified open drainage of pleural cavity	1				1	1		
T08.9: Unspecified open drainage of pleural cavity	1				1	1		
T09.3: Mechanical open pleurodesis	1				1	1		
T09.4: Chemical open pleurodesis	1				1	1		
T09.5: Open pleurodesis NEC	1				1	1		
T09.8: Other specified other open operations on pleura	1				1	1		
T09.9: Unspecified other open operations on pleura	1				1	1		
T10.2: Endoscopic pleurodesis using talc		1			1	1		
T10.3: Endoscopic pleurodesis NEC		1			1	1		
T10.8: Other specified therapeutic endoscopic operations on pleura		1			1	1		
T10.9: Unspecified therapeutic endoscopic operations on pleura		1			1	1		
T11.1: Diagnostic endoscopic examination of pleura and biopsy of lesion of pleura		1			1	1		
T11.2: Diagnostic endoscopic examination of pleura and biopsy of lesion of intrathoracic organ NEC		1			1	1		
T11.8: Other specified diagnostic endoscopic examination of pleura		1			1	1		
T11.9: Unspecified diagnostic endoscopic examination of pleura		1			1	1		
T12.1: Drainage of lesion of pleura NEC	1				1	1		
T12.2: Drainage of pleural cavity NEC	1				1	1		
T12.3: Aspiration of pleural cavity	1				1	1		
T12.4: Insertion of tube drain into pleural cavity	1				1	1		
T12.5: Attention to tube drain into pleural cavity	1				1	1		
T12.6: Insertion of tunnelled catheter into pleural cavity	1				1	1		

OPCS-4 code and description	Major	Minor	HD	GS	OA	CDH	PUV	NEC
T12.7: Attention to tunnelled catheter in pleural cavity	1				1	1		
T12.8: Other specified puncture of pleura	1				1	1		
T12.9: Unspecified puncture of pleura	1				1	1		
T13.1: Insufflation of talc into pleural cavity NEC	1				1	1		
T13.2: Introduction of sclerosing substance into pleural cavity NEC	1				1	1		
T13.3: Introduction of cytotoxic substance into pleural cavity	1				1	1		
T13.4: Introduction of therapeutic substance into pleural cavity	1				1	1		
T13.8: Other specified introduction of substance into pleural cavity	1				1	1		
T13.9: Unspecified introduction of substance into pleural cavity	1				1	1		
T14.8: Other specified other operations on pleura	1					1		
T14.9: Unspecified other operations on pleura	1					1		
T15.1: Repair of traumatic rupture of diaphragm	1					1		
T15.2: Repair of postoperative rupture of diaphragm	1					1		
T15.8: Other specified repair of rupture of diaphragm	1					1		
T15.9: Unspecified repair of rupture of diaphragm	1					1		
T16.1: Insertion of prosthesis for repair of diaphragm	1					1		
T16.2: Plication of diaphragm	1					1		
T16.3: Closure of fistula of diaphragm	1					1		
T16.4: Repair of congenital diaphragmatic hernia	1					1		
T16.5: Suture of diaphragm NEC	1					1		
T16.8: Other specified other repair of diaphragm	1					1		
T16.9: Unspecified other repair of diaphragm	1					1		
T17.1: Excision of lesion of diaphragm	1					1		
T17.2: Destruction of lesion of diaphragm	1					1		
T17.8: Other specified other operations on diaphragm	1					1		
T17.9: Unspecified other operations on diaphragm	1					1		
T24.1: Repair of umbilical hernia using insert of natural material		1	1	1	1	1	1	1
T24.2: Repair of umbilical hernia using insert of prosthetic material		1	1	1	1	1	1	1

OPCS-4 code and description	Major	Minor	HD	GS	OA	CDH	PUV	NEC
T24.3: Repair of umbilical hernia using sutures		1	1	1	1	1	1	1
T24.4: Removal of prosthetic material from previous repair of umbilical hernia		1	1	1	1	1	1	1
T24.8: Other specified primary repair of umbilical hernia		1	1	1	1	1	1	1
T24.9: Unspecified primary repair of umbilical hernia		1	1	1	1	1	1	1
T25.1: Primary repair of incisional hernia using insert of natural material		1	1	1	1	1	1	1
T25.2: Primary repair of incisional hernia using insert of prosthetic material		1	1	1	1	1	1	1
T25.3: Primary repair of incisional hernia using sutures		1	1	1	1	1	1	1
T25.8: Other specified primary repair of incisional hernia		1	1	1	1	1	1	1
T25.9: Unspecified primary repair of incisional hernia		1	1	1	1	1	1	1
T26.1: Repair of recurrent incisional hernia using insert of natural material		1	1	1	1	1	1	1
T26.2: Repair of recurrent incisional hernia using insert of prosthetic material		1	1	1	1	1	1	1
T26.3: Repair of recurrent incisional hernia using sutures		1	1	1	1	1	1	1
T26.4: Removal of prosthetic material from previous repair of incisional hernia		1	1	1	1	1	1	1
T26.8: Other specified repair of recurrent incisional hernia		1	1	1	1	1	1	1
T26.9: Unspecified repair of recurrent incisional hernia		1	1	1	1	1	1	1
T27.1: Repair of ventral hernia using insert of natural material		1	1	1	1	1	1	1
T27.2: Repair of ventral hernia using insert of prosthetic material		1	1	1	1	1	1	1
T27.3: Repair of ventral hernia using sutures		1	1	1	1	1	1	1
T27.4: Removal of prosthetic material from previous repair of ventral hernia		1	1	1	1	1	1	1
T27.8: Other specified repair of other hernia of abdominal wall		1	1	1	1	1	1	1
T27.9: Unspecified repair of other hernia of abdominal wall		1	1	1	1	1	1	1
T28.1: Closure of gastroschisis		1		1				

OPCS-4 code and description	Major	Minor	HD	GS	OA	CDH	PUV	NEC
T28.2: Suture of anterior abdominal wall		1		1				
T28.3: Resuture of previous incision of anterior abdominal wall		1		1				
T28.8: Other specified other repair of anterior abdominal wall		1		1				
T28.9: Unspecified other repair of anterior abdominal wall		1		1				
T29.1: Excision of umbilicus		1		1				
T29.2: Excision of urachus		1		1				
T29.3: Extirpation of lesion of umbilicus		1		1				
T29.5: Excision of fistula of umbilicus		1		1				
T29.6: Plastic operations on umbilicus		1		1				
T29.8: Other specified operations on umbilicus		1		1				
T29.9: Unspecified operations on umbilicus		1		1				
T30.1: Reopening of abdomen and re-exploration of intra-abdominal operation site and surgical arrest of postoperative bleeding	1		1	1	1	1	1	1
T30.2: Reopening of abdomen and re-exploration of intra-abdominal operation site NEC	1		1	1	1	1		1
T30.3: Reopening of abdomen NEC	1		1	1	1	1		1
T30.4: Opening of abdomen and exploration of groin	1		1	1	1	1		1
T30.5: Packing of abdominal cavity	1		1	1	1	1		1
T30.8: Other specified opening of abdomen	1		1	1	1	1		1
T30.9: Unspecified opening of abdomen	1		1	1	1	1		1
T31.2: Excision of lesion of anterior abdominal wall and insert of prosthetic material into anterior abdominal wall	1		1	1	1	1		1
T31.3: Excision of lesion of anterior abdominal wall NEC	1		1	1	1	1		1
T31.4: Destruction of lesion of anterior abdominal wall	1		1	1	1	1		1
T31.5: Drainage of anterior abdominal wall	1		1	1	1	1		1
T31.7: Exploration of groin NEC	1		1	1	1	1		1
T31.8: Other specified other operations on anterior abdominal wall	1		1	1	1	1		1

OPCS-4 code and description	Major	Minor	HD	GS	OA	CDH	PUV	NEC
T31.9: Unspecified other operations on anterior abdominal wall	1		1	1	1	1		1
T32.1: Reconstruction of anterior abdominal wall using insert of natural material	1			1				
T32.2: Reconstruction of anterior abdominal wall using insert of prosthetic material	1			1				
T32.3: Reconstruction of anterior abdominal wall using flap NEC	1			1				
T32.4: Reconstruction of anterior abdominal wall using insert of prosthetic material and flap NEC	1			1				
T32.8: Other specified reconstruction of anterior abdominal wall	1			1				
T32.9: Unspecified reconstruction of anterior abdominal wall	1			1				
T34.1: Open drainage of subphrenic abscess	1		1	1	1	1		1
T34.2: Open drainage of pelvic abscess	1		1	1	1	1		1
T34.3: Open drainage of abdominal abscess NEC	1		1	1	1	1		1
T34.8: Other specified open drainage of peritoneum	1		1	1	1	1		1
T34.9: Unspecified open drainage of peritoneum	1		1	1	1	1		1
T37.4: Repair of mesentery of small intestine	1		1	1	1	1		1
T37.8: Other specified operations on mesentery of small intestine	1		1	1	1	1		1
T37.9: Unspecified operations on mesentery of small intestine	1		1	1	1	1		1
T38.4: Repair of mesentery of colon	1		1	1	1	1		1
T38.8: Other specified operations on mesentery of colon	1		1	1	1	1		1
T38.9: Unspecified operations on mesentery of colon	1		1	1	1	1		1
T39.8: Other specified operations on posterior peritoneum	1		1	1	1	1		1
T39.9: Unspecified operations on posterior peritoneum	1		1	1	1	1		1
T41.1: Open biopsy of lesion of peritoneum NEC	1		1	1	1	1		1
T41.2: Division of band of peritoneum	1		1	1	1	1		1
T41.3: Freeing of adhesions of peritoneum NEC	1		1	1	1	1		1
T41.5: Freeing of extensive adhesions of peritoneum	1		1	1	1	1		1
T41.6: Excision of peritoneum	1		1	1	1	1		1

OPCS-4 code and description	Major	Minor	HD	GS	OA	CDH	PUV	NEC
T41.8: Other specified other open operations on peritoneum	1		1	1	1	1		1
T41.9: Unspecified other open operations on peritoneum	1		1	1	1	1		1
T42.3: Endoscopic division of adhesions of peritoneum		1	1	1	1	1		1
T43.3: Diagnostic endoscopic ultrasound examination of peritoneum		1	1	1	1	1		1
T43.4: Diagnostic endoscopic ultrasound examination of peritoneum and biopsy of intra-abdominal organ		1	1	1	1	1		1
T43.8: Other specified diagnostic endoscopic examination of peritoneum		1	1	1	1	1		1
T43.9: Unspecified diagnostic endoscopic examination of peritoneum		1	1	1	1	1		1
T45.1: Image controlled percutaneous drainage of subphrenic abscess		1	1	1	1	1		1
T45.2: Image controlled percutaneous drainage of pelvic abscess		1	1	1	1	1		1
T45.3: Image controlled percutaneous drainage of abdominal abscess NEC		1	1	1	1	1		1
T45.4: Image controlled percutaneous drainage of lesion of abdominal cavity NEC		1	1	1	1	1		1
T45.8: Other specified image controlled operations on abdominal cavity		1	1	1	1	1		1
T45.9: Unspecified image controlled operations on abdominal cavity		1	1	1	1	1		1
T46.1: Paracentesis abdominis for ascites		1	1	1	1	1		1
T46.2: Drainage of ascites NEC		1	1	1	1	1		1
T46.3: Irrigation of peritoneal cavity		1	1	1	1	1		1
T46.8: Other specified other drainage of peritoneal cavity		1	1	1	1	1		1
T46.9: Unspecified other drainage of peritoneal cavity		1	1	1	1	1		1
T48.8: Other specified other operations on peritoneum		1	1	1	1	1		1
T48.9: Unspecified other operations on peritoneum		1	1	1	1	1		1

OPCS-4 code and description	Major	Minor	HD	GS	OA	CDH	PUV	NEC
T57.1: Freeing of adhesions of fascia		1	1	1	1	1		1
T57.3: Repair of fascia	1	1	1	1	1	1		1
T57.8: Other specified other operations on fascia		1	1	1	1	1		1
T57.9: Unspecified other operations on fascia		1	1	1	1	1		1
T89.3: Ligation of lymphatic duct	1				1	1		
T97.1: Repair of recurrent umbilical hernia using insert of natural material	1		1	1	1	1	1	1
T97.2: Repair of recurrent umbilical hernia using insert of prosthetic material	1		1	1	1	1	1	1
T97.3: Repair of recurrent umbilical hernia using sutures	1		1	1	1	1	1	1
T97.8: Other specified repair of recurrent umbilical hernia	1		1	1	1	1	1	1
T97.9: Unspecified repair of recurrent umbilical hernia	1		1	1	1	1	1	1
T98.1: Repair of recurrent ventral hernia using insert of natural material	1		1	1	1	1	1	1
T98.2: Repair of recurrent ventral hernia using insert of prosthetic material	1		1	1	1	1	1	1
T98.3: Repair of recurrent ventral hernia using sutures	1		1	1	1	1	1	1
T98.8: Other specified repair of recurrent other hernia of abdominal wall	1		1	1	1	1	1	1
T98.9: Unspecified repair of recurrent other hernia of abdominal wall	1		1	1	1	1	1	1
V38.1: Primary fusion of joint of thoracic spine	1				1	1		
V38.2: Primary posterior interlaminar fusion of joint of lumbar spine	1				1	1		
V38.3: Primary posterior fusion of joint of lumbar spine NEC	1				1	1		
V38.4: Primary intertransverse fusion of joint of lumbar spine NEC	1				1	1		
V38.5: Primary posterior interbody fusion of joint of lumbar spine	1				1	1		
V38.6: Primary transforaminal interbody fusion of joint of lumbar spine	1				1	1		
V38.8: Other specified primary fusion of other joint of spine	1				1	1		

OPCS-4 code and description	Major	Minor	HD	GS	OA	CDH	PUV	NEC
V38.9: Unspecified primary fusion of other joint of spine	1				1	1		
V39.2: Revisional fusion of joint of thoracic spine	1				1	1		
V39.3: Revisional posterior interlaminar fusion of joint of lumbar spine	1				1	1		
V39.4: Revisional posterior fusion of joint of lumbar spine NEC	1				1	1		
V39.5: Revisional intertransverse fusion of joint of lumbar spine NEC	1				1	1		
V39.6: Revisional posterior interbody fusion of joint of lumbar spine	1				1	1		
V39.7: Revisional transforaminal interbody fusion of joint of lumbar spine	1				1	1		
V39.8: Other specified revisional fusion of joint of spine	1				1	1		
V39.9: Unspecified revisional fusion of joint of spine	1				1	1		
V40.1: Non-rigid stabilisation of spine	1				1	1		
V40.3: Posterior instrumented fusion of thoracic spine NEC	1				1	1		
V40.4: Posterior instrumented fusion of lumbar spine NEC	1				1	1		
V40.5: Removal of instrumentation from spine	1				1	1		
V40.8: Other specified stabilisation of spine	1				1	1		
V40.9: Unspecified stabilisation of spine	1				1	1		
V41.1: Posterior attachment of correctional instrument to spine	1				1	1		
V41.2: Anterior attachment of correctional instrument to spine	1				1	1		
V41.3: Removal of correctional instrument from spine	1				1	1		
V41.4: Anterior and posterior attachment of correctional instrument to spine	1				1	1		
V41.5: Posterior attachment of spinal growing system	1				1	1		
V41.6: Attention to spinal growing system	1				1	1		
V41.7: Surgical distraction of spinal growing system	1				1	1		
V41.8: Other specified instrumental correction of deformity of spine	1				1	1		
V41.9: Unspecified instrumental correction of deformity of spine	1				1	1		

OPCS-4 code and description	Major	Minor	HD	GS	OA	CDH	PUV	NEC
V42.2: Epiphysiodesis of spinal apophyseal joint for correction of deformity	1				1	1		
V42.3: Anterolateral release of spine for correction of deformity and graft HFQ	1				1	1		
V42.4: Anterior and posterior epiphysiodesis of spine for correction of deformity	1				1	1		
V42.5: Anterior epiphysiodesis of spine for correction of deformity NEC	1				1	1		
V42.6: Posterior epiphysiodesis of spine for correction of deformity NEC	1				1	1		
V42.8: Other specified other correction of deformity of spine	1				1	1		
V42.9: Unspecified other correction of deformity of spine	1				1	1		
X41.1: Insertion of ambulatory peritoneal dialysis catheter		1					1	
X41.2: Removal of ambulatory peritoneal dialysis catheter		1					1	
X41.8: Other specified placement of ambulatory apparatus for compensation for renal failure		1					1	
X41.9: Unspecified placement of ambulatory apparatus for compensation for renal failure		1					1	
X42.1: Insertion of temporary peritoneal dialysis catheter		1					1	
X42.8: Other specified placement of other apparatus for compensation for renal failure		1					1	
X42.9: Unspecified placement of other apparatus for compensation for renal failure		1					1	
X58.1: Extracorporeal membrane oxygenation	1				1	1		
X58.8: Other specified artificial support for body system	1				1	1		
X58.9: Unspecified artificial support for body system	1				1	1		
Y18.1: Freeing of adhesions of organ NOC		1	1	1	1	1	1	1
Y32.1: Re-exploration of organ and surgical arrest of postoperative bleeding NOC	1		1	1	1	1	1	1

OPCS-4 code and description	Major	Minor	HD	GS	OA	CDH	PUV	NEC
Y32.2: Re-exploration of organ and other repair of organ NOC	1		1	1	1	1	1	1
Y32.3: Re-exploration of organ and packing of organ NOC	1		1	1	1	1	1	1
Y32.8: Other specified re-exploration of organ NOC	1		1	1	1	1	1	1
Y32.9: Unspecified re-exploration of organ NOC	1		1	1	1	1	1	1
Y40.3: Balloon dilation of organ NOC		1			1			
Y49.1: Median sternotomy approach	1				1	1		
Y49.2: Transthoracic approach to spine	1				1	1		
Y49.3: Thoracotomy approach NEC	1				1	1		
Y49.4: Transapical approach to heart	1				1	1		
Y49.8: Other specified approach through thoracic cavity	1				1	1		
Y49.9: Unspecified approach through thoracic cavity	1				1	1		
Y50.2: Laparotomy approach NEC	1		1	1	1	1	1	1
Y50.8: Other specified approach through abdominal cavity	1		1	1	1	1	1	1
Y50.9: Unspecified approach through abdominal cavity	1		1	1	1	1	1	1
Y51.1: Approach to organ through oesophagostomy		1			1	1		
Y51.2: Approach to organ through gastrostomy		1	1	1	1	1	1	1
Y51.3: Approach to organ through ileostomy		1	1	1	1	1	1	1
Y51.4: Approach to organ through colostomy		1	1	1	1	1	1	1
Y51.5: Approach to organ through appendicostomy		1	1	1	1	1	1	1
Y51.8: Other specified approach to organ through artificial opening into gastrointestinal tract		1	1	1	1	1	1	1
Y51.9: Unspecified approach to organ through artificial opening into gastrointestinal tract		1	1	1	1	1	1	1
Y52.1: Approach to organ through tracheostomy					1	1		
Y52.2: Approach to organ through urethrostomy							1	
Y52.3: Approach to organ through cystostomy		1					1	
Y52.4: Peranal transrectal approach to organ		1	1	1		1		1
Y74.1: Thoracoscopically assisted approach to thoracic cavity	1				1	1		

OPCS-4 code and description	Major	Minor	HD	GS	OA	CDH	PUV	NEC
Y74.2: Thoracoscopic approach to thoracic cavity NEC	1				1	1		
Y74.3: Robotic minimal access approach to thoracic cavity	1				1	1		
Y74.4: Thoracoscopic video-assisted approach to thoracic cavity	1				1	1		
Y74.5: Mediastinoscopic approach to mediastinal cavity	1				1	1		
Y74.8: Other specified minimal access to thoracic cavity	1				1	1		
Y74.9: Unspecified minimal access to thoracic cavity	1				1	1		
Y75.1: Laparoscopically assisted approach to abdominal cavity	1		1	1	1	1	1	1
Y75.2: Laparoscopic approach to abdominal cavity NEC	1		1	1	1	1	1	1
Y75.3: Robotic minimal access approach to abdominal cavity	1		1	1	1	1	1	1
Y75.4: Hand assisted minimal access approach to abdominal cavity	1		1	1	1	1	1	1
Y75.5: Laparoscopic ultrasonic approach to abdominal cavity	1		1	1	1	1	1	1
Y75.8: Other specified minimal access to abdominal cavity	1		1	1	1	1	1	1
Y75.9: Unspecified minimal access to abdominal cavity	1		1	1	1	1	1	1
Z24.2: Larynx					1	1		
Z24.3: Trachea					1	1		
Z24.4: Carina					1	1		
Z24.5: Bronchus					1	1		
Z24.6: Lung					1	1		
Z24.7: Mediastinum					1	1		
Z24.8: Specified other respiratory tract NEC					1	1		
Z24.9: Other respiratory tract NEC					1	1		
Z27.1: Oesophagus					1	1		
Z27.2: Stomach				1	1	1		
Z27.3: Pylorus				1	1	1		1
Z27.4: Duodenum			1	1	1	1		1
Z27.5: Jejunum			1	1	1	1		1
Z27.6: Ileum			1	1	1	1		1

OPCS-4 code and description	Major	Minor	HD	GS	OA	CDH	PUV	NEC
Z27.7: Small intestine			1	1	1	1		1
Z27.8: Specified upper digestive tract NEC			1	1	1	1		1
Z27.9: Upper digestive tract NEC			1	1	1	1		1
Z28.1: Appendix			1	1	1	1		1
Z28.2: Caecum			1	1	1	1		1
Z28.3: Ascending colon			1	1	1	1		1
Z28.4: Transverse colon			1	1	1	1		1
Z28.5: Descending colon			1	1	1	1		1
Z28.6: Sigmoid colon			1	1	1	1		1
Z28.7: Colon NEC			1	1	1	1		1
Z28.8: Specified large intestine NEC			1	1	1	1		1
Z28.9: Large intestine NEC			1	1	1	1		1
Z29.1: Rectum			1	1		1		1
Z29.2: Anus			1	1		1		1
Z29.3: Perianal tissue			1	1		1		1
Z29.4: Colorectal			1	1	1	1		1
Z29.8: Specified part of bowel NEC			1	1	1	1		1
Z29.9: Bowel NEC			1	1	1	1		1
Z30.1: Liver NEC			1	1	1	1		1
Z41.1: Kidney							1	
Z41.2: Ureteric orifice							1	
Z41.3: Ureter NEC							1	
Z41.4: Renal pelvis NEC							1	
Z41.8: Specified upper urinary tract NEC							1	
Z41.9: Upper urinary tract NEC							1	
Z42.1: Bladder NEC							1	
Z42.2: Prostate							1	
Z42.3: Outlet of bladder							1	

OPCS-4 code and description	Major	Minor	HD	GS	OA	CDH	PUV	NEC
Z42.4: Urethral orifice							1	
Z42.5: Urethra NEC							1	
Z42.6: Prepuce							1	
Z42.7: Penis							1	
Z42.8: Specified lower urinary tract NEC							1	
Z42.9: Lower urinary tract NEC							1	
Z52.1: Pleura					1	1		
Z52.2: Pleural cavity					1	1		
Z52.8: Specified chest wall NEC					1	1		
Z52.9: Chest wall NEC					1	1		
Z53.1: Diaphragm					1	1		
Z53.2: Umbilicus			1	1	1	1		1
Z53.3: Peritoneum			1	1	1	1		1
Z53.4: Peritoneal cavity			1	1	1	1		1
Z53.5: Omentum			1	1	1	1		1
Z53.6: Mesentery			1	1	1	1		1
Z53.7: Abdominal cavity			1	1	1	1		1
Z53.8: Specified abdominal wall NEC			1	1	1	1		1
Z53.9: Abdominal wall NEC			1	1	1	1		1
Z66.4: Thoracic vertebra					1	1		
Z66.5: Lumbar vertebra					1	1		
Z66.8: Specified vertebra NEC					1	1		
Z66.9: Vertebra NEC					1	1		
Z87.8: Specified part of musculoskeletal system NEC					1	1		
Z87.9: Musculoskeletal system NEC					1	1		
Z88.8: Specified respiratory tract NEC					1	1		
Z88.9: Respiratory tract NEC					1	1		
Z92.4: Chest NEC					1	1		

OPCS-4 code and description	Major	Minor	HD	GS	OA	CDH	PUV	NEC
Z92.5: Back NEC					1	1		
Z92.6: Abdomen NEC			1	1	1	1	1	1
Z92.7: Trunk NEC			1	1	1	1	1	1
O11.1: Gastro-oesophageal junction					1	1		
O11.8: Specified other upper digestive tract NEC					1	1		
O11.9: Other upper digestive tract NEC					1	1		
O30.1: Hepatic flexure			1	1	1	1		1
O30.2: Splenic flexure			1	1	1	1		1
O30.8: Specified other large intestine NEC			1	1	1	1		1
O30.9: Other large intestine NEC			1	1	1	1		1
O34.1: Lobe of liver NEC			1	1	1	1		1
O34.2: Quadrate lobe of liver			1	1	1	1		1
O34.3: Caudate lobe of liver			1	1	1	1		1
O34.4: Porta hepatis			1	1	1	1		1
O34.5: Falciform ligament of liver			1	1	1	1		1
O53.1: Prostatic urethra								
O53.2: Bulbar urethra							1	
O53.3: Penile urethra							1	
O53.8: Specified other lower urinary tract NEC							1	
O53.9: Other lower urinary tract NEC							1	