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Predictors of mortality for preterm infants with intraventricular hemorrhage: a population-based study

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Abstract

Purpose—The goal of this longitudinal, population-level study was to examine factors affecting mortality in preterm infants with intraventricular hemorrhage (IVH).

Methods—The study examined patients who were born at 36 weeks estimated gestational age (EGA) or less with a diagnosis of IVH between the years 2005–2014 using data from the New

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Authors' Contributions

R.H.H. performed literature review, study design, data analysis, and drafted the manuscript. A.M. performed data collection and analysis. T.S.C. performed data analysis and critically revised the manuscript. B.S.B. critically revised the manuscript. A.M.M., C.D.S., J.M.S., M.A.O., and D.D.L. performed literature review, study design, and critically revised the manuscript.

Conflict of interest

Dr. Limbrick receives research funds and/or research equipment for unrelated projects from Medtronic, Inc., Karl Storz, Inc., and Microbot Medical, Inc. Dr. Limbrick has received philanthropic equipment contributions for humanitarian relief work from Karl Storz, Inc. and Aesculap, Inc. The authors have no personal, financial, or institutional interest in any of the drugs, materials, or devices described in this article.

Research involving human participants and/or animals

All procedures performed were in accordance with the ethical standards of the Washington University in St. Louis Institutional Review Board and with the 1964 Helsinki declaration and its later amendments. For this type of study formal consent is not required. This article does not contain any studies with animals performed by any of the authors.

Data availability

The data that support the findings of this study are available in the State Inpatient Databases produced by the Healthcare Cost and Utilization Project of the Agency for Healthcare Research and Quality, <http://www.hcup-us.ahrq.gov/sidoverview.jsp>.

York and Nebraska State Inpatient Databases. Potential predictors for mortality were investigated with multivariable survival analysis.

Results—The cohort included 7,437 preterm infants with IVH. All-cause inpatient mortality occurred in 746 (10.0%). The majority of deaths were in infants born at less than 25 weeks EGA (378 or 50.7%) and with birthweight less than 750 g (459 or 61.5%). Mortality was highest for children with grade IV IVH (306/848 or 36.1%), followed by grades III (203/955 or 21.3%), II (103/1,328 or 7.8%), and I (134/4,306 or 3.1%). Hydrocephalus was diagnosed within 6 months in 627 (8.4%) patients, with cerebrospinal fluid shunts required in 237 (3.2%). Shunts were eventually revised in 122 (51.5% of shunts), and 43 (18.1%) had infections. Multivariable Cox survival analyses found male sex (HR 1.3 [95% CI 1.1-1.5]), Asian race (HR 1.5 [1.1-2.2]), lower EGA (HR 9.9 [6.3-15.5] for <25 weeks), higher IVH grade (HR 6.1 [4.9-7.6] for grade IV), gastrostomy (HR 4.0 [2.0-7.7]), tracheostomy (HR 3.5 [1.7-7.1]), and shunt infection (HR 3.2 [1.0-9.9]) to be independently associated with increased mortality risk.

Conclusions—This database is the first of its kind assembled for population-based investigations of long-term neurosurgical outcomes in preterm infants with IVH.

Keywords

State Inpatient Databases; preterm neonates; survival analysis, *ICD-9-CM*

Introduction

Intraventricular hemorrhage (IVH) remains a substantial challenge in the care of preterm infants and is associated with significant neurological morbidity, including cerebral palsy and hydrocephalus [1, 4]. Most studies on IVH outcomes have relied on single-institution data, collaborative networks, or patient registries, but there is a dearth of longitudinal, population-level data regarding IVH [8, 17, 23, 25, 34, 43]. Few studies have investigated the long-term neurosurgical outcomes of infants affected with IVH, such as shunt complications [2, 9, 10, 21, 29, 30, 39, 40]. Several studies have made use of the Nationwide Inpatient Sample (NIS) and Kids' Inpatient Database (KID) which, while providing a representative sample of national inpatient discharges, have the important limitation of only capturing a single admission and therefore cannot follow outcomes longitudinally across subsequent hospitalizations [3, 7, 18, 28, 36].

By providing data on all inpatient admissions in a given state and supplying an encrypted identifier to locate follow-up admissions, the State Inpatient Databases (SID) fill a critical void in this important field [15, 16, 45]. Compared to smaller single- and multi-institution reports, the SID provide a larger sample of patients treated at all types of hospitals rather than just tertiary and quaternary referral centers. Additionally, the ability to track admissions over time allows investigations of long-term care (e.g. neurosurgical management) and delayed outcomes not previously explored in population-based IVH studies. This initial paper using the SID-based IVH database focuses on predictors of mortality for preterm infants diagnosed with IVH in New York and Nebraska.

Methods

Data Source

Data were retrieved from the SID produced by the Healthcare Cost and Utilization Project (HCUP) of the Agency for Healthcare Research and Quality (<http://www.hcup-us.ahrq.gov/sidoverview.jsp>) [46]. The SID are administrative databases containing billing information including diagnoses and procedures from nonfederal hospital admissions in participating states. Some states include an encrypted patient identifier to link hospitalizations over time, and the New York and Nebraska SIDs are unique in that their versions of the identifier are robust for newborns thus permitting longitudinal assessment of outcomes for preterm infants with IVH. This study was considered exempt by the Washington University Human Research Protection Office.

Inclusion/Exclusion Criteria

International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes (Table 1) were used to identify patients in New York or Nebraska with a diagnosis of IVH (diagnosis codes 772.11-772.14) who were born at 36 weeks estimated gestational age (EGA) or less (diagnosis codes 765.21-765.28), and who were younger than 6 months of age between 2005-2014. The record identified in this manner was designated the “index admission”. For patients who were not coded for IVH on their birth hospitalization, the encrypted identifier was used to link to a prior birth record. Nine hundred and sixty-six individuals were excluded from the database due to missing the encrypted identifier, and 1,642 were excluded for missing EGA or IVH grade. An additional 454 patients were excluded because their home state was different from the state where they had their index admission, since these patients may be readmitted to an out-of-state hospital not included in the New York or Nebraska SIDs.

Outcome and Predictor Variables

The primary endpoint in this study was mortality at any point during the entire follow-up duration. *ICD-9-CM* codes for a number of predictor variables and potential confounders are shown in Table 1. Based on diagnosis codes, EGA was grouped into <25, 25-26, 27-28, 29-30, 31-32, or 33-36 weeks. Similarly, birthweight was categorized as <750, 750-999, 1000-1249, 1250-1499, 1500-1999, and 2000 g or over. IVH grade was defined as I through IV by the Papile system [27]. Variables preexisting in the SID included sex, race, and hospital length of stay. Intensive care unit (ICU) stay during the index admission was defined by revenue center codes (0174-0175 for neonatal ICU, 0203 for pediatric ICU, 0200-0202 and 0206-0209 for general ICU). Hospital characteristics including urban or rural location, teaching status, and number of short-term beds were collected from the American Hospital Association annual survey. Hospital IVH and preterm birth volumes were calculated as average number of cases per year of available data. Additional variables created included hydrocephalus diagnosed in the first 6 months of life, permanent cerebrospinal fluid (CSF)-diverting shunt, shunt revision, and shunt infection (see Table 1 for details). Endoscopic third ventriculostomies were not identified due to previously noted ambiguity in *ICD-9-CM* coding for this procedure [22].

Comorbidities

The impact of various comorbidities on outcomes was evaluated using categories identified in the complex chronic conditions (CCCs) [12]. The CCCs include diagnoses relevant to pediatric populations (e.g. respiratory malformations, chronic respiratory disease, and cystic fibrosis make up the respiratory category; heart and great vessel malformations, cardiomyopathies, conduction disorders, and dysrhythmias make up the cardiovascular category) and have been used previously to study pediatric neurosurgical outcomes [16, 33, 34]. In this categorization, comorbidities are described as neuromuscular, cardiovascular, respiratory, renal, gastrointestinal, hematologic or immunologic, metabolic, other congenital or genetic defect, or malignancy. This study used a modified version of the CCCs which redefines the neuromuscular and malignancy categories to exclude indications for CSF shunts [13, 36]. In agreement with previous hydrocephalus studies, children were categorized as having no CCCs (excepting hydrocephalus) or one or two or more CCCs [35, 37]. All CCCs were identified during the index admission. Additionally, dates of tracheostomy and gastrostomy procedures were recorded, as these have been identified as relevant to hydrocephalus management in previous studies [32, 33].

Statistical Analysis

All data management and analyses were performed using SAS Enterprise Guide 7.1 (SAS Institute Inc., Cary, NC). Descriptive statistics were used to summarize the demographic and clinical characteristics of the study cohort. Cells with frequencies less than or equal to 10 were suppressed to protect patient confidentiality [15, 16]. Univariate and multivariable Cox proportional hazards models were used to study predictors of overall mortality in the population. Subjects were censored if they had not experienced the event by the end of the study period. Gastrostomy, tracheostomy, CSF shunt, shunt revision, and shunt infection were treated as time-dependent covariates, because these variables' values could change during the study period. For example, the model compares hazards among children who do and do not have shunts at a given point in time, rather than among children who will or will not ever have a shunt.

Potential predictors included *a priori* in the multivariable model were sex, EGA, IVH grade, and presence of a CSF shunt. Additional variables were evaluated for inclusion in the model using stepwise regression with criterion for entry of $p \leq 0.05$ and criterion for removal of $p > 0.05$ [33]. All hazard ratios (HR) were presented with 95% confidence intervals (CI). Functional forms of continuous covariates and the proportional hazards assumption for all variables were evaluated with the “assess” statement within the “phreg” procedure [24]. Outliers were identified by plotting likelihood displacement scores to assess influence on each model. All tests of significance were conducted at the 0.05 level.

Results

Patient Characteristics

Baseline characteristics for the 7,437 children in the cohort are shown in Table 2. Median follow-up duration was 4.1 (interquartile range [IQR] 1.6-6.9, max 10.5) years. The patients were predominantly male (3,980 or 53.5%) and white (2,445 or 32.9%). Mortality due to

any cause occurred in 746 (10.0%), and the median age at death was 9 (IQR 3-23) days. The majority of deaths were in infants born at less than 25 weeks EGA (378 or 50.7%) and with birthweight less than 750 g (459 or 61.5%). IVH grades were I in 4,306 (57.9%), II in 1,328 (17.9%), III in 955 (12.8%), and IV in 848 (11.4%). One CCC was found in 2,803 (37.7%) patients while 1,581 (21.3%) had two or more CCCs. The most common CCCs were cardiovascular (3,248 or 43.7%) and respiratory (1,928 or 25.9%). Out of the entire cohort, gastrostomy was performed in 186 (2.5%), and tracheostomy in 103 (1.4%). Hydrocephalus was diagnosed within 6 months of index admission in 627 (8.4%) patients, and 237 (3.2%) received CSF shunts. Shunts were eventually revised in 122 (51.5% of shunts), and 43 (18.1% of shunts) had infections.

Hospital characteristics and features of the index admission are summarized in Table 3. The vast majority of the cohort was treated in a teaching hospital (6,816 or 91.7%) in an urban location (7,418 or 99.7%). Most resided in New York (7,007 or 94.2%) rather than Nebraska, and no differences by state were observed in any of the variables investigated. Median hospital length of stay for the index admission was 44 (IQR 23-76) days. ICU stays occurred during index admissions for 6,664 (89.6%) patients, and during subsequent readmissions for 918 (12.3%). Eight hundred and seventy-one (11.7%) patients had ICU stays during both index and readmissions.

Hydrocephalus Treatment and Mortality Rates

Rates of CSF shunts and shunt complications cross-tabulated by IVH grade are shown in Table 4. Values are shown as frequency and percentage of subjects in each IVH grade experiencing the event. CSF shunts were most frequently used in grade IV IVH (118/848 or 13.9%), followed by grades III (85/955 or 8.9%), II (20/1,328 or 1.5%), and I (14/4,306 or 0.3%). Of the 6691 patients who were alive at the end of follow-up, CSF shunt rates were 111/542 (20.5%) for grade IV, 82/752 (10.9%) for grade III, 18/1225 (1.5%) for grade II, and 14/4172 (0.3%) for grade I.

Mortality rates cross-tabulated by IVH grade are shown in Table 5 for the entire follow-up duration, index admission, readmissions, and within 30 and 90 days of birth. Mortality was highest for children with grade IV IVH (306/848 or 36.1%), followed by grades III (203/955 or 21.3%), II (103/1,328 or 7.8%), and I (134/4,306 or 3.1%). Kaplan-Meier survival curves showing days from index admission to death are shown in Figure 1. Most of the deaths occurred within 90 days of index admission, and the lower two categories for EGA (378/1,080 [35.0%] for <25 weeks, 207/1,358 [15.2%] for 25-26 weeks) and birthweight (459/1,427 [32.2%] for <750g, 157/1,454 [10.8%] for 750-999g) carried particularly high mortality rates. Significant differences were detected in each set of curves by the log rank test ($p < 0.001$).

Predictors of Overall Mortality

Results of univariate (unadjusted) Cox proportional hazards survival analyses are shown in Table 6. Each variable in the table is shown with its HR of death compared either to the reference group or to not having the risk factor. Without controlling for other factors, male sex (HR 1.3 [95% CI 1.1-1.5]), lower EGA (HR 20.5 [13.2-31.8] for <25 weeks), lower

birthweight (HR 13.1 [8.5-20.0] for <750g), higher IVH grade (HR 14.3 [11.7-17.6] for grade IV), gastrostomy (HR 8.5 [5.4-13.4]), tracheostomy (HR 11.9 [7.4-19.1]), CSF shunt (HR 2.6 [1.5-4.7]), shunt revision (HR 7.4 [3.6-15.1]), and shunt infection (HR 10.6 [3.9-28.8]) were associated with increased mortality risk. Although several of the CCCs were associated with reduced risk, this was attributed to bias due to the infants having survived long enough to develop these ‘chronic’ conditions, and was not explored further in the present study.

Next, multivariable Cox survival analyses were performed with sex, EGA, IVH grade, and presence of CSF shunt included *a priori* in the model (Table 7). Stepwise regression was used to evaluate additional variables in Table 6 for inclusion. Birthweight was removed from the final model due to significant collinearity with EGA as tested by the variance inflation factor. After adjusting for all other variables in the model, male sex (HR 1.3 [1.1-1.5]), Asian race (HR 1.5 [1.1-2.2]), lower EGA (HR 9.9 [6.3-15.5] for <25 weeks), higher IVH grade (HR 6.1 [4.9-7.6] for grade IV), gastrostomy (HR 4.0 [2.0-7.7]), tracheostomy (HR 3.5 [1.7-7.1]), and CSF shunt infection (HR 3.2 [1.0-9.9]) were significantly associated with increased mortality risk.

Discussion

This article represents the first population-level longitudinal study of IVH with up to 10.5 years of follow-up data on over 7,400 preterm infants with IVH in New York and Nebraska. Our multivariable survival analysis identified a number of variables as independently predictive of all-cause inpatient mortality for preterm infants with IVH, including male sex, Asian race, lower EGA, higher IVH grade, gastrostomy, tracheostomy, and CSF shunt infection.

Our finding of shunt infection as an independent risk factor for mortality is further accentuated by the fact that 43 out of the 237 shunts (18.1%) were complicated by infections. This is higher than the 3-11% that has been reported in recent literature for hydrocephalus of all etiologies [19, 31-33], but is more consistent with previous reports for IVH-related hydrocephalus specifically [5, 6, 14, 43, 44]. One possible explanation for the apparently higher shunt infection rate in this cohort is that previous studies have used more strict criteria for infection (e.g. CSF culture-positive) compared to the coding-based definition used here. Furthermore, our *ICD-9-CM* code for shunt infection (996.63, ‘infection due to nervous system device, implant, or graft’) may in fact be nonspecific or prone to miscoding. Nevertheless, this is a potentially significant finding that should be explored further to reduce etiology-specific infection rates. Shunt infections may indeed be more common after IVH in preterm newborns compared to other types of hydrocephalus, and young age at shunt placement is a previously observed risk factor [32, 34, 38, 42]. Because the literature on shunt infections for IVH-related hydrocephalus in children is surprisingly limited, and because the rate may be as high as 18.1%, future work should search for any modifiable risk factors in this high-risk subpopulation.

We identified IVH grade as an independent predictor of mortality, as well as particularly high mortality rates for children with grades III (21.3%) and IV (36.1%) hemorrhage. The

majority of infants with high-grade IVH who die do so in the neonatal period (median age at death was 9 [IQR 3-23] days in this study), presumably with withdrawal of support or redirection of care. We are unable to determine which patients underwent withdrawal of care within the SID, so the cause of death in these subjects (complications related to high-grade IVH vs. withdrawal of care) remains unclear. Although we included presence of a CSF shunt *a priori* in the multivariable model, we found no clear relationship between shunt implantation itself and mortality (adjusted HR 0.7 [0.4-1.5], $p=0.4$).

Previous studies on mortality rates and risk factors in preterm infants have not explored the potential added risks of neurosurgical intervention. In the Australian and New Zealand Neonatal Network, analysis of 11,498 high-risk infants found that those with lower EGA and male sex had increased odds of death [11]. Reports from the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Neonatal Research Network, which included over 34,000 infants between 1993 and 2012, have shown increased mortality rates and rates of IVH with lower EGA [39, 40]. A study using the Korean Neonatal Network found a 9.6% total mortality rate and a distribution of IVH grades similar to ours in 2,386 very low birthweight infants [2]. Results from the present study are in agreement with these prior findings, and extend the analysis to include additional variables of potential concern to neurosurgeons. Importantly, CSF shunt infection was associated with more than a 3-fold increase in mortality risk after adjusting for other factors, a finding that further emphasizes the need for improved prevention measures [19, 20]. Although gastrostomy and tracheostomy were included in the database as risk factors for shunt complications, they were found to be independently predictive of mortality. Finally, Asian race has been previously reported to reduce risk for all types of pediatric hydrocephalus [41], so the increased mortality rate shown here warrants further investigation in future studies.

Two major reports in the literature have used cross-sectional population-level data to examine trends and disparities in the care of preterm infants with IVH [7, 18]. Our study has extended the follow-up duration from a single admission to up to 10.5 years. It should be emphasized that the NIS and KID, which were the data sources for the previous studies, sample the SIDs from individual states to develop the nationally representative datasets. Therefore, while these prior analyses reflect the broader experience across the entire United States, our study narrows the cohort to two states but features a longitudinal design. As expected, we found similar rates of IVH, hydrocephalus, CSF shunts, and mortality by IVH grade [7]. While Christian et al. focused on trends over the study period, we added several new variables including the CCCs, gastrostomy, and tracheostomy in a multivariable prediction model for overall mortality. In a separate paper, the same group built multivariable models for preterm infants with IVH focusing on the impact of racial and economic disparities on various treatment outcomes [18]. Their model for mortality also identified lower EGA and higher IVH grade as significant risk factors. Our study confirms these results with a longer follow-up duration and explores the additional impact of CSF shunting on mortality.

The primary limitation of this study is its reliance on an administrative database and *ICD-9-CM* coding. Billing data are imperfect with different coding practices between hospitals and varying levels of miscoding. Furthermore, although we chose our study cohort based on a

coded neonatal diagnosis of IVH, some heterogeneity remains in this population. For example, IVH can occur in near-term infants due to choroid plexus hemorrhage or vascular malformation, or the hemorrhage may be related to birth trauma. As noted previously, endoscopic third ventriculostomies were not identified due to ambiguous *ICD-9-CM* coding. Another important limitation is that our study population included only infants born in New York and Nebraska, both states with lower preterm birth rates than the national average [26]. Therefore, while our restricted cohort allowed us to use a longitudinal design, generalizability of our results to newborns in other states or countries is necessarily limited. Finally, because the SID only contain data on inpatient admissions, we do not have information on mortality rates outside of a hospital. Therefore, the true mortality rate is likely higher than what is reported here, especially for infants who survive their index hospitalization or whose families seek a palliative course at home.

In conclusion, we have described the first longitudinal population-level study of IVH neurosurgical outcomes with up to 10.5 years of follow-up data on over 7,400 preterm infants with IVH in the United States. Variables that were identified as independently predictive of mortality included male sex, Asian race, lower EGA, higher IVH grade, gastrostomy, tracheostomy, and CSF shunt infection. Future analyses will focus on subpopulations including those with CSF shunts or high-grade IVH.

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Fig. 1. Kaplan-Meier survival curves showing days from index admission to death for the entire cohort (top left), by IVH grade (top right), by EGA (bottom left), and by birthweight (bottom right). Tick marks indicate censoring due to end of follow-up. Significant differences were detected in each set of curves by the log rank test ($p < 0.001$)

Table 1:Variables created from the SID and corresponding *ICD-9-CM* codes

Variable	Description	<i>ICD-9-CM</i> codes ^a
Preterm birth	Extreme immaturity (with birthweight)	765.00-765.09
	Other preterm infants (with birthweight)	765.10-765.19
Estimated gestational age	36 completed weeks or less	765.21-765.28
Intraventricular hemorrhage	Grade I	772.11
	Grade II	772.12
	Grade III	772.13
	Grade IV	772.14
Tracheostomy	Temporary/permanent tracheostomy	PR 31.1, 31.21, 31.29; V 44.0
Gastrostomy	--	PR 43.11, 43.19; V 44.1
Hydrocephalus	Communicating hydrocephalus	331.3
	Obstructive hydrocephalus	331.4
	Congenital hydrocephalus ('hydrocephalus in newborn')	742.3
CSF shunt	Extracranial ventricular shunt	PR 02.31-02.35, 02.39
CSF shunt revision	Revision/removal/irrigation of ventricular shunt	PR 02.41-02.43
CSF shunt infection	Infection due to nervous system device/implant/graft	996.63

^a All *ICD-9-CM* codes are diagnosis codes unless specified as procedure (PR) or V codes.

Table 2:Characteristics of the study cohort ($N = 7,437$)

Variable	n (%) ^a
Expired ^b	746 (10.0)
Sex	
Male	3980 (53.5)
Female	3457 (46.5)
Race	
White	2445 (32.9)
Black	1920 (25.8)
Hispanic	905 (12.2)
Asian or Pacific Islander	270 (3.6)
Other	1897 (25.5)
Estimated gestational age	
<25 weeks	1080 (14.5)
25-26 weeks	1358 (18.3)
27-28 weeks	1273 (17.1)
29-30 weeks	1301 (17.5)
31-32 weeks	1414 (19.0)
33-36 weeks	1011 (13.6)
Birthweight	
Missing	238 (3.2)
<750g	1427 (19.2)
750-999g	1454 (19.6)
1,000-1,249g	1119 (15.0)
1,250-1,499g	1052 (14.1)
1,500-1,999g	1390 (18.7)
2,000g and over	757 (10.2)
IVH Grade	
I	4306 (57.9)
II	1328 (17.9)
III	955 (12.8)
IV	848 (11.4)
Complex chronic conditions	
None (excepting hydrocephalus)	3053 (41.0)
One	2803 (37.7)
Two or more	1581 (21.3)
Neuromuscular	12 (0.2)
Cardiovascular	3248 (43.7)
Respiratory	1928 (25.9)
Renal	220 (3.0)
Gastrointestinal	84 (1.1)

Variable	<i>n</i> (%) ^a
Hematologic or immunologic	51 (0.7)
Metabolic	401 (5.4)
Other congenital or genetic defect	177 (2.4)
Malignancy	114 (1.5)
Gastrostomy	186 (2.5)
Tracheostomy	103 (1.4)
Hydrocephalus ^c	627 (8.4)
CSF shunt	237 (3.2)
CSF shunt revision	122 (1.6)
CSF shunt infection	43 (0.6)

^aValues are frequency (percent of entire cohort).

^bMortality at any point during entire follow-up duration (1 to 10.5 years).

^cHydrocephalus diagnosis in the first six months of life.

Table 3:Hospital and index admission characteristics ($N = 7,437$)

Variable	<i>n</i> (%) ^a
Hospital characteristics	
State – Nebraska	430 (5.8)
State – New York	7007 (94.2)
Location – Urban	7418 (99.7)
Location – Rural	19 (0.3)
Teaching hospital	6816 (91.7)
Number of short-term beds – median (IQR)	635 (461 – 895)
IVH volume (cases/year) – median (IQR)	40 (16 – 57)
Preterm birth volume (cases/year) – median (IQR)	427 (239 – 569)
Hospital length of stay (days) – median (IQR)	44 (23 – 76)
ICU stay during index admission	6664 (89.6)

^aValues are frequency (percent of entire cohort) unless otherwise indicated.

IQR, interquartile range; ICU, intensive care unit.

Table 4:Rates of CSF shunts and shunt complications by IVH grade ($N = 7,437$)^a

IVH grade (<i>n</i>)	CSF Shunt	Shunt Revision	Revisions per shunt	Shunt Infection	Infections per shunt
I (4306)	14 (0.3)	-- ^b	-- ^b	-- ^b	-- ^b
II (1328)	20 (1.5)	-- ^b	-- ^b	-- ^b	-- ^b
III (955)	85 (8.9)	40 (4.2)	0.47	11 (1.2)	0.13
IV (848)	118 (13.9)	70 (8.3)	0.59	26 (3.1)	0.22

^a All values are frequency (percent of IVH grade).^b Suppressed due to cell size of 10 or less.

Table 5:Mortality rates by IVH grade at various time-points ($N = 7,437$)^a

IVH grade (n)	Total mortality	Index admission	Readmission	30 days	90 days
I (4306)	134 (3.1)	114 (2.6)	20 (0.5)	90 (2.1)	117 (2.7)
II (1328)	103 (7.8)	95 (7.2)	-- ^b	71 (5.3)	92 (6.9)
III (955)	203 (21.3)	191 (20.0)	12 (1.3)	164 (17.2)	190 (19.9)
IV (848)	306 (36.1)	297 (35.0)	-- ^b	257 (30.3)	286 (33.7)
Total (7437)	746 (10.0)	697 (9.4)	49 (0.7)	582 (7.8)	685 (9.2)

^a All values are frequency (percent of IVH grade).^b Suppressed due to cell size of 10 or less.

Table 6:Predictors of overall mortality, results from unadjusted survival analysis ($N = 7,437$)

Variable	Expired, n (%) ^a	Alive, n (%) ^a	Unadjusted HR (95% CI)	p -value
Total	746 (10.0)	6691 (90.0)		
Sex				
Male	443 (59.4)	3537 (52.9)	1.3 (1.1 – 1.5)	0.0007
Female	303 (40.6)	3154 (47.1)	Referent	
Race				
White	233 (31.2)	2212 (33.1)	Referent	
Black	200 (26.8)	1720 (25.7)	1.1 (0.9 – 1.3)	0.37
Hispanic	78 (10.5)	827 (12.4)	0.9 (0.7 – 1.2)	0.40
Asian or Pacific Islander	33 (4.4)	237 (3.5)	1.3 (0.9 – 1.9)	0.17
Other	202 (27.1)	1695 (25.3)	1.1 (0.9 – 1.4)	0.24
Estimated gestational age				
<25 weeks	378 (50.7)	702 (10.5)	20.5 (13.2 - 31.8)	<0.0001
25-26 weeks	207 (27.7)	1151 (17.2)	7.8 (5.0 – 12.2)	<0.0001
27-28 weeks	75 (10.1)	1198 (17.9)	2.9 (1.8 - 4.7)	<0.0001
29-30 weeks	40 (5.4)	1261 (18.8)	1.5 (0.9 – 2.5)	0.14
31-32 weeks	25 (3.3)	1389 (20.8)	0.8 (0.5 – 1.5)	0.58
33-36 weeks	21 (2.8)	990 (14.8)	Referent	
Birthweight				
Missing	13 (1.7)	225 (3.3)	1.9 (1.0 – 3.8)	0.07
<750g	459 (61.5)	968 (14.5)	13.1 (8.5 – 20.0)	<0.0001
750-999g	157 (21.0)	1297 (19.4)	3.9 (2.5 – 6.0)	<0.0001
1,000-1,249g	49 (6.6)	1070 (16.0)	1.5 (0.9 – 2.5)	0.11
1,250-1,499g	26 (3.5)	1026 (15.3)	0.8 (0.5 – 1.5)	0.56
1,500-1,999g	20 (2.7)	1370 (20.5)	0.5 (0.3 – 0.9)	0.02
2,000g and over	22 (3.0)	735 (11.0)	Referent	
IVH Grade				
I	134 (18.0)	4172 (62.4)	Referent	
II	103 (13.8)	1225 (18.3)	2.5 (2.0 – 3.3)	<0.0001
III	203 (27.2)	752 (11.2)	7.6 (6.1 – 9.5)	<0.0001
IV	306 (41.0)	542 (8.1)	14.3 (11.7 – 17.6)	<0.0001
Complex chronic conditions				
None (excepting hydrocephalus)	300 (40.2)	2753 (41.1)	Referent	
One	331 (44.4)	2472 (37.0)	1.2 (1.0 – 1.4)	0.03
Two or more	115 (15.4)	1466 (21.9)	0.7 (0.6 – 0.9)	0.002
Neuromuscular	-- ^e	11 (0.2)	0.8 (0.1 – 5.7)	0.83
Cardiovascular	377 (50.5)	2871 (42.9)	1.3 (1.1 – 1.5)	0.0002

Variable	Expired, <i>n</i> (%) ^a	Alive, <i>n</i> (%) ^a	Unadjusted HR (95% CI)	<i>p</i> -value
Respiratory	120 (16.1)	1808 (27.0)	0.5 (0.4 – 0.6)	<0.0001
Renal	28 (3.8)	192 (2.9)	1.3 (0.9 – 1.9)	0.19
Gastrointestinal	-- ^e	74 (1.1)	1.2 (0.6 – 2.2)	0.61
Hematologic or immunologic	-- ^e	50 (0.7)	0.2 (0.0 – 1.3)	0.09
Metabolic	31 (4.2)	370 (5.5)	0.7 (0.5 – 1.1)	0.11
Other congenital or genetic defect	26 (3.5)	151 (2.3)	1.5 (1.0 – 2.2)	0.04
Malignancy	-- ^e	110 (1.6)	0.3 (0.1 – 0.9)	0.03
Gastrostomy ^b	20 (2.7)	166 (2.5)	8.5 (5.4 – 13.4)	<0.0001
Tracheostomy ^b	18 (2.4)	85 (1.3)	11.9 (7.4 – 19.1)	<0.0001
Hydrocephalus ^c	74 (9.9)	553 (8.3)	1.2 (0.9 – 1.5)	0.18
CSF shunt ^b	12 (1.6)	225 (3.4)	2.6 (1.5 – 4.7)	0.001
CSF shunt revision ^b	-- ^e	113 (1.7)	7.4 (3.6 – 15.1)	<0.0001
CSF shunt infection ^b	-- ^e	39 (0.6)	10.6 (3.9 – 28.8)	<0.0001
Hospital characteristics				
State – Nebraska	40 (5.4)	390 (5.8)	0.9 (0.7 – 1.3)	0.66
State – New York	706 (94.6)	6301 (94.2)	Referent	
Location – Urban	746 (100.0)	6672 (99.7)	Referent	
Location – Rural	0	19 (0.3)	n/a	n/a
Teaching hospital	681 (91.3)	6135 (91.7)	1.0 (0.7 – 1.2)	0.69
Number of short-term beds ^d	635 (461 – 840)	635 (461 – 895)	1.0 (1.0 – 1.0)	0.46
IVH volume (cases/year) ^d	43 (16 – 57)	40 (16 – 57)	1.0 (1.0 – 1.0)	0.59
Preterm birth volume (cases/year) ^d	427 (239 – 569)	427 (239 – 569)	1.0 (1.0 – 1.0)	0.15
ICU stay during index admission	681 (91.3)	5983 (89.4)	1.2 (1.0 – 1.6)	0.11

^aValues are frequency (percent of mortality status) unless otherwise indicated.

^bVariable treated as a time-dependent covariate.

^cHydrocephalus diagnosis in the first six months of life.

^dValues are median (interquartile range).

^eSuppressed due to cell size of 10 or less.

HR, hazard ratio; ICU, intensive care unit; n/a, not applicable.

Table 7:Predictors of overall mortality, results from multivariable survival analysis ($N = 7,437$)

Variable	Adjusted HR (95% CI)	p-value
Sex		
Male	1.3 (1.1 – 1.5)	0.001
Female	Referent	
Race		
White	Referent	
Black	0.9 (0.7 – 1.0)	0.11
Hispanic	0.8 (0.6 – 1.1)	0.13
Asian or Pacific Islander	1.5 (1.1 – 2.2)	0.03
Other	1.0 (0.8 – 1.2)	0.99
Estimated gestational age		
<25 weeks	9.9 (6.3 – 15.5)	<0.0001
25-26 weeks	4.4 (2.8 – 6.9)	<0.0001
27-28 weeks	2.0 (1.2 – 3.2)	0.007
29-30 weeks	1.3 (0.8 – 2.2)	0.32
31-32 weeks	0.9 (0.5 – 1.6)	0.72
33-36 weeks	Referent	
IVH Grade		
I	Referent	
II	1.5 (1.1 – 1.9)	0.004
III	3.8 (3.0 – 4.8)	<0.0001
IV	6.1 (4.9 – 7.6)	<0.0001
Gastrostomy ^a	4.0 (2.0 – 7.7)	<0.0001
Tracheostomy ^a	3.5 (1.7 – 7.1)	0.0004
CSF shunt ^a	0.7 (0.4 – 1.5)	0.39
CSF shunt infection ^a	3.2 (1.0 – 9.9)	0.04

^aVariable treated as a time-dependent covariate.

HR, hazard ratio.