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ORIGINAL PAPER

Time-to-event analysis of surgically treated posthemorrhagic hydrocephalus in preterm infants: a single-institution retrospective study

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Abstract
Purpose The purpose of this study is to report time points relevant to the neurosurgical management of posthemorrhagic hydrocephalus (PHH).
Methods Data were collected retrospectively on 104 preterm infants with intraventricular hemorrhage (IVH) who received neurosurgical intervention for PHH at St. Louis Children's Hospital from 1994 to 2016. Kaplan-Meier curves were constructed for various endpoints.
Results IVH grade on head ultrasound obtained through routine clinical care was II, III, and IV in 5 (4.8%), 33 (31.7%), and 66 (63.5%) of the patients, respectively. Neither IVH size nor location appeared to affect development of PHH. Days from birth to IVH, ventriculomegaly, temporizing neurosurgical procedure (TNP), and permanent neurosurgical intervention were 2.0 (95% CI 1.7–2.3), 3.0 (2.5–3.5), 24.0 (22.2–25.8), and 101.0 (90.4–111.6), respectively. Grades III and IV IVH did not differ in age at IVH diagnosis (X^2 (1 d.f.) = 1.32, p = 0.25), ventriculomegaly (X^2 = 0.73, p = 0.40), TNP (X^2 = 0.61, p = 0.43), or permanent intervention (X^2 = 2.48, p = 0.17). Ventricular reservoirs and ventriculosubgaleal shunts were used in 71 (68.3%) and 30 (28.8%), respectively. Eighty (76.9%) of the patients ultimately received a VPS. Five (4.8%) underwent a primary endoscopic third ventriculostomy (ETV), and two (1.9%) had ETV for a revision procedure. Four of the seven ETVs had choroid plexus cauterization.
Conclusions Although most infants who develop IVH and ventriculomegaly will do so within a few days of birth, at-risk infants should be observed for at least 4 weeks with serial head ultrasounds to monitor for PHH requiring surgery.

Keywords Intraventricular hemorrhage · Ventriculomegaly · Ventriculoperitoneal shunt · Temporizing neurosurgical procedure

Introduction

Intraventricular hemorrhage (IVH) remains a serious challenge in the care of preterm infants and is associated with significant morbidities, including cognitive deficits, cerebral palsy, and vision and hearing impairment [1]. The incidence of IVH is well documented, and 25–28% of infants with grade III and IV IVH develop posthemorrhagic hydrocephalus (PHH) during their initial admission [6, 11, 35, 36]. Even with appropriate intervention, children with PHH have chronic neurological deficits and poor developmental outcomes [3, 32].

Initial management of PHH frequently utilizes temporizing neurosurgical procedures (TNP) such as ventricular reservoirs (VRs) or ventriculosubgaleal shunts (VSGS) [12, 17, 27]. Permanent long-term surgical options for PHH include placement of a ventriculoperitoneal shunt (VPS) or endoscopic third ventriculostomy (ETV) with or without choroid plexus

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cauterization. These surgical procedures and their implementation have been well documented by a number of groups over the years [15, 39, 41].

While a number of studies have examined the timing of IVH development in preterm neonates [2, 4, 8–10, 18–20, 24, 33, 38], the few that have focused on the time-course of PHH included only a small number of subjects who developed the condition [14, 22, 26, 37]. Understanding the temporal profile of this disease may elucidate the optimal diagnosis and treatment timeframe and help improve clinical management. This study examined the timing of IVH, PHH, and surgical treatment in affected preterm infants.

Methods

Patient population

This study was approved by the Washington University in St. Louis Human Research Protection Office and is in accordance with the 1964 Helsinki declaration and its later amendments.

Data were collected retrospectively on all preterm infants (estimated gestational age at birth [EGA] ≤ 34 weeks) admitted to St. Louis Children's Hospital (SLCH) from 1994 to 2016 with a diagnosis of IVH, and who required a neurosurgical procedure to treat PHH either during or after their NICU course. Standard neurosurgical care of preterm infants with IVH and PHH at SLCH has been detailed in a previous article [15]; though the current study and the previous report investigate different aspects of PHH management, there is some overlap in the subjects analyzed (54 of 104 subjects). Among these infants, head ultrasound (HUS) examinations were obtained in the setting of abrupt clinical change or acute event requiring resuscitation (e.g., chest compressions or epinephrine use). In infants without acute clinical status changes, HUS was performed routinely on day of life 3 to screen for IVH. Of the 104 subjects in the study, 23 (22.1%) were scanned on day 0, 45 (43.3%) on day 1, 23 (22.1%) on day 2, and 13 (12.5%) on day 3. Those found to have IVH then had HUS at least 1–2 times per week to monitor for PHH. No HUS was performed beyond what was required for clinical purposes.

All study subjects developed IVH, ventriculomegaly, and required surgical treatment for PHH. Ventriculomegaly was defined by semi-quantitative assessment of ventricular size and frontal-occipital horn ratio (FOR) ≥ 0.5 [41]. PHH was defined by clinical criteria including progressive increase in occipitofrontal circumference, full fontanel (palpated above the level of surrounding bone), and splaying of the sagittal suture ≥ 2 mm in the mid-parietal region [21, 23, 40, 41]. All patients displaying these parameters underwent neurosurgical intervention at the earliest possible date; therefore, TNP was used as a proxy for PHH diagnosis. Initial neurosurgical intervention was with VR or VSGS, depending on the surgeon's training or preference.

Data collection

Primary time points of interest included the dates of initial IVH diagnosis, initial ventriculomegaly diagnosis, PHH diagnosis or TNP, permanent neurosurgical intervention (VPS or ETV), and first revision. The Papile system was used to assign IVH grade [25]. FOR was calculated at three time points (first imaging study, ventriculomegaly diagnosis, and first procedure) for the 75 subjects with imaging available in the electronic medical record. Rates of known risk factors for shunt complications including placement of a tracheostomy or gastrostomy tube, surgery for necrotizing enterocolitis or intestinal perforation, and surgery for patent ductus arteriosus (PDA) were collected [30, 31, 34]. Additional variables queried included sex, race, birthweight, EGA at birth, and initial procedure type (VR or VSGS). Volume of cerebrospinal fluid (CSF) removed during the temporization phase was not routinely recorded in the medical records and was thus not included in the current study.

Statistical analysis

Statistical analyses were performed using SPSS version 24 (IBM Corporation, NY, USA). Baseline characteristics were summarized as percentage of the total cohort, mean with standard deviation for normally distributed variables, and median with interquartile range for other numerical variables. Kaplan-Meier (KM) survival curves were constructed for time from birth to IVH, ventriculomegaly, TNP, VPS or ETV, and first revision. Significant differences between curves were detected using the log rank test. Cox proportional hazards regression was used to test effects of continuous predictors on time to revision. Differences between FOR at the three time points were determined with repeated measures ANOVA and post hoc pairwise comparisons with Bonferroni adjustment for multiple comparisons. All tests of significance were conducted at a predetermined alpha level of 0.05.

Results

Baseline characteristics

All 104 preterm infants who met the inclusion criteria were included in the analysis. Baseline characteristics for the subjects are included in Table 1. Duration of follow-up ranged from 11.1 to 202.2 months. Highest documented IVH grade was II for 5 patients (4.8%), III for 33 (31.7%), and IV for 66 (63.5%). Representative HUS for each of the IVH grades are shown in Fig. 1, and

Table 1 Baseline characteristics, all subjects ($N = 104$)

Characteristic	Count (%)	Values[a]
Sex		
Male	58 (55.8)	
Female	46 (44.2)	
Race		
Caucasian	49 (47.1)	
African American	50 (48.1)	
Other	5 (4.8)	
Birthweight (g)	104 (100)	860 (700–1166)
EGA at birth (weeks)	104 (100)	26 (24–28)
Highest IVH grade		
II	5 (4.8)	
III	33 (31.7)	
IV	66 (63.5)	
Temporizing procedure type		
Ventricular reservoir	71 (68.3)	
Ventriculosubgaleal shunt	30 (28.8)	
PMA at temporizing procedure (weeks)	101 (97.1)	30 (28–32)
All ventriculoperitoneal shunts	80 (76.9)	
Shunt revisions within 6 months ($N = 80$ shunts)	36 (45.0[b])	
Shunt infection[c] ($N = 80$ shunts)	2 (2.5[b])	
PMA at initial shunt insertion (weeks)	80 (76.9)	39 (37–43)
Risk factors		
Patent ductus arteriosus	39 (37.5)	
Tracheostomy	4 (3.8)	
Gastrostomy tube	24 (23.1)	
Intestinal perforation	13 (12.5)	
Necrotizing enterocolitis	7 (6.7)	
Frontal-occipital horn ratio		
First imaging study	74 (71.2)	0.456 ± 0.058
Ventriculomegaly	75 (72.1)	0.517 ± 0.054
Temporizing procedure	75 (72.1)	0.647 ± 0.061

[a] Summary statistics are median (interquartile range) for birthweight and EGA, and mean ± standard deviation for frontal-occipital horn ratio measurements

[b] Percentage out of 80 shunts

[c] Infections of first ever shunt prior to any revisions

EGA, estimated gestational age; *IVH*, intraventricular hemorrhage; *g*, grams

characteristics of the IVH on HUS including size and location are summarized in Table 2. All subjects developed ventriculomegaly and underwent neurosurgical intervention for PHH. Seventy-one (68.3%) subjects were treated initially with a VR and 30 (28.8%) with a VSGS. Eighty (76.9%) of the patients ultimately received a VPS during the entire follow-up duration. Two (2.5%) of the shunted patients experienced an infection of their primary shunt (described in Table 3). Thirty-six (45.0%) of the shunted patients required at least one revision within 6 months of shunt insertion.

Changes in frontal-occipital horn ratio

FOR measured at the time of each subject's first ever imaging study (mean ± standard deviation, 0.456 ± 0.058), ventriculomegaly diagnosis (0.517 ± 0.054), and TNP (0.647 ± 0.061) are summarized in Fig. 2. The FOR values were significantly different on repeated measures ANOVA (F (2 d.f.) = 235.52, $p < 0.001$), and they increased significantly between each of the three time points (adjusted $p < 0.001$ for all post hoc comparisons).

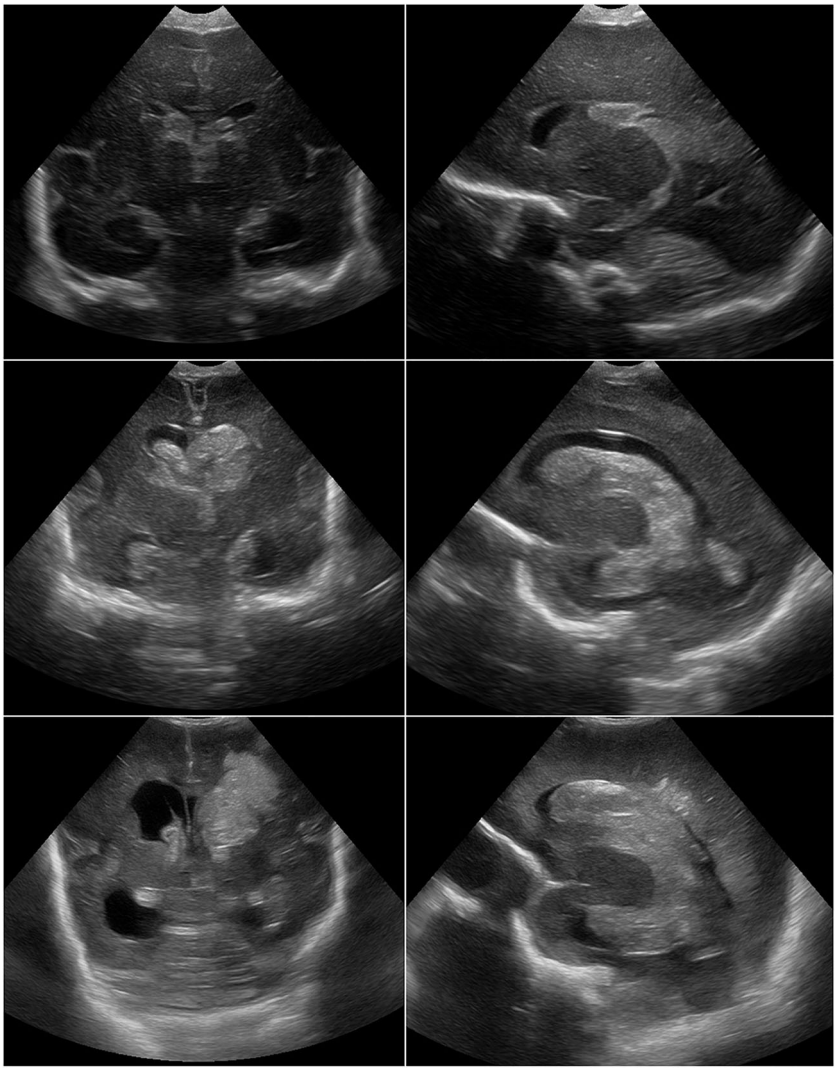

Fig. 1 Coronal (left) and sagittal (right) head ultrasound screen captures from patients with grade II (top row), III (middle row), and IV (bottom row) IVH, respectively

Time-course for intraventricular hemorrhage

KM survival curves showing time from birth to development of IVH are displayed in the top row of Fig. 3. Curves are shown for the entire pooled cohort (left), as well as broken down by grade for those with grades III and IV IVH (right). Median time to IVH for the pooled cohort was 2.0 (95% CI 1.7–2.3) days. No significant difference was found in age at IVH (X^2 (1 d.f.) = 1.32, p = 0.25) between patients with grades III (median 2.0 [95% CI 1.4–2.6] days) or IV IVH (2.0 [1.7–2.3] days).

Time-course for ventriculomegaly

KM survival curves showing time from birth to development of ventriculomegaly are displayed in the middle row of Fig. 3. Median time to ventriculomegaly for the pooled cohort was 3.0 (95% CI 2.5–3.5) days. No significant difference was found in age at ventriculomegaly (X^2 (1 d.f.) = 0.73, p = 0.40) between patients with grades III (median 3.0 [95% CI 1.6–4.4] days) or IV IVH (2.0 [1.5–2.5] days).

Time-course for temporizing neurosurgical procedure

Median postmenstrual age (PMA) at TNP was 29.6 (interquartile range, IQR 28.1–31.6) weeks for the pooled cohort. KM survival curves showing time from birth to TNP are displayed in the bottom row of Fig. 3. Median time to intervention for the pooled cohort was 24.0 (95% CI 22.2–25.8) days. No significant difference was found in age at intervention (X^2 (1 d.f.) = 0.61, p = 0.43) between patients with grades III (median 23.0 [95% CI 20.2–25.8] days) or IV IVH (24.0 [22.0–26.0] days).

Time-course for permanent neurosurgical procedure

Among subjects with grade III IVH, 23 of 33 (69.7%) required a permanent neurosurgical intervention (VPS or ETV); among

Table 2 IVH characteristics on neonatal head ultrasound ($N = 74$)[a]

Characteristic	Left hemisphere	Right hemisphere
IVH grade[b]		
I	1 (1.4)	3 (4.1)
II	9 (12.2)	11 (14.9)
III	30 (40.5)	31 (41.9)
IV	34 (45.9)	26 (35.1)
Location		
Frontal horn	40 (54.1)	32 (43.2)
Body	65 (87.8)	59 (79.7)
Atrium	62 (83.8)	56 (75.7)
Occipital horn	35 (47.3)	34 (45.9)
Temporal horn	17 (23.0)	14 (18.9)
Maximum coronal dimension (cm)	0.95 ± 0.41	0.86 ± 0.45
Maximum sagittal dimension (cm)	1.05 ± 0.34	0.95 ± 0.43

[a] Values are count (%) for IVH grade and location, and mean ± standard deviation for dimensions

[b] Highest IVH grade was II or above for all subjects

IVH, intraventricular hemorrhage; *cm*, centimeters

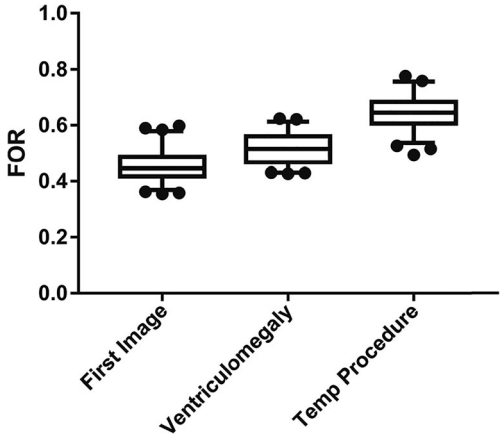

Fig. 2 Boxplots of FOR measured at the time of each subject's first ever imaging study, ventriculomegaly diagnosis, and TNP. Boxes indicate interquartile ranges, lines inside boxes represent medians, and whiskers are at 5 to 95 percentiles

subjects with grade IV IVH, 54 of 66 (81.8%) required permanent intervention. Rates of permanent interventions were not significantly different between grades III and IV IVH (X^2 (1 d.f.) = 1.87, p = 0.17). Five (4.8%) of the patients underwent an ETV for their first permanent neurosurgical intervention, and 2 (1.9%) had ETV for a revision procedure. Four of the seven ETVs also had choroid plexus cauterization.

Median PMA at permanent neurosurgical intervention was 38.4 (IQR 36.7–42.9) weeks for the 80 patients who received a VPS or ETV. KM survival curves showing time from birth to permanent intervention are displayed in Fig. 4. Curves are shown for all 104 subjects (left), as well as broken down by grade for those with grades III and IV IVH (right). Censoring is represented by tick marks for patients who had not yet

Table 3 Characteristics of the two patients who had infections of their primary shunt

Characteristic	Patient 1	Patient 2
Sex	Male	Male
Race	Caucasian	Caucasian
Birthweight (g)	1275	1230
EGA at birth (weeks)	29	28
Highest IVH grade	3	4
Initial procedure type	VR	VSGS
EGA at initial procedure (weeks)	33	31
Risk factors		
Patent ductus arteriosus	Yes	Yes
Tracheostomy	No	No
Gastrostomy tube	Yes	No
Intestinal perforation	No	No
Necrotizing enterocolitis	No	No
Loculation	No	No
Birth to IVH (days)	2	2
Birth to ventriculomegaly (days)	2	2
Birth to first procedure (days)	25	20
Birth to initial shunt insertion (days)	104	67
EGA at initial shunt insertion (weeks)	44	38
Initial shunt insertion to infection (days)	63	28
Organism cultured	Coagulase-negative staphylococcus	*S. aureus*

EGA, estimated gestational age; *IVH*, intraventricular hemorrhage; *g*, grams

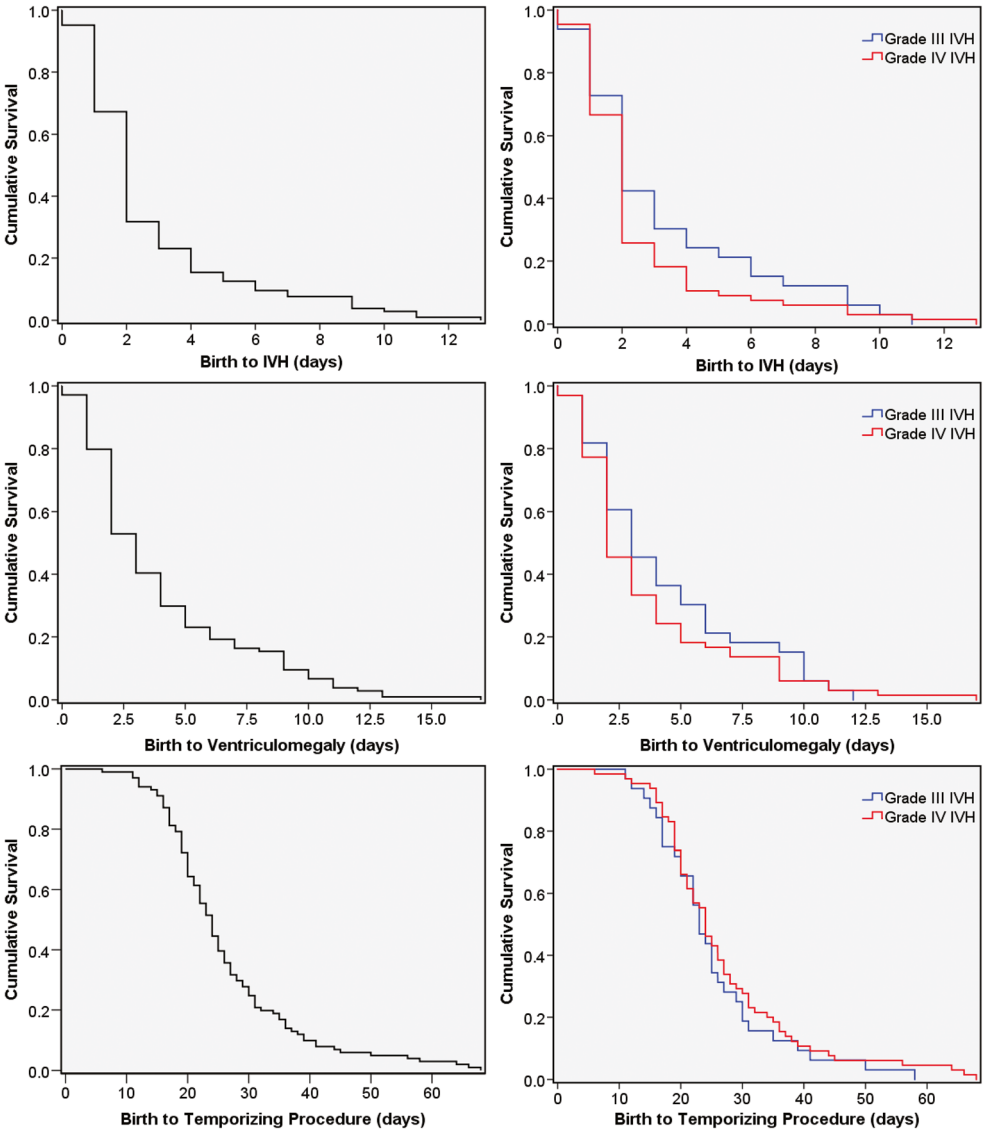

Fig. 3 KM survival curves showing time from birth to IVH diagnosis (top row), ventriculomegaly diagnosis (middle row), and TNP (bottom row). Data are shown for all 104 preterm infants (left column) and separated by IVH grade for 33 infants with grade III and 66 infants with grade IV IVH (right column). All subjects experienced the events, and none were censored

received a VPS or ETV by the end of the study period, and for 1 patient who died from non-neurological causes. Median time from birth to permanent intervention for all 104 subjects was 101.0 (95% CI 90.4–111.6) days. There was no significant difference in age at permanent intervention (X^2 (1 d.f.) = 2.48, $p = 0.17$) between patients with grades III (median 118.0 [95% CI 62.9–173.1] days) or IV IVH (95.0 [81.5–108.5] days). None of the patient characteristics shown in Table 1 were significantly predictive of time to VPS or ETV by log rank test or unadjusted Cox regression.

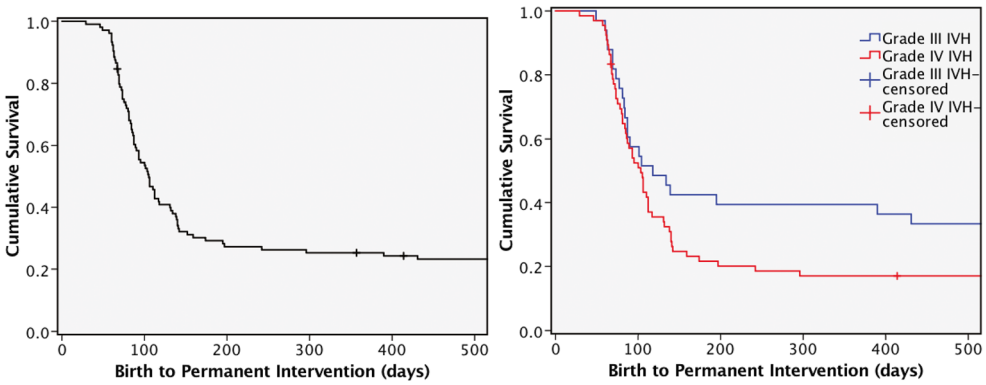

Fig. 4 KM survival curves showing time from birth to permanent neurosurgical intervention. Data are shown for all 104 preterm infants (left) and separated by IVH grade for 33 infants with grade III and 66 infants with grade IV IVH (right). Tick marks indicate censoring due to end of study period or death (1 subject)

Time-course for first revision

Median PMA at the time of first revision procedure (VPS or ETV) was 52.8 (IQR 43.7–95.3) weeks for the 54 patients who required revisions. KM survival curves showing time from initial permanent intervention to first revision are displayed in Fig. 5. Curves are shown for all 80 patients who required a VPS or ETV (left), as well as broken down by grade for those with grades III and IV IVH (right). Censoring is represented by tick marks for patients who had not yet had a revision by the end of the study period. Median time from initial permanent intervention to revision for the 80 patients was 50.4 (95% CI 17.9–82.9) weeks. There was no significant difference in time to first revision (X^2 (1 d.f.) = 0.58, $p = 0.45$) between patients with grades III (median 57.6 [95% CI 5.5–109.6] weeks) or IV IVH (22.9 [0.0–53.7] weeks). None of the patient characteristics or risk factors shown in Table 1 were significantly predictive of time to first shunt revision by log rank test or unadjusted Cox regression.

Discussion

The goal of this study was to report the time-course of development of IVH, ventriculomegaly, and PHH requiring surgery in preterm infants who ultimately underwent surgical intervention, as well as our institution's experience with timing of temporary and permanent CSF diversion. While a number of studies have examined the timing of IVH development in preterm neonates, few have detailed the other endpoints in a sample of this size. In general, we found that patients who received subsequent surgical intervention developed IVH, ventriculomegaly, and PHH by day of life 2, 3, and 24, respectively. There were no differences in IVH or PHH timing between IVH grades III and IV in our study population. These findings suggest that although most infants who develop IVH and ventriculomegaly will do so within a few days of birth, at-risk infants should be observed for at least 4 weeks with serial HUS to monitor for development of PHH requiring surgery.

Our findings are in agreement with existing literature on IVH and PHH timing. A 2014 meta-analysis by Al-Abdi and Al-Aamri incorporated five prospective studies and found two major modes of IVH timing in 279 cases—0–6 h (48% of cases) and after 24 h of life (38%) [2, 4, 9, 10, 18, 19]. Although our retrospective review was unable to provide more resolution within the first day of life due to the hours when routine HUS were available, we showed that the majority of IVH occurs within the first 2 days, a finding that is consistent with previous studies [38]. Two studies have touched on timing of ventriculomegaly associated with IVH. In 1983, Partridge et al. reported PHH in 18 patients, with 6% diagnosed by day 1, 39% by day 4, 56% by day 7, 83% by day 14, and 94% by day 28 [26]. In 1984, Szymonowicz and Yu performed HUS every 12 h until 72 h of age in infants with IVH, and weekly thereafter until discharge or death. They reported the optimal timing for diagnosis of ventriculomegaly at 2–3 weeks, although they only had 5 cases of ventricular dilatation in 30 patients with IVH [37]. In our cohort of infants ultimately receiving surgical intervention, we found a more rapid course of ventriculomegaly with median time-to-event of 3 days. We agree that diagnosis of ventriculomegaly is likely to be made within the first weeks of life.

We used TNP as a proxy for PHH, and found that this develops three weeks after IVH. Few papers have focused on timing of temporary or permanent CSF diversion in infants with PHH. Wang et al. reported VR insertion at mean 33 days of life (31.8 weeks EGA, $n = 44$) and VSGS insertion at mean 29 days of life (30.1 weeks EGA, $n = 46$) [39]. They also described VPS placement at mean 81.7 and 109.5 days of life for patients with VR and VSGS, respectively. Likewise, Karas et al. reported VSGS at median 25 days of life (30.3 weeks EGA, $n = 10$) and VPS placement at 61 days of life ($n = 9$) [13]. Christian et al. found in 91 patients that those receiving a VR or VSGS as initial procedure did so at a mean age of 29 days, and initial permanent shunt by 56 days [7]. Our results are consistent with these studies (median 24 days for VR and VSGS). Time from initial permanent intervention to first revision varies across the literature from 59 to 156 weeks

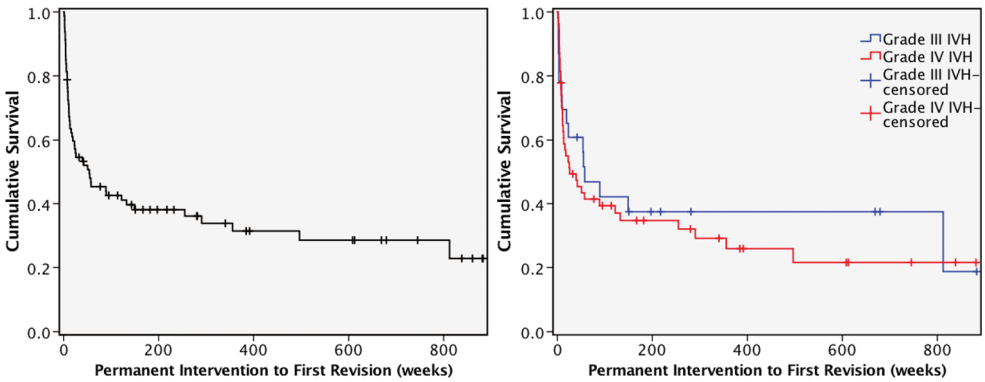

Fig. 5 KM survival curves showing time from initial permanent intervention to first revision. Data are shown for all 80 preterm infants who required a VPS or ETV (left) and separated by IVH grade for 23 infants with grade III and 54 infants with grade IV IVH (right). Tick marks indicate censoring due to end of study period or death

[5, 29]. We report a median time of 50.4 (95% CI 17.9–82.9) weeks, which is consistent with previous studies.

FOR was first described as a ratio of linear measures of ventricular size that accounts for disproportionate occipital horn enlargement in pediatric hydrocephalus [23] and has been used in a number of recent studies due to its ability to approximate ventricular volumes [16, 28, 31]. Compared to FOR at time of first ever image, FOR is significantly larger at time of ventriculomegaly diagnosis and is even larger at TNP, which provides evidence of the concurrent validity of this measure for distinguishing between patients at various stages of the PHH disease course.

A primary limitation of this study is that our database only contained patients who developed IVH and PHH requiring neurosurgical intervention. Therefore, our results are not generalizable to the population of all preterm infants with IVH or ventriculomegaly, but only to the more severe subset of this group that is managed by neurosurgeons. Patients who have lower grade IVH that does not progress to PHH may be expected to have a more prolonged or "arrested" time-course. Additionally, because the timing and frequency of HUS were not standardized in this retrospective study, the time resolution of endpoints is limited. A larger, prospective study examining the incidence of ventriculomegaly and PHH in the broader population of all IVH patients (grades I–IV) would facilitate clinical decision making at the onset of disease. However, the timings described in this study may be used to inform expectations regarding the time-course of high grade IVH and PHH. Finally, this single-institution series only captures the experience at SLCH, and a multi-institutional study on PHH timing would produce more generalizable results.

In conclusion, we report the typical time-course of development of IVH, ventriculomegaly, PHH, VPS or ETV, and first revision in preterm infants who ultimately require neurosurgery. We also show a significantly increasing trend in FOR between first imaging study, ventriculomegaly diagnosis, and TNP. Our data suggest that at-risk infants should be observed for at least 4 weeks with serial HUS to monitor for development of PHH. Future studies should aim to generalize our results to all preterm infants who develop IVH, as well as validate the findings at other institutions.

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Authors' contributions R.H.H. and D.B. performed literature review, study design, collected data, and wrote the manuscript. R.H.H. performed data analysis. B.S.B. wrote and critically revised the manuscript. M.G. and D.M.M. collected data and critically revised the manuscript. A.M.M., C.D.S., J.M.S., and D.D.L. designed the study and critically revised the manuscript.

Compliance with ethical standards

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 datasets during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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