

Supplement

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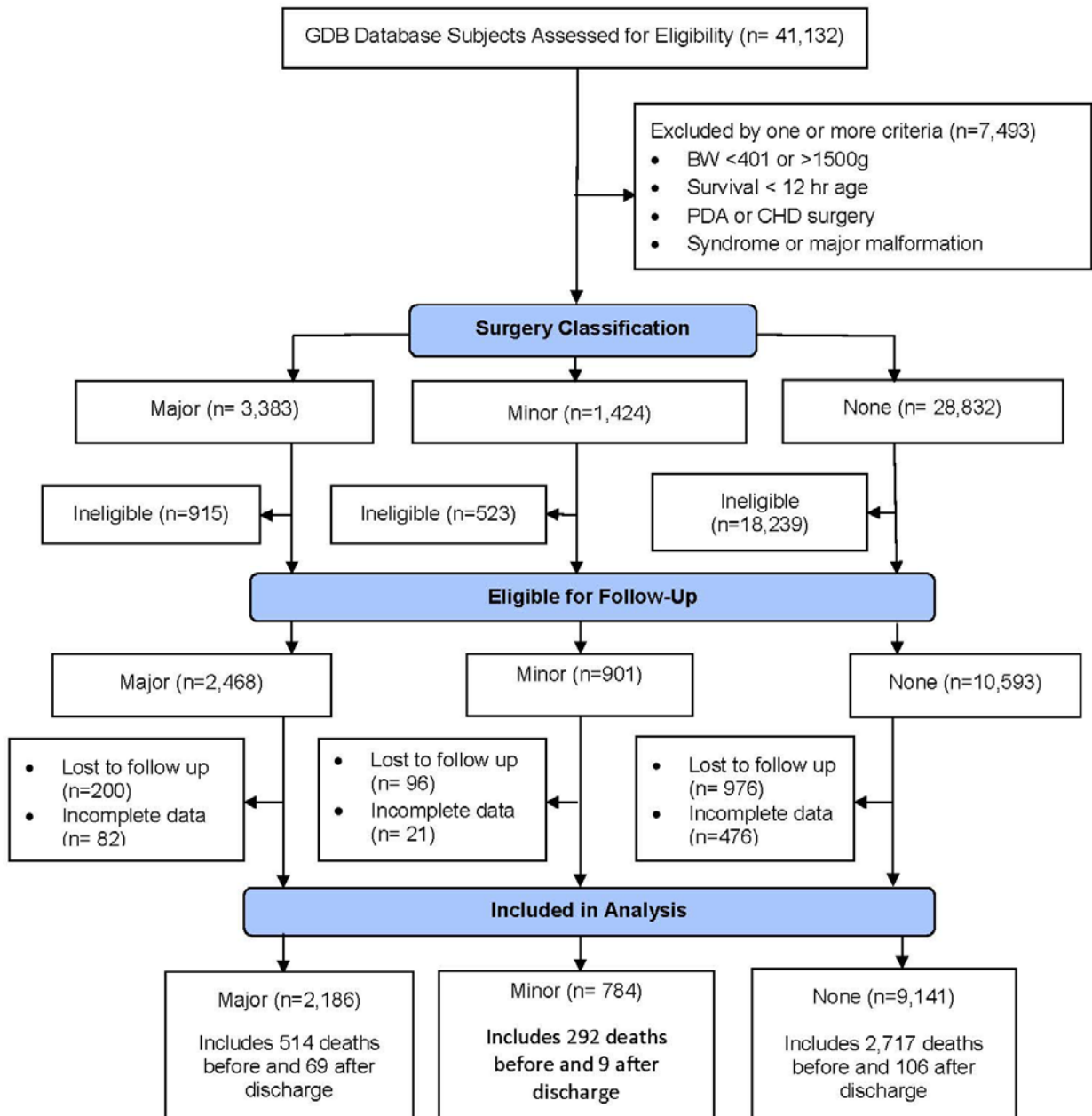
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Patient Flow Diagram



eFigure. Patient Flow Diagram. Eligibility for follow-up evaluation changed during the period studied. Before 2008, patients with birth weights ≤ 1 Kg

were eligible; subsequently, patients who were inborn and whose gestational age was <27 weeks gestation were eligible. Consequently, some patients were not eligible for followup. Among the Major surgery patients, 569 were born before 2008, but had birth weights >1 kg, 49 were born after 2007, but were outborn, 243 were born after 2007, but were ≥ 27 weeks gestational age, and 54 were born after 2007, but were outborn and ≥ 27 weeks gestational age. Among the Minor surgery patients, 360 were born before 2008, but had birth weights > 1 kg, 23 were born after 2007, but were outborn, 130 were born after 2007, but were ≥ 27 weeks gestational age, 9 were born after 2007, but were outborn and had gestational ages ≥ 27 weeks, and 1 was missing gestational age at followup. Among the None surgery patients, 13 780 were born before 2008, but had birth weights > 1 kg, 160 were born after 2007, but were outborn, 3999 were born after 2007, but had gestational ages ≥ 27 weeks, 298 were born after 2007, but were outborn and had gestational ages ≥ 27 weeks, 1 had missing gestational age at followup, and 1 had missing final status information.

eTable 1. Conditions Excluded from Analysis

Chromosomal anomalies

Trisomy 13

Trisomy 18

Trisomy 21

Turner syndrome

Other chromosomal anomalies (includes triploidy, DiGeorge, Klinefelter & Wolf-Hirschhorn syndrome)

Named syndromes, sequences, and associations

Nervous system

Anencephaly

Meningomyelocele ± hydrocephalus

Congenital hydrocephalus

Hydranencephaly

Holoprosencephaly

Myotonic dystrophy/myopathy

Other nervous system anomalies

Cardiovascular

All anomalies

Genitourinary

Bilateral renal agenesis (Potter's syndrome)

Bilateral polycystic, multicystic, or dysplastic kidneys

Obstructive uropathy with congenital hydronephrosis

Exstrophy of the urinary bladder

Other genitourinary anomalies

Bone and skeletal anomalies

Miscellaneous single system anomalies

Inborn errors of metabolism

Other multiple system anomalies (includes conjoined twins, VATER)

Surgery for patent ductus arteriosus

eTable 2. Procedures Classified as Major or Minor^a

Major:

Ventriculostomy
Placement of ventricular reservoir
Placement of ventricular shunt for hydrocephalus
Removal of ventricular shunt
Placement of a subgaleal shunt
Partial resection of brain tumor
Elevation and reconstruction of skull fracture
Craniotomy for abscess drainage; and direct laryngoscopy and bronchoscopy
Burr hole evacuation of subdural hematoma
Resection of encephalocele and occipital scalp
Eye exam under anesthesia
Removal of dacryocystocele
Cataract removal, vitrectomy, lensectomy
Trabeculotomy of both eyes
Eye surgery for cycloplegia-iridial adhesions
Bilateral vitrectomy
Surgery for detached retina
Tracheostomy
Subglottic granuloma reduction
Anterior cricoid split
Placement of nasal stints and drainage of elbow abscess
Resection of cystic adenomatoid malformation
Flexible laryngoscopy under general anesthesia
Bronchoscopy
Micro laryngoscopy and laryngotracheoplasty
Correction of choanal atresia
Repair of cleft lip
Supraglottoplasty
Removal of and replacement of chest tube under general anesthesia
Thoracotomy
Repair of thoracic duct for chylothorax
Thoracic duct ligation and placement of Broviac catheters
Pleurodesis for chylothorax
Pulmonary lobectomy
Resection of pneumatocele
Tracheoesophageal fistula and esophageal atresia repair
Aneurysm ligation
Thoracotomy, exploratory laparotomy and ostomy takedown
Ventricular epicardial pacemaker placement
Surgical removal of retained central catheter from iliac vein to right atrium
Silo placement
Silo closure
Laparotomy
Laparotomy and extraction of meconium plug
Pyloromyotomy
Pyloroplasty
Ileostomy
Ileocectomy
Ileostomy revision and takedown
Jejunostomy
Colostomy
Laparoscopic cholecystotomy
Bowel resection and end-to-end anastomosis
Resection and ileostomy; resection and jejunostomy; placement of drain
Resection of bowel stricture
Resection and repair of bowel perforation

eTable 2. Procedures Classified as Major or Minor (continued)

Ostomy takedown and reanastomosis
 Excision of vitelline omphalomesenteric duct and necrotic bowel
 Appendectomy
 Repair of esophageal perforation
 Repair of gastric perforation
 Repair of colonic perforation
 Diaphragmatic hernia repair
 Hiatal hernia repair
 Fundoplication
 Diaphragmatic plication
 Nissen plication of diaphragm and placement of gastrostomy tube
 Abdominal mesh replacement
 Abdominoplasty
 Abdominal patch closure, abdominal wound debridement and skin closure
 Hartman's pouch
 Open liver biopsy
 Removal of liver hematoma
 Repair of rupture of dome of right lobe of liver
 Drainage of liver abscess and rectal biopsy
 Repair of malrotation
 Reduction of volvulus
 Ladd's procedure
 Omentectomy
 Hemicolectomy
 Colectomy
 Bowel evisceration and reanastomosis
 Duodenal atresia repair with gastrostomy tube placement
 Extensive lysis of adhesions
 Lysis of adhesions and lavage of meconium
 Adrenectomy
 Resection of teratoma
 Biopsy of large intestine
 Rectal biopsy; and debridement of arm abscess
 Rectal irrigation and contrast enema under general anesthesia
 Repair of exstrophy of the bladder
 Radical nephrectomy; and central line placement
 Repair of bladder perforation and T-tube placement
 Urinary diversion
 Renal exploration
 Double nephrostomy and catheter placement
 Nephrostomy
 Orchiopexy (with other procedures)
 Resection of ovarian cyst
 Oophorectomy, lysis of adhesions, aspiration of ovarian cyst
 Nasolabial repair
 Neck resection
 Incision and drainage of neck abscess
 Incision and drainage of axilla abscess with general anesthesia
 Incision and debridement of shoulder mass
 Repair of fascia with retention sutures
 Amputation of forearm
 Amputation below elbow
 Amputation of hand
 Amputation of 4 necrotic digits
 Reattachment of finger tip
 Hand skin graft
 Bilateral lower extremity amputation

eTable 2. Procedures Classified as Major or Minor (continued)

Above knee amputation

Amputation of foot and ankle
Arm surgery for osteomyelitis
Debridement of hand wound
Debridement and graft
Irrigation and debridement of thigh with biopsy of the soft tissue
Arthrotomy and aspiration arthrogram of multiple joints
Wound dehiscence repair
Release of congenital amniotic band

Minor:

Central venous line placement
Venous access port
Cutdown to remove peripherally inserted central catheter
Surgical removal of peripherally inserted central catheter fragment
Surgical removal of broken-off umbilical vein catheter; and tap pericardial effusion
Removal of Broviac catheter
Removal of infected line
Excision of saphenous vein
Extracorporeal membrane oxygenation cannulation
Ventricular tap
Needle aspiration of brain abscess
Incision and drainage of axillary abscess
Incision and drainage of glenohumeral joint abscess
Incision and drainage of antecubital fossa abscess
Incision and drainage of chest wall abscess
Incision and drainage of scrotal abscess
Incision and drainage of left hip
Incision and drainage of thigh abscess
Hip and femur aspiration
Cyst excision
Washout of wound
Repair of ear laceration
Repair of chest wall and back laceration
Wound closure
Laser treatment of granuloma
Laser surgery for elbow hemangioma
Cryotherapy
Diagnostic laparoscopy
Telescopic laryngoscopy
Diagnostic thoracoscopy and tube placement
Removal of laryngeal granulation tissue
Supraglottoplasty (laser)
Subglottic cyst removed
Thoracentesis
Chest tube placement
Pericardial drain
Pericardiocentesis
Pacemaker insertion
Liver biopsy
Rectal biopsy
Gastrostomy and feeding tube placement
Peritoneal and abdominal drain
Gastroschisis repair
Omphalocele repair
Incisional hernia repair
Inguinal hernia repair

eTable 2. Procedures Classified as Major or Minor (continued)

Umbilical hernia repair
Orchiopexy (only)

Hydrocele repair
Testicular torsion repair
Vesicostomy
Nephrostomy tube placement
Removal of bilateral supernumerary digits
Repair of laceration to dorsal aspect wrist and hand
Hip arthrotomy
Hip drain and femoral bone aspiration and arthrotomy
Revision right knee amputation
Surgical debridement and drainage of septic knee
Leg fasciotomy
Amputation of toes
Fascial closure

^a Annotations also indicated when multiple procedures were performed under one episode of general anesthesia and included a procedure that usually is performed under non-general anesthesia. If an infant was exposed to both types of procedure on the same occasion, the infant was classified with the major surgery group. The classifications of selected procedures were changed for sensitivity analyses.

eTable 3. Distribution of Surgical Procedures between Patient Subgroups

Surgical Procedure Anatomical System or Number/Patient	Major Surgery^a	Minor Surgery
Gastrointestinal, column No./row total (%)	1962/2559 (77)	597/2559 (23)
Pulmonary, column No./row total (%)	173/177 (98)	4/177 (2)
Genitourinary, column No./row total (%)	8/14 (57)	6/14 (43)
Head and neck, column No./row total (%)	5/5 (100)	0/5 (0)
Central nervous system, column No./row total (%)	170/172 (99)	2/172 (1)
Ophthalmologic, column No./row total (%)	1021/1022 (100)	1/1022 (0)
Orthopedic, column No./row total (%)	14/20 (70)	6/20 (30)
Other, column No./row total (%)	672/680 (99)	8/680 (1)
Number of procedures/patient		
1, No.	1128	762
2, No.	516	21
≥3, No.	542	1

^aWith or without additional minor surgical procedure

eTable 4. Model 2: Multivariable Logistic Regression Analysis of the Secondary Outcome Neurodevelopmental Impairment among Survivors at 18-22 Months' Corrected Age with Two-Level Surgery Predictor Variable

Variable ^a	Adjusted Odds Ratio		
	Estimate	95% CI	
Surgery vs no surgery	1.31	1.09	1.59
Number of surgeries (for each additional surgery)	1.20	1.10	1.31
Birth weight (for each 250 g increase in weight)	0.68	0.58	0.80
Small-for-gestational-age	1.26	1.09	1.47
Male	1.65	1.43	1.90
Multiple birth cohort	1.32	1.16	1.50
Caucasian	0.79	0.70	0.88
5-min Apgar score ≤ 3	1.27	1.04	1.56
Antenatal corticosteroid exposure	0.82	0.70	0.97
Postnatal corticosteroid exposure	1.43	1.21	1.70
Seizures	2.71	2.12	3.47
Severe intracranial hemorrhage and/or cystic periventricular leukomalacia	2.15	1.80	2.58
Bronchopulmonary dysplasia (supplemental O2 at 36 wk)	1.35	1.15	1.60
Sepsis and/or meningitis	1.21	1.02	1.43
Necrotizing enterocolitis (Bell stage ≥ IIA)	1.11	0.72	1.71
Patent ductus arteriosus, excluding surgically closed patients	1.07	0.95	1.21
Caregiver highest educational level:			
10-12 y vs ≤9 y	0.86	0.68	1.08
>12 y vs ≤9 y	0.64	0.52	0.78

eTable 4. Model 2: Multivariable Logistic Regression Analysis of the Secondary Outcome Neurodevelopmental Impairment among Survivors at 18-22 Months' Corrected Age with Two-Level Surgery Predictor Variable (continued)

Variable ^a	Adjusted Odds Ratio		
	Estimate	95% CI	
Birth year: 2006-2009 vs. 1998-2002 ^b	0.48	0.41	0.56
Inborn	0.76	0.61	0.94
Propensity score- surgery ^c , AOR per 10% increase in the predicted probability	1.03	0.93	1.14

^aNeonatal Research Network center

variable is also included in the model.

^bBirth year variable parameters changed to obtain optimal estimate of confidence interval.

^cIncluded in the PS model were BW, SGA, sex, race, 5-minute Apgar score, ICH, BPD, sepsis and/or meningitis, NEC, PDA, multiple birth cohort, ANS, PNS, highest level of education attained by primary caregiver, birth year, and center.

eTable 5. Model 4: Multivariable Logistic Regression Analysis of the Secondary Outcome Neurodevelopmental Impairment among Survivors at 18-22 Months' Corrected Age with Three-Level Surgery Predictor Variable

Variable ^a	Adjusted Odds Ratio		
	Estimate	95% CI	
Major surgery vs no surgery	1.56	1.26	1.93
Major surgery vs minor surgery	1.47	1.14	1.89
Minor surgery vs no surgery	1.06	0.84	1.35
Number of surgeries (for each additional surgery)	1.15	1.05	1.26
Birth weight (for each 250 g increase in weight)	0.70	0.60	0.81
Small-for-gestational-age	1.33	1.14	1.56
Male	1.78	1.51	2.09
Multiple birth cohort	1.35	1.19	1.54
Caucasian	0.76	0.68	0.86
5-min Apgar score ≤ 3	1.24	1.01	1.51
Antenatal corticosteroid exposure	0.82	0.70	0.96
Postnatal corticosteroid exposure	1.47	1.24	1.75
Seizures	2.66	2.07	3.40
Severe intracranial hemorrhage and/or cystic periventricular leukomalacia	2.07	1.74	2.47
Bronchopulmonary dysplasia (supplemental O2 at 36 wk)	1.32	1.13	1.55
Sepsis and/or meningitis	1.17	0.10	1.37
Necrotizing enterocolitis (Bell stage ≥IIA)	1.07	0.72	1.60
Patent ductus arteriosus, excluding surgically closed patients	1.09	0.96	1.23
Caregiver highest educational level:			
10-12 y vs ≤9 y	0.86	0.68	1.08
>12 y vs ≤9 y	0.64	0.52	0.78

eTable 5. Model 4: Multivariable Logistic Regression Analysis of the Secondary Outcome Neurodevelopmental Impairment among Survivors at 18-22 Months' Corrected Age with Three-Level Surgery Predictor Variable (continued)

Variable ^a	Adjusted Odds Ratio		
	Estimate	95% CI	
Birth year ^b : 2006-2009 vs 1998-2005	0.46	0.40	0.54
Inborn	0.76	0.62	0.95
Propensity score ^c , minor surgery AOR per 10% increase in the predicted probability	0.89	0.73	1.09
Propensity score ^c , major surgery AOR per 10% increase in the predicted probability	1.06	0.96	1.16

variable is also included in the model.
to obtain optimal estimate of confidence interval.

^aNeonatal Research Network center
^bBirth year variable parameters changed
^cIncluded in the PS model were BW, SGA, sex, race, 5-minute Apgar score, ICH, BPD, sepsis and/or meningitis, NEC, PDA, multiple birth cohort, ANS, PNS, highest level of education attained by primary caregiver, birth year, and center.

eTable 6. Demonstration of Propensity Score Achievement of Balanced Distribution of Covariates.

Covariates in the Model	Overall Effect of Surgery Unadjusted	Overall Effect of Surgery Adjusted for the Propensity Scores
	P-Value	P-Value
Male	<.0001	0.6374
Birth weight	<.0001	0.5584
Small-for-gestational-age	<.0001	0.6494
Multiple birth cohort	0.0209	0.9486
5 minute Apgar \leq 3	0.0099	0.6588
Postnatal corticosteroid exposure	<.0001	0.5088
Severe ICH	<.0001	0.0100 ^a , 0.1054 ^b
Bronchopulmonary dysplasia	<.0001	0.8603
Sepsis and/or meningitis	<.0001	0.3517
Necrotizing enterocolitis	<.0001	0.3777 ^c
Patent ductus arteriosus	<.0001	0.8939
Birth year	<.0001	0.9104
Inborn	0.0003	0.1733

To determine how successful the propensity score is in balancing the distribution of the covariates across the surgery groups, we chose key covariates that seem to have a significant association with surgery (major, minor, and no surgery). We regressed each of these covariates on the three-level surgery variable and the propensity score quintiles of major and minor surgery. If the overall surgery effect is not significant, this implies that the covariate is balanced across the three surgery groups. Taking quintiles of the two propensity scores amounts to dividing the entire cohort into 5X5= 25 groups with similar propensity scores of major and minor surgeries. To determine if we have achieved the balancing of covariates across the treatment groups, we compared the means and proportions across the treatment levels for these 25 groups, which we achieved by regressing the covariates on treatment and propensity score quintiles/ propensity scores.

^aAdjusting for the propensity score quintiles shows the surgery effect to be still significant.

^bHowever, adjusting for the propensity scores of major and minor surgery shows the surgery effect to be not significant, indicating that balance is achieved.

^cThe model for NEC did not converge with the propensity score quintiles, so the propensity scores of major and minor surgery were used.