Outcomes Following Post-Hemorrhagic Ventricular Dilatation among Infants of Extremely Low Gestational Age

Seetha Shankaran, MD[1], Monika Bajaj, MD[1], Girija Natarajan, MD[1], Shampa Saha, PhD[2], Athina Pappas, MD[1], Alexis S. Davis, MD[3], Susan R. Hintz, MD[3], Ira Adams-Chapman, MD[4], Abhik Das, PhD[5], Edward F. Bell, MD[6], Barbara J. Stoll, MD[7], Michele C. Walsh, MD MS[8], Abbot R. Laptook, MD[9], Waldemar A. Carlo, MD[10], Krisa P. Van Meurs, MD[3], Pablo J. Sánchez, MD[11], M. Bethany Ball, BS, CCRC[3], Ellen C. Hale, BS, RN, CCRC[4], Ruth Seabrook, MD[11], Rosemary D. Higgins, MD[12], for the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Neonatal Research Network

Objective To assess outcomes following post-hemorrhagic ventricular dilatation (PHVD) among infants born at ≤26 weeks of gestation.

Study design Observational study of infants born April 1, 2011, to December 31, 2015, in the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Neonatal Research Network and categorized into 3 groups: PHVD, intracranial hemorrhage without ventricular dilatation, or normal head ultrasound. PHVD was treated per center practice. Neurodevelopmental impairment at 18-26 months was defined by cerebral palsy, Bayley Scales of Infant and Toddler Development, 3rd edition, cognitive or motor score <70, blindness, or deafness. Multivariable logistic regression examined the association of death or impairment, adjusting for neonatal course, center, maternal education, and parenchymal hemorrhage.

Results Of 4216 infants, 815 had PHVD, 769 had hemorrhage without ventricular dilatation, and 2632 had normal head ultrasounds. Progressive dilatation occurred among 119 of 815 infants; the initial intervention in 66 infants was reservoir placement and 53 had ventriculoperitoneal shunt placement. Death or impairment occurred among 68%, 39%, and 28% of infants with PHVD, hemorrhage without dilatation, and normal head ultrasound, respectively; aOR (95% CI) were 4.6 (3.8-5.7) PHVD vs normal head ultrasound scan and 2.98 (2.3-3.8) for PHVD vs hemorrhage without dilatation. Death or impairment was more frequent with intervention for progressive dilatation vs no intervention (80% vs 65%; aOR 2.2 [1.38-3.8]). Death or impairment increased with parenchymal hemorrhage, intervention for PHVD, male sex, and surgery for retinopathy; odds decreased with each additional gestational week.

Conclusions PHVD was associated with high rates of death or impairment among infants with gestational ages ≤26 weeks; risk was further increased among those with progressive ventricular dilation requiring intervention. *(J Pediatr 2020;226:36-44)*.

See related articles, p 16 and p 28

Infants born at extremely low gestational ages (≤26 weeks) are at high risk for neurodevelopmental disabilities in childhood and adolescence. Risk factors associated with poor outcome include neonatal brain injury (intracranial hemorrhage in the intraventricular, parenchymal or cerebellar region, white matter injury, cystic periventricular leukomalacia, porencephaly, and ventricular dilation), lung disease including bronchopulmonary dysplasia with or without postnatal corticosteroid steroid use, sepsis, necrotizing enterocolitis, and exposure to surgery.[1-6] Infants of any gestational age who develop post-hemorrhagic ventricular dilation (PHVD) are also at high risk for cerebral palsy as well as cognitive, functional, attention, and visual perception challenges at

Bayley III	Bayley Scales of Infant and Toddler Development, 3rd edition
HUS	Head ultrasound
NICHD	*Eunice Kennedy Shriver* National Institute of Child Health and Human Development
PHVD	Post-hemorrhagic ventricular dilation
VPS	Ventriculoperitoneal shunt

From the [1]Department of Pediatrics, Wayne State University, Detroit, MI; [2]Social, Statistical and Environmental Sciences Unit, RTI International, Research Triangle Park, NC; [3]Department of Pediatrics, Division of Neonatal and Developmental Medicine, Stanford University School of Medicine and Lucile Packard Children's Hospital, Palo Alto, CA; [4]Emory University School of Medicine, Department of Pediatrics, Children's Healthcare of Atlanta, Atlanta, GA; [5]Social, Statistical and Environmental Sciences Unit, RTI International, Rockville, MD; [6]Department of Pediatrics, University of Iowa, Iowa City, IA; [7]Department of Pediatrics, McGovern Medical School at The University of Texas Health Science Center at Houston, Houston, TX; [8]Department of Pediatrics, Rainbow Babies & Children's Hospital, Case Western Reserve University, Cleveland, OH; [9]Department of Pediatrics, Women & Infants Hospital, Brown University, Providence, RI; [10]Division of Neonatology, University of Alabama at Birmingham, Birmingham, AL; [11]Department of Pediatrics, Nationwide Children's Hospital, Ohio State Univ. College of Medicine, Columbus, OH; and [12]College of Health and Human Services, George Mason University, Fairfax, VA

Clinical Trials.gov ID: Generic Database: NCT00063063.

Funding and conflict of interest statements available in the **Appendix** (www.jpeds.com).

https://doi.org/10.1016/j.jpeds.2020.07.080

school age.[7-10] The risk of neurodevelopmental impairment is greater if the PHVD is progressive and requires intervention in the neonatal period.[11-13] Although there is insufficient evidence to recommend a specific weight or cerebrospinal fluid parameter to direct the timing of shunt placement in infants born preterm with PHVD,[14] the risk of deficits may be reduced by an early temporizing approach to treating PHVD.[7,8,15] Data on the outcome of PHVD among infants of extremely low gestational age are sparse. The goal of our study was to examine outcomes of death or neurodevelopmental impairment among infants born at ≤26 weeks of gestation who developed PHVD. We hypothesized that infants requiring intervention for PHVD would be at greatest risk for death or impairment compared with those with PHVD not requiring intervention, those with hemorrhage without PHVD, and those with normal cranial head ultrasound (HUS) scans.

Methods

This study was conducted at 17 clinical centers in the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) Neonatal Research Network. Infants born at ≤26 weeks of gestation from April 1, 2011, to December 31, 2015, were included. Results of the most severe abnormality in HUS, including intracranial hemorrhage and ventricular size, evaluated by clinical center radiology readings closest to 2 time points, 28 days and 36 weeks of postmenstrual age, were documented as part of the ongoing data registry. Blood in the germinal matrix/subependymal area was coded as grade I hemorrhage, blood within the ventricular system without ventricular enlargement as grade II, ventricular size enlarged with concurrent or previous blood was grade III, and blood within the parenchyma was coded as grade IV hemorrhage. Information on follow-up was obtained from the NICHD Neonatal Research Network follow-up data registry. PHVD was diagnosed based on enlarged ventricles with preceding hemorrhage on serial HUS performed closest to 28 days and 36 weeks of postmenstrual age. The intervention for progressive PHVD was per clinical center practice; ventricular reservoir placement with subsequent serial reservoir taps or insertion of a ventriculoperitoneal shunt (VPS). Infants with reservoir placement who did not have resolution of PHVD had insertion of a VPS before discharge. The age of the infant at reservoir and/or VPS insertion was recorded. Details of the frequency of cerebrospinal fluid removal or volumes removed from reservoir taps were not collected. Information on the perinatal and neonatal course until infant's discharge home, transfer, or death on or before 120 days, as well as death if hospitalized beyond 120 days, was also collected. Neonatal data collected included surfactant receipt within 72 hours of birth, late-onset sepsis, defined as a positive blood culture after 72 hours of age, necrotizing enterocolitis using modified Bell's staging ≥ IIA,[16] bronchopulmonary dysplasia, defined as need for oxygen at 36 weeks of postmenstrual age, and severe retinopathy of prematurity treated with surgery.

Study exclusion criteria were death within 12 hours of age, major anomaly, the decision to not provide intensive care at or following birth, and HUS data that were unavailable or missing for hemorrhage status. Infants were categorized into 3 groups based on the HUS data; PHVD, hemorrhage without PHVD, and normal HUS. In the PHVD group, infants were classified as having no surgical intervention when PHVD resolved or stabilized as documented on the discharge diagnosis, whereas those with progressive PHVD were categorized based on initial intervention, reservoir, or VPS placement. Infants with reservoir placement who had VPS insertion as a second intervention remained in the reservoir group.

Outcome Measures

All infants were followed to 18-22 months of corrected age if they were born before July 1, 2012, and at 22-26 months of corrected age if born after July 1, 2012. Assessments at the follow-up study visit included a standardized neurologic examination[17] and the Bayley Scales of Infant and Toddler Development, 3rd edition (Bayley III) administered by trained and certified site examiners. The Bayley III cognitive, language, and motor composite scores (normalized to a mean 100, SD 15) and scaled scores for fine and gross motor skills, and receptive and expressive language, (mean 10, SD 3) were obtained.[18] Infants who were not successfully tested due to severe developmental delay, blindness, or profound hearing loss were assigned a cognitive score of 54 and language and motor scores of 46. Neurodevelopmental impairment was defined per the 2010 definition used in NICHD Neonatal Research Network as any of the following: moderate or severe cerebral palsy based on the gross motor functional classification system level ≥2,[19] Bayley III cognitive or motor scores <70, bilateral blindness, or deafness defined as profound hearing loss despite amplification. Normal survivors were defined as infants without any cerebral palsy, Bayley III cognitive and motor scores >85, and with normal vision and hearing assessments.

Statistical Analyses

To evaluate for bias, maternal and infant characteristics were compared among infants seen in follow-up and those who survived to neonatal intensive care unit discharge but were lost to follow-up. The maternal and neonatal characteristics were then examined among infants seen in follow-up categorized by 3 study groups (PHVD, hemorrhage without PHVD, and those with normal HUS) to evaluate for group differences, with χ^2 tests and Fisher exact tests for categorical variables and Wilcoxon test for continuous outcomes. Similar comparisons were performed within the PHVD group among infants who received an intervention for progressive PHVD, either a ventricular reservoir as the first intervention for PHVD or insertion of a VPS, and those who had PHVD that stabilized or improved without any intervention.

The primary outcome of the study was death or neurodevelopmental impairment at the follow-up visit, because death is a competing outcome in this extremely low gestational age group. Secondary outcomes included components of the primary outcome, hospitalizations following discharge, and measurement of growth at the follow-up evaluation. Risk for the primary outcome and components of impairment were assessed between the 3 study groups by ORs and 95% CIs for categorical outcomes using generalized linear mixed models. For continuous outcomes, adjusted estimates were obtained using generalized linear models. Covariates included in all models were center, male sex, antenatal steroids, histologic chorioamnionitis and hypertension, mode of delivery, mother's education, and gestational age. Center was included as a random effect for categorical outcomes. A similar analysis was conducted to evaluate risk for death or neurodevelopment impairment among infants with PHVD with and without intervention, adjusting for additional factors (delivery room intubation, receipt of surfactant, late-onset sepsis, necrotizing enterocolitis, receipt of oxygen at 36 weeks, parenchymal hemorrhage, and surgery for retinopathy of prematurity). Other than delivery room intubation and receipt of surfactant, the data of occurrence of the remaining variables were not available in the registry data; hence, it is not known if they occurred before PHVD. A P value <.05 was considered significant. All statistical analyses were conducted by the data coordinating center at RTI International using SAS (version 9.3; SAS Institute, Cary, North Carolina) software. The birth and follow-up registries were approved by the institutional review board at each site, and the study protocol was approved by the NICHD Neonatal Research Network.

Results

From April 1, 2011, to December 31, 2015, there were 5600 infants born at ≤26 weeks of gestation in the NICHD Neonatal Research Network centers. Of the 4216 infants in the study cohort, 815 (19.3%) infants had PHVD, 769 (18.2%) had intracranial hemorrhage without PHVD, and 2632 (62.4%) had normal HUS (**Figure 1**; available at www.jpeds.com). Of the 3069 infants who attended the follow-up visit, data needed for evaluating neurodevelopmental impairment were incomplete for 177 infants (116 missing either Bayley cognitive or motor scores, 33 missing all the components of impairment, and 28 missing some of the components of impairment). The majority of infants were seen at 22-26 months of corrected age; 9% were evaluated at 18-22 months of corrected age. Data for assessing neurodevelopmental impairment were available for 453 infants with PHVD (95.5%), 506 with hemorrhage without ventricular dilatation (92.2%), and 1933 infants (94.4%) with normal HUS. To evaluate for bias, baseline maternal and neonatal characteristics were evaluated for the 3069 infants who attended the follow-up visit and those who were lost to follow-up. Compared with mothers of infants seen in follow-up, mothers of those lost to follow-up were younger with infants of greater gestational age (**Table I**; available at www.jpeds.com).

Maternal and Neonatal Characteristics

The maternal and neonatal characteristics of the infants in the study are presented in **Table II**. Mothers of infants with PHVD were younger, had lower rates of antenatal steroid administration, hypertension/preeclampsia, and greater rates of histologic chorioamnionitis. Vaginal delivery differed by group; 42% of PHVD, 45% hemorrhage without PHVD, and 32% in the normal HUS groups ($P < .0001$). Compared with infants with hemorrhage without PHVD and those with normal HUS, infants with PHVD were younger in gestation, had lower birth weights, more neonatal interventions, and greater rates of morbidity including delivery room intubation, surfactant use, oxygen need at 36 weeks of postmenstrual age, necrotizing enterocolitis, late-onset sepsis, and retinopathy of prematurity requiring surgery. Male sex was similar in the PHVD and hemorrhage without PHVD groups; there were fewer male patients in the normal HUS group ($P < .001$). Among the 815 infants with PHVD, 119 (14.6%) infants had surgical intervention for progressive PHVD, based on center practice. The first intervention for progressive PHVD occurred at a median age of 29 days (at 29.1 weeks of postmenstrual age) for placement of a ventricular reservoir or at a median age of 39 days (at 30.7 weeks of postmenstrual age) for placement of a VPS. Among infants whose first intervention was a reservoir (n = 66), 36 (54.5%) had a VPS inserted for continued drainage at a postmenstrual age of 36 ± 2 weeks at 84 ± 17 days (mean ± SD).

Infants with PHVD who had an intervention for progressive PHVD were compared with those who did not have an intervention; those with an intervention had greater rates of parenchymal hemorrhage, oxygen use at 36 weeks of postmenstrual age, and necrotizing enterocolitis (**Table III**).

Outcomes

The follow-up outcomes of infants in the 3 groups are presented in **Table IV**. The primary outcome of death or neurodevelopmental impairment was observed among 68% of infants with PHVD compared with 39% of infants with hemorrhage without PHVD and 28% of the normal HUS group. Neurodevelopmental impairment occurred in 47% of infants with PHVD, 18% of those with hemorrhage without PHVD and 14% of those with normal HUS. The rate of cerebral palsy was 43% in the PHVD group compared with 13% in the hemorrhage without PHVD group and 9% in the normal HUS group. Compared with the other 2 groups, more infants in the PHVD group had Bayley III cognitive scores <85 or motor scores <85 and more infants had hearing impairment and vision impairment.

Table II. Maternal and neonatal characteristics of infants by study group

Characteristics	PHVD group N = 815	Intracranial hemorrhage without PHVD N = 769	Normal HUS N = 2632	*P* value*
Maternal variables				
Age of mother, y, mean (SD)	N = 813 27.55 (6.38)	N = 768 28.07 (6.42)	28.21 (6.13)	.02
Antenatal steroids, n (%)	650/813 (80.0)	660/767 (86.0)	2419/2629 (92.0)	<.01
Complete, n (%)	423/648 (65.3)	482/656 (73.5)	1922/2411 (79.7)	<.01
Partial, n (%)	225/648 (34.7)	174/656 (26.5)	489/2411 (20.3)	<.01
Delivery mode: vaginal, n (%)	343/815 (42.1)	344/769 (44.7)	854/2632 (32.4)	<.01
Histologic chorioamnionitis, n (%)	446/710 (62.8)	398/685 (58.1)	1296/2325 (55.7)	<.01
Hypertension/preeclampsia, n (%)	136/812 (16.7)	162/766 (21.1)	649/2626 (24.7)	<.01
Maternal education < high school, n (%)	137/616 (22.2)	127/609 (20.9)	389/2066 (18.8)	.14
Race				
Black, n (%)	357/779 (45.8)	334/751 (44.5)	1140/2563 (44.5)	.79
White, n (%)	395/779 (50.7)	370/751 (49.3)	1266/2563 (49.4)	.80
Other, n (%)	27/779 (3.5)	47/751 (6.3)	157/2563 (6.1)	.01
Neonatal variables				
Outborn, n (%)	38/815 (4.66)	29/769 (3.77)	83/2632 (3.15)	.12
Gestational age, wk, mean (SD)	24.32 (1.16)	24.65 (1.12)	24.95 (1.03)	<.01
Birth weight, g, mean (SD)	706.31 (161.88)	729.19 (164.04)	746.62 (168.62)	<.01
Male, n (%)	456/815 (56.0)	430/767 (56.1)	1284/2630 (48.8)	<.01
Delivery room intubation, n (%)	734/815 (90.1)	630/768 (82.0)	2043/2632 (77.6)	<.01
Surfactant use, n (%)	792/815 (97.2)	716/769 (93.1)	2370/2632 (90.0)	<.01
Postnatal steroids, n (%)	178/745 (23.9)	160/718 (22.3)	558/2429 (23.0)	.76
Oxygen at 36 wk, n (%)	425/565 (75.2)	383/619 (61.9)	1414/2319 (61.0)	<.01
Necrotizing enterocolitis > stage 2, n (%)	106/815 (13.0)	78/769 (10.1)	275/2632 (10.4)	.09
Late-onset sepsis, n (%)	253/761 (33.2)	240/740 (32.4)	642/2587 (24.8)	<.01
Retinopathy of prematurity requiring therapy, n (%)	134/580 (23.1)	104/621 (16.7)	261/2309 (11.3)	<.01
Hemorrhage grade				
Grade I	22/815 (2.7)	343/769 (44.6)	–	–
Grade II	37/815 (4.5)	324/769 (42.1)	–	–
Grade III	354/815 (43.4)	0/769 (0.0)	–	–
Grade IV	402/815 (49.3)	102/769 (13.3)	–	–
Days to first intervention for PHVD, median (IQR)				
Overall	N = 119 33 (25, 56)			
VPS	N = 53 39 (31, 78)			
Ventricular reservoir	N = 66 29 (23, 44)			
PMA at first intervention for PHVD, wk, median (IQR)				
Overall	N = 119 29.7 (28.6, 32.0)			
VPS	N = 53 30.7 (29.0, 36.6)			
Ventricular reservoir	N = 66 29.1 (27.9, 31.3)			

*P values obtained using the χ^2 test or Fisher exact test for categorical and nonparametric Wilcoxon test for continuous outcomes.

Infants in the PHVD group had more hospitalizations after neonatal intensive care unit discharge, including those for seizures or VPS revisions than infants with hemorrhage without PHVD and those with normal HUS. The head circumference at follow-up was smaller among infants with PHVD compared with the other groups; more infants with PHVD had a head circumference below the 10th percentile.

The outcomes of the 91 infants with progressive PHVD who received an intervention was compared with the 383 infants with PHVD stabilizing without intervention (Table V). Death or neurodevelopmental impairment and impairment among survivors was greater among infants with PHVD with intervention than among infants with no intervention; 9.9% of infants with PHVD with intervention had normal outcomes.

Predictors of Death or Neurodevelopmental Impairment

There was no association between age at the first intervention for PHVD and death or neurodevelopmental impairment following adjustment for center, gestational age of the infant, and maternal education (aOR 0.98 [0.97-1.00]); similarly, there was no association between age at first intervention and impairment among survivors (aOR 0.99 [0.97-1.00]). Factors associated with death or impairment among infants with PHVD with aOR (95% CI) were intervention for progressive PHVD, 4.57 (2.34-8.94); surgery for retinopathy of prematurity, 2.61 (1.46-4.64); parenchymal hemorrhage, 2.25 (1.32-3.84); and male sex, 1.70 (1.07-2.71); each advancing week of gestation decreased odds of death or impairment, 0.76 (0.61-0.94) (Figure 2;

Table III. Maternal and neonatal characteristics of infants who had no intervention vs intervention in PHVD group

Characteristics	No intervention N = 696	Intervention N = 119	*P* value*
Maternal variables			
Age of mother, y, mean (SD)	N = 694 27.52 (6.49)	27.71 (5.72)	.53
Antenatal steroids, n (%)	556/694 (80.1)	94/119 (79.0)	.78
Complete, n (%)	367/555 (66.1)	56/93 (60.2)	.27
Partial, n (%)	188/555 (33.9)	37/93 (39.8)	.29
Delivery mode: vaginal, n (%)	302/696 (43.4)	41/119 (34.5)	.07
Histologic chorioamnionitis, n (%)	382/608 (62.8)	64/102 (62.7)	.99
Hypertension/preeclampsia, n (%)	119/693 (17.2)	17/119 (14.3)	.44
Maternal education < high school, n (%)	119/533 (22.3)	18/83 (21.7)	.90
Race			
Black, n (%)	293/663 (44.2)	64/116 (55.2)	.03
White, n (%)	346/663 (52.2)	49/116 (42.2)	.05
Other, n (%)	24/663 (3.6)	3/116 (2.6)	.78
Neonatal variables			
Outborn, n (%)	32/696 (4.60)	6/119 (5.04)	.83
Gestational age, wk, mean (SD)	24.32 (1.17)	24.33 (1.13)	.91
Birth weight, g, mean (SD)	703.32 (165.20)	723.81 (140.21)	.10
Male, n (%)	397/696 (57.0)	59/119 (49.6)	.13
Delivery room intubation, n (%)	622/696 (89.4)	112/119 (94.1)	.11
Surfactant use, n (%)	675/696 (97.0)	117/119 (98.3)	.56
Postnatal steroids, n (%)	145/637 (22.8)	33/108 (30.6)	.08
Intraventricular hemorrhage, n (%)	351/696 (50.4)	40/119 (33.6)	<.01
Parenchymal hemorrhage, n (%)	325/696 (46.7)	77/119 (64.7)	<.01
Oxygen at 36 wk, n (%)	327/450 (72.7)	98/115 (85.2)	.01
Necrotizing enterocolitis > stage 2, n (%)	83/696 (11.9)	23/119 (19.3)	.03
Late-onset sepsis, n (%)	207/642 (32.2)	46/119 (38.7)	.17
Retinopathy of prematurity requiring therapy, n (%)	101/463 (21.8)	33/117 (28.2)	.14

*P values obtained using the χ^2 test or Fisher exact test for categorical and nonparametric Wilcoxon test for continuous outcomes.

available at www.jpeds.com). More infants with intervention for PHVD were hospitalized and had lack of head growth at follow-up assessment compared with infants with no intervention for PHVD. Fewer infants in the PHVD group with intervention had Bayley III cognitive and motor scores in the normal range, and more of them had very low cognitive and motor scores and impaired vision (Table V).

Discussion

In this observational study of prospectively collected data, infants born at ≤26 weeks of gestation who had PHVD compared with those with hemorrhage without PHVD or those with a normal HUS had a greater risk of death or neurodevelopmental impairment at follow-up at 18-22 months or 22-24 months of corrected age, and a lower likelihood of normal outcome. Within the PHVD group, infants requiring intervention for progressive ventricular dilatation with either a ventricular reservoir or VPS insertion had very high disability rates (cerebral palsy 76%, hearing impairment 8%, and vision impairment 13%). Only 13% of infants receiving intervention had a normal Bayley III cognitive or motor composite score (>85).

A systematic literature review evaluated optimal treatment strategies for progressive PHVD in infants born preterm.[14] Level 1 evidence did not support use of intraventricular thrombolytic agents and systemic acetazolamide and furosemide as optimal methods to reduce the need for permanent drainage with VPS. Evidence was insufficient to recommend a specific weight or cerebrospinal fluid component to direct timing of shunt placement in infants born preterm with progressive PHVD. However, the impact of early intervention using temporizing measures for progressive PHVD on outcomes of infants born preterm is currently being investigated.[20] In the Early vs Late Ventricular Intervention Study (ELVIS), a multicenter, randomized controlled trial of lower vs higher threshold for intervention for PHVD in 126 infants ≤34 weeks of gestational age, de Vries et al noted there was no significant difference in the primary composite outcome of death or VPS placement in infants treated at a lower vs higher threshold for intervention.[8] Low threshold was defined as a ventricular index greater than the 97th percentile and anterior horn width >6 mm, whereas the greater threshold was a ventricular index greater than the 97th percentile +4 mm and anterior horn width >10 mm. However, in a substudy of ELVIS, neonatal magnetic resonance imaging at term-equivalent age demonstrated more brain injury and larger ventricular volumes in the high-vs low-threshold group.[20] The neurodevelopmental outcome of ELVIS trial participants has been published.[21]

An observational study by Leijser et al at the Hospital for Sick Children (Canada) and 2 institutions in the Netherlands evaluated 127 infants with gestational ages ≤30 weeks, comparing an early approach (n = 78) using ventricular measurements (standard of care in Dutch centers) and a late approach (n = 49, standard of care in the

Table IV. 18-26 months of corrected age outcome among infants with PHVD, intracranial hemorrhage without PHVD, and normal HUS

Outcomes	PHVD group	Intracranial hemorrhage without PHVD	Normal HUS	aOR (95% CI)* or adjusted estimates (95% CI)*		
				PHVD vs normal	Hemorrhage, no PHVD vs normal	PHVD vs hemorrhage without PHVD
Death or neurodevelopmental impairment, n (%)	506/748 (67.7)	269/682 (39.4)	649/2316 (28.0)	4.65 (3.77-5.73)†	1.56 (1.27-1.92)†	2.98 (2.31-3.82)†
Neurodevelopmental impairment‡	211/453 (46.6)	93/506 (18.4)	266/1933 (13.8)	4.96 (3.84-6.41)†	1.34 (1.01-1.78)§	3.70 (2.67-5.11)†
Death, n (%) (before¶/after D/C)	295/814 (36.2)	176/768 (22.9)	383/2627 (14.6)	2.54 (2.05-3.15)†	1.58 (1.25-1.99)†	1.61 (1.25-2.08)†
Normal outcome-survivors,** n (%)	123/460 (26.7)	265/516 (51.4)	1105/1953 (56.6)	0.28 (0.22-0.36)†	0.84 (0.67-1.04)	0.34 (0.25-0.46)†
Cerebral palsy, n (%)	202/471 (42.9)	68/540 (12.6)	178/2016 (8.8)	7.16 (5.46-9.38)†	1.47 (1.06-2.04)§	4.86 (3.44-6.88)†
Bayley III cognitive						
>85, n (%)	150/452 (33.2)	283/523 (54.1)	1141/1966 (58.0)	0.37 (0.29-0.47)†	0.85 (0.69-1.06)	0.43 (0.32-0.58)†
70-85, n (%)	168/452 (37.2)	181/523 (34.6)	672/1966 (34.2)	1.05 (0.82-1.33)	1.00 (0.80-1.25)	1.05 (0.79-1.41)
69-55, n (%)	111/452 (24.6)	58/523 (11.1)	135/1966 (6.9)	4.11 (3.01-5.61)†	1.79 (1.26-2.53)†	2.30 (1.58-3.35)†
<55,† n (%)	23/452 (5.1)	1/523 (0.2)	18/1966 (0.9)	–	–	–
Bayley III motor composite score						
>85, n (%)	149/434 (34.3)	290/508 (57.1)	1168/1946 (60.0)	0.35 (0.27-0.45)†	0.91 (0.72-1.14)	0.39 (0.29-0.52)†
70-85, n (%)	125/434 (28.8)	154/508 (30.3)	605/1946 (31.1)	0.86 (0.66-1.11)	0.97 (0.76-1.22)	0.89 (0.65-1.21)
69-55, n (%)	77/434 (17.7)	41/508 (8.1)	110/1946 (5.7)	3.39 (2.40-4.79)†	1.37 (0.91-2.05)	2.48 (1.60-3.85)†
<55,† n (%)	83/434 (19.1)	23/508 (4.5)	63/1946 (3.2)	5.77 (3.90-8.52)†	1.25 (0.74-2.11)	4.61 (2.73-7.81)†
Hearing impairment, n (%)	25/469 (5.3)	11/534 (2.1)	48/2004 (2.4)	1.87 (1.08-3.23)§	0.87 (0.43-1.76)	2.15 (0.99-4.68)§
Vision impairment, n (%)	27/469 (5.8)	4/540 (0.7)	12/2019 (0.6)	9.04 (4.28-19.29)†	0.92 (0.25-3.34)	9.83 (2.91-33.28)†
Rehospitalized, n (%)	277/474 (58.4)	268/547 (48.9)	973/2040 (47.7)	1.33 (1.06-1.66)††	0.96 (0.78-1.18)	1.38 (1.05-1.82)§
Rehospitalization for seizures or VPS revision, n (%)	46/276 (16.7)	7/268 (2.6)	34/971 (3.5)	5.18 (3.08-8.70)†	0.67 (0.27-1.63)	7.78 (3.20-18.92)†
Growth						
Weight, kg, mean (SD)	N = 471 11.55 (4.24)	N = 539 11.49 (1.92)	N = 2009 11.43 (1.68)	0.12 (−0.13, 0.38)	0.09 (−0.14, 0.33)	0.03 (−0.28, 0.34)
Height, cm, mean (SD)	N = 463 83.94 (5.07)	N = 535 84.49 (4.78)	N = 1995 84.34 (4.64)	−0.41 (−0.92, 0.09)	0.26 (−0.20, 0.72)	−0.68 (−1.29, −0.07)§
Head circumference, cm, mean (SD)	N = 469 46.83 (2.57)	N = 532 47.32 (2.43)	N = 1992 47.34 (2.10)	−0.36 (−0.60, −0.13)††	0.07 (−0.15, 0.29)	−0.43 (−0.72, −0.14)††
Weight <10th percentile	110/471 (23.4)	99/539 (18.4)	358/2009 (17.8)	1.41 (1.08-1.84)††	1.05 (0.81-1.37)	1.34 (0.96-1.86)
Height <10th percentile, n (%)	181/463 (39.1)	159/535 (29.7)	592/1995 (29.7)	1.55 (1.23-1.96)†	0.96 (0.76-1.20)	1.62 (1.21-2.16)††

(*continued*)

Table IV. Continued

Outcomes	PHVD group	Intracranial hemorrhage without PHVD	Normal HUS	aOR (95% CI)* or adjusted estimates (95% CI)*		
				PHVD vs normal	Hemorrhage, no PHVD vs normal	PHVD vs hemorrhage without PHVD
Head circumference <10th percentile, n (%)	149/469 (31.8)	108/532 (20.3)	369/1992 (18.5)	1.82 (1.41-2.36)†	0.99 (0.76-1.30)	1.84 (1.33-2.54)†
Corrected age at follow-up, mo, mean (SD)	N = 474 23.88 (3.52)	N = 545 23.77 (3.39)	N = 2036 23.64 (3.37)	0.08 (−0.27, 0.43)	0.17 (−0.15, 0.50)	−0.09 (−0.52, 0.33)

D/C, discharge.
*aOR (95% CI) for categorical outcomes were obtained using generalized linear mixed models. For continuous outcomes, adjusted estimates (95% CI) were obtained using generalized linear models. Covariates adjusted in all models were center, male, antenatal steroids, histologic chorioamnionitis, hypertension, mode of delivery, mother's education, and gestational age. Center variations have been adjusted as a random effect for categorical outcomes.
†$P < .001$.
‡Neurodevelopmental impairment is defined as moderate/severe cerebral palsy or Bayley III cognitive or motor score <70, blindness, or deafness.
§$P < .05$.
¶Withdrawal of respiratory support among those who died before hospital discharge was 23.1% among infants with PHVD, 14.1% among ICH no PHVD, and 7.6% among those with normal HUS, $P < .001$.
**Normal outcome in survivors is defined as no cerebral palsy, Bayley III cognitive composite score ≥85, motor composite score ≥85, normal vision and hearing.
††$P < .01$.

Canadian center). The early approach with lumbar punctures or reservoir placement was initiated at a mean of 29.4 weeks of postmenstrual age and the late approach was 2 weeks later; all late approach infants were outborn and transferred once there were signs of increased intracranial pressure and/or intervention was deemed necessary.[7] The 18- to 24-month outcomes among those with early intervention for PHVD were within the normal range and indistinguishable from those without intervention.

Ventricular measurements (as a basis for intervention) are not routinely performed in most US and Canadian centers and were not collected in the NICHD Neonatal Research Network Registry. The timing of the first intervention in our study was 29.7 (median) 28, 32 (IQR) weeks postmenstrual age; we found no association between time to first intervention and death or neurodevelopmental impairment at follow-up among infants with progressive PHVD requiring therapy.

The rate of conversion of temporary drainage with a reservoir to VPS insertion was 54.5% in our study, which is greater than the study by Leijser et al[7] (24%) but lower than that reported among ≤1500 g neonates with PHVD from the Hydrocephalus Clinical Research Network (69%)[22] or from the St Louis Children's Hospital report on infants born at ≤34 weeks of gestation with PHVD (77%).[23]

It is unclear whether the greater rates of neurodevelopmental impairment in our study are related to extreme prematurity. The rate of cerebral palsy was 27%-32% in the study by Leijser et al among infants with gestational ages ≤30 weeks with PHVD without intervention compared with 25%-94% with intervention,[7] whereas in our study of infants with gestational ages ≤26 weeks, cerebral palsy rates were 35% without intervention and 76% among those with intervention. In a longitudinal study of 25 children with PHVD ranging in gestational age from 25-37 weeks, born between 1996 and 2003 and a control group matched for gestation, sex and year of birth, the rate of cerebral palsy at 10 years of age was 28% compared with 12% among the matched group. Within the PHVD group, IQ was significantly lower in those who had undergone surgical intervention (n = 12).[9]

The strengths of our study are that data were collected prospectively in a multicenter setting, the focus was on the infants of extremely low gestational age, the cohort with PHVD is the largest one evaluated to date, and outcomes in infancy included the composite of death (a competing outcome) or neurodevelopmental impairment, as well as components of impairment. Similarly collected information on a comparison groups of infants with hemorrhage without PHVD and those with normal HUS is also a strength of our study. The limitations of our study include lack of central reading for HUS and assessment of rapidity of progression of ventricular dilatation. We did not have sonographic ventricular measurements or have magnetic resonance imaging data. The details of clinical indications for intervention for progressive PHVD, indicators of intracranial pressure, and differences in indications for intervention among centers is also a limitation. We did not collect details of VPS shunt

Table V. 18-26 months of corrected age outcome among infants with no intervention vs intervention among infants with PHVD only

Outcomes	No intervention	With intervention (VPS or VR)	aOR (95% CI)* or estimates (95% CI)* PHVD with intervention vs PHVD with no intervention
Death or neurodevelopmental impairment, n (%)	420/641 (65.5)	86/107 (80.4)	1.97 (1.15-3.38)†
Neurodevelopmental impairment‡	142/363 (39.1)	69/90 (76.7)	4.28 (2.44-7.51)§
Death, n (%) (before¶/after D/C)	278/695 (40.0)	17/119 (14.3)	0.18 (0.10-0.32)§
Normal outcome in survivors,** n (%)	114/369 (30.9)	9/91 (9.9)	0.32 (0.15-0.69)††
Cerebral palsy, n (%)	133/380 (35.0)	69/91 (75.8)	4.56 (2.63-7.93)§
Bayley III cognitive >85, n (%)	139/369 (37.7)	11/83 (13.3)	0.28 (0.14-0.57)§
70-85, n (%)	142/369 (38.5)	26/83 (31.3)	0.79 (0.47-1.36)
69-55, n (%)	73/369 (19.8)	38/83 (45.8)	2.85 (1.66-4.88)§
<55, n (%)	15/369 (4.07)	8/83 (9.64)	2.50 (0.95-6.62)
Bayley III motor composite score >85, n (%)	138/353 (39.1)	11/81 (13.6)	0.30 (0.15-0.60)§
70-85, n (%)	111/353 (31.4)	14/81 (17.3)	0.48 (0.26-0.92)†
69-55, n (%)	52/353 (14.7)	25/81 (30.9)	2.23 (1.24-4.00)††
<55, n (%)	52/353 (14.7)	31/81 (38.3)	3.17 (1.75-5.73)§
Hearing impairment, n (%)	18/378 (4.76)	7/91 (7.69)	1.85 (0.71-4.85)
Vision impairment, n (%)	15/379 (3.96)	12/90 (13.3)	3.53 (1.51-8.27)††
Rehospitalized, n (%)	208/383 (54.3)	69/91 (75.8)	2.41 (1.40-4.14)††
Rehospitalization for seizures or VPS revision, n (%)	20/207 (9.7)	26/69 (37.7)	5.07 (2.48-10.37)§
Growth			
Weight, kg, mean (SD)	N = 381 11.66 (4.64)	N = 90 11.09 (1.63)	−0.34 (−1.37, 0.68)
Height, cm, mean (SD)	N = 373 84.13 (5.06)	N = 90 83.15 (5.07)	−0.88 (−2.08, 0.31)
Head circumference, cm, mean (SD)	N = 378 47.05 (2.42)	N = 91 45.93 (2.98)	−1.07 (−1.67, −0.48)§
Weight <10th percentile, n (%)	82/381 (21.5)	28/90 (31.1)	1.38 (0.81-2.36)
Height <10th percentile, n (%)	139/373 (37.3)	42/90 (46.7)	1.37 (0.84-2.23)
Head circumference <10th percentile, n (%)	102/378 (27.0)	47/91 (51.6)	2.50 (1.52-4.11)§

*aOR (95% CI) for categorical outcomes has been obtained using generalized linear mixed models. For continuous outcome, adjusted estimates (95% CI) were obtained using generalized linear models. Covariates adjusted in all models are center, mothers' education, and gestational age and parenchymal hemorrhage. Center variations have been adjusted as a random effect for categorical outcomes.
†$P < .05$.
‡Neurodevelopmental impairment was defined as moderate/severe cerebral palsy or Bayley III cognitive or motor score <70, blindness, or deafness.
§P <. 001.
¶Withdrawal of respiratory support among those who died before hospital discharge (D/C) was 26.7% among infants with no intervention and 5.9% among those with intervention, $P < .001$.
**Normal outcome in survivors is defined as no cerebral palsy, Bayley III cognitive composite score ≥85, motor composite score ≥85, normal vision and hearing.
††$P < .01$.

obstructions and infections; factors known to influence outcome.[24]

The outcome in childhood of infants of extremely low gestational age is influenced by their neonatal morbidity; Cheong et al followed 499 infants born at <28 weeks of gestation to 8 years of age; 241 (48%) had no major postnatal events and had the greatest probability of survival without a major disability.[1] Four major morbidities were associated with disability; grade 3 or 4 hemorrhage, cystic periventricular leukomalacia, lung disease treated with postnatal steroids, and any surgical condition. Holsti et al evaluated infants born at 23-25 weeks of gestation at 10 years of age; 21 of 132 adolescent survivors had a major disability that was associated with bronchopulmonary dysplasia, retinopathy of prematurity, and neonatal brain injuries.[2] Details of occurrence of PHVD are not mentioned in these 2 studies. Lastly, in a subset of infants born extremely preterm with imaging data drawn from a randomized trial, cystic periventricular leukomalacia, porencephaly, moderate or severe ventricular dilatation, ventricular peritoneal shunts, and cerebellar injury were all associated with disability at age 6-7 years.[3]

Neonatal intensive care is now being offered to infants born extremely preterm, and their survival rates are improving.[25] Our study demonstrates that infants born with gestational ages ≤26 weeks are at risk for severe intracranial hemorrhage, often with the complication of PHVD. Infants requiring intervention for progressive PHVD have a guarded prognosis. The interventions for infants with PHVD are evolving, with additional surgical interventions being attempted such as endoscopic third ventriculostomy with or without choroid plexus cauterization[26]; the impact of these interventions on outcomes needs to be evaluated. The challenge for clinicians is to optimize care for infants and to lower rates of brain injury, especially PHVD, which is associated with the greatest odds of death or survival with a poor outcome. ■

Submitted for publication Apr 6, 2020; last revision received Jul 24, 2020; accepted Jul 27, 2020.

Reprint requests: Seetha Shankaran, MD, Children's Hospital of Michigan, 3901 Beaubien Blvd., Detroit, MI 48201. E-mail: sshankar@med.wayne.edu

Data Statement

Data sharing statement available at www.jpeds.com.

References

1. Cheong JLY, Lee KJ, Boland RA, Spittle AJ, Opie GF, Burnet AC, et al. Changes in long-term prognosis with increasing postnatal survival and the occurrence of postnatal morbidities in extremely preterm infants offered intensive care: a prospective observational study. Lancet Child Adolesc Health 2018;2:872-9.
2. Holsti A, Serenius F, Farooqi A. Impact of major neonatal morbidities on adolescents born at 23–25 weeks of gestation. Acta Paediatr 2018;107:1893-901.
3. Hintz SR, Vohr BR, Bann CM, Taylor HG, Das A, Gustafson KE, et al. Preterm neuroimaging and school-age cognitive outcomes. Pediatrics 2018;142:e20174058.
4. Cayam-Rand D, Guo T, Grunau RE, Benavente-Fernández I, Synnes A, Chau V, et al. Predicting neurodevelopmental outcome in preterm infants: a simple white matter imaging rule. Neurology 2019;93:e1231-40.
5. Morriss FH Jr, Saha S, Bell EF, Colaizy TT, Stoll BJS, Hintz SR, et al. Surgery and neurodevelopmental outcome in very low-birth-weight infants. JAMA Pediatr 2014;168:746-54.
6. Fullerton BS, Hong CR, Velazco CS, Mercier CE, Morrow KA, Edwards EM, et al. Severe neurodevelopmental disability and healthcare needs among survivors of medical and surgical necrotizing enterocolitis: a prospective cohort study. J Pediatr Surg 2018;53:101-7.
7. Leijser LM, Miller SP, van Wezel-Meijler G, Brouwer A, Traubici JT, van Haastert IC, et al. Posthemorrhagic ventricular dilatation in preterm infants, when best to intervene? Neurology 2018;90:698-706.
8. de Vries LS, Groenendaal F, Liem KD, Heep A, Brouwer AJ, The ELVIS study group, et al. Treatment thresholds for intervention in posthaemorrhagic ventricular dilation: a randomized controlled trial. Arch Dis Child Fetal Neonatal Ed 2018;104:F70-5.
9. Holwerda JC, van Braeckel KNJA, Roze E, Hoving EW, Masthuis CGB, Brouwer O, et al. Functional outcome at school age of neonatal posthemorrhagic ventricular dilatation. Early Human Dev 2016;96:15-20.
10. Srinivasakumar P, Limbrick D, Munro R, Mercer D, Rao R, Inder T, et al. Post hemorrhagic Ventricular dilatation-impact on early neurodevelopmental outcome. Am J Perinatal 2013;30:207-14.
11. Shankaran S, Koepke T, Woldt E, Bedard MP, Dajani R, Eisenbrey AB, et al. Outcome following post hemorrhagic ventriculomegaly in comparison with mild hemorrhage without ventriculomegaly. J Pediatr 1989;114:109-14.
12. Adams-Chapman I, Hansen NI, Stoll BJ, Higgins R, for the NICHD Neonatal Research Network. Neurodevelopmental outcome of extremely low birth weight infants with posthemorrhagic hydrocephalus requiring shunt insertion. Pediatrics 2008;121:e1167-77.
13. Brouwer A, Groenendaal F, van Haastert, Rademaker K, Hanlo P, de Vries L. Neurodevelopmental outcome of preterm infants with severe intraventricular hemorrhage and therapy for post-hemorrhagic ventricular dilatation. J Pediatr 2008;152:648-54.
14. Mazzola CA, Choudhri AF, Auguste KI, Limbrick DD Jr, Rogido M, for the Pediatric Hydrocephalus Systematic Review and Evidenced-Based Guidelines Task Force, et al. Pediatric hydrocephalus: systematic literature review and evidence-based guidelines. Part 2: management of posthemorrhagic hydrocephalus in premature infants. J Neurosurg Pediatr 2014;1:8-23.
15. Bassan H, Eshel E, Golan I, Kohelet D, Sira LB, for the External Ventricular Drainage Study Investigators, et al. Timing of external ventricular drainage and neurodevelopmental outcome in preterm infants with post hemorrhagic hydrocephalus. Eur J Pediatr Neurol 2012;16:662-70.
16. Bell MJ, Ternberg JL, Feigin RD, Keating JP, Marshall R, Barton L, et al. Neonatal necrotizing enterocolitis. Therapeutic decisions based upon clinical staging. Ann Surg 1978;187:1-7.
17. Newman JE, Bann CM, Vohr BR, Dusick AM, Higgins RD , Follow-Up Study Group of Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network. Improving the Neonatal Research Network annual certification for neurologic examination of the 18-22 month child. J Pediatr 2012;161:1041-6.
18. Bayley N. Bayley scales of infant and toddler development. third edition. San Antonio (TX): Harcourt Assessment, Inc; 2006.
19. Palisano R, Rossenbaum P, Walter S, Russell D, Wood E, Galuppi B. Development and reliability of a system to classify gross motor function in children with cerebral palsy. Dev Med Child Neurol 1997;39:214-23.
20. Cizmeci MN, Khalili N, Claessens HP, Groenendaal F, Liem KD, Heep A, et al. Assessment of brain injury and brain volumes after posthemorrhagic ventricular dilatation: a nested substudy of the randomized ELVIS trial. J Pediatr 2019;208:191-7.
21. Cizmeci MN, Groenendaal F, Liem KD, van Haastert IC, Benavente-Fernández I, van Straaten HLM, et al. Randomized controlled early versus late ventricular intervention study (ELVIS) in posthemorrhagic ventricular dilatation: outcome at 2 years. J Pediatr 2020. https://doi.org/10.1016/j.jpeds.2020.08.014.
22. Wellons JC 3rd, Shannon CN, Holubkov R, Riva-Cambrin J, Kulkarni J, Limbrick DD Jr, et al. Shunting outcomes in posthemorrhagic hydrocephalus: results of a Hydrocephalus Clinical Research Network prospective cohort study. J Neurosurg Pediatr 2017;20:19-29.
23. Han RH, Berger D, Gabir M, Baksh BS, Morales DM, Mathur AM, et al. Time-to-event analysis of surgically treated post hemorrhagic hydrocephalus in preterm infants: a single- institution retrospective study. Childs Nerv Syst 2017;33:1917-26.
24. Romero L, Ros B, Rius F, Gonzalez L, Medina JM, Martin A, et al. Ventriculoperitoneal shunt as the primary neurosurgical procedure in newborn posthemorrhagic hydrocephalus: report of a series of 47 shunted patients. Childs Nerv Syst 2014;1:91-7.
25. Younge N, Goldstein RF, Bann CM, Hintz SR, Patel RM, Smith PB, et al. Survival and neurodevelopmental outcomes among periviable Infants. N Engl J Med 2017;376:617-28.
26. Koschnitzky JE, Keep RF, Limbrick DD, McAllister JP, Morris JA, Strahle J, et al. Opportunities in posthemorrhagic hydrocephalus research: outcomes of the Hydrocephalus Association Posthemorrhagic Hydrocephalus Workshop. Fluids Barriers CNS 2018;15:1-22.

Funding and conflict of interest

The National Institutes of Health and the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) provided grant support for the Neonatal Research Network's on-going Birth Registry and Follow-up Registry through cooperative agreements. There is no potential conflict of interest, real or perceived, with the study sponsor. The sponsor did not have a role in the study design, collection of data, analysis and interpretation of data, writing the report or decision to submit the manuscript for publication. The National Institutes of Health and the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) (U10 HD21373, UG1 HD21364, UG1 HD21385, UG1 Funding Sources: The National Institutes of Health and NICHD (U10 HD21373, UG1 HD21364, UG1 HD21385, UG1 HD27851, UG1 HD27853, UG1 HD27856, UG1 HD27880,UG1 HD27904, UG1 HD34216, UG1 HD36790, UG1 HD40492, UG1 HD40689, UG1 HD53089, UG1 HD53109, UG1 HD68244, UG1 HD68270, UG1 HD68278, UG1 HD68263, UG1 HD68284; UG1 HD87226, UG1 HD87229) and the National Center for Advancing Translational Sciences (NCATS) (UL1 TR6, UL1 TR41, UL1 TR42, UL1 TR77, UL1 TR93, UL1 TR105, UL1 TR442, UL1 TR454, UL1 TR1117, provided grant support for the Neonatal Research Network, including for the follow-up study.

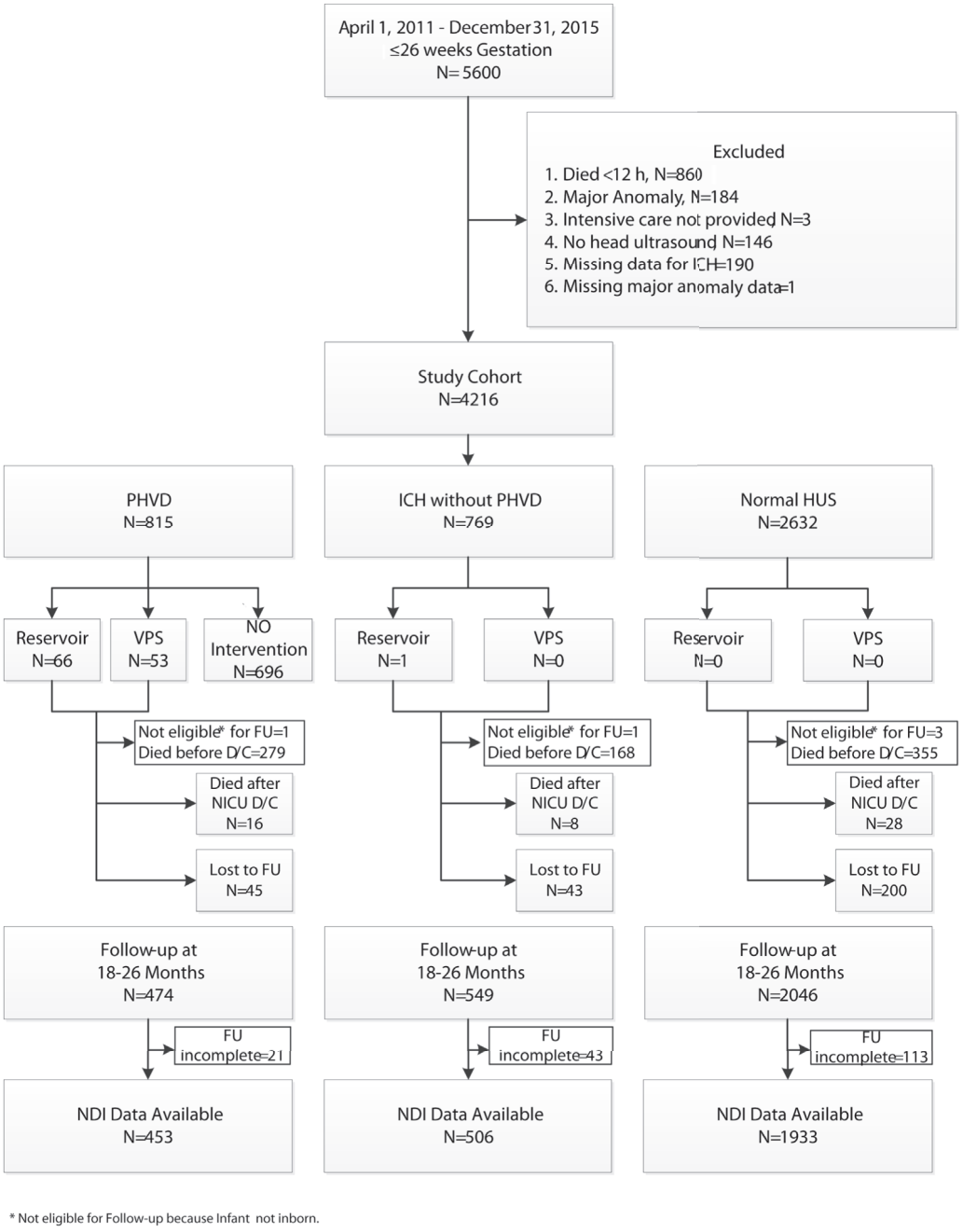

Figure 1. Flow of infants of extremely low gestational age through a study of outcomes following PHVD. *D/C*, discharge; *FU*, follow-up; *ICH*, intracranial hemorrhage; *NICU*, neonatal intensive care unit.

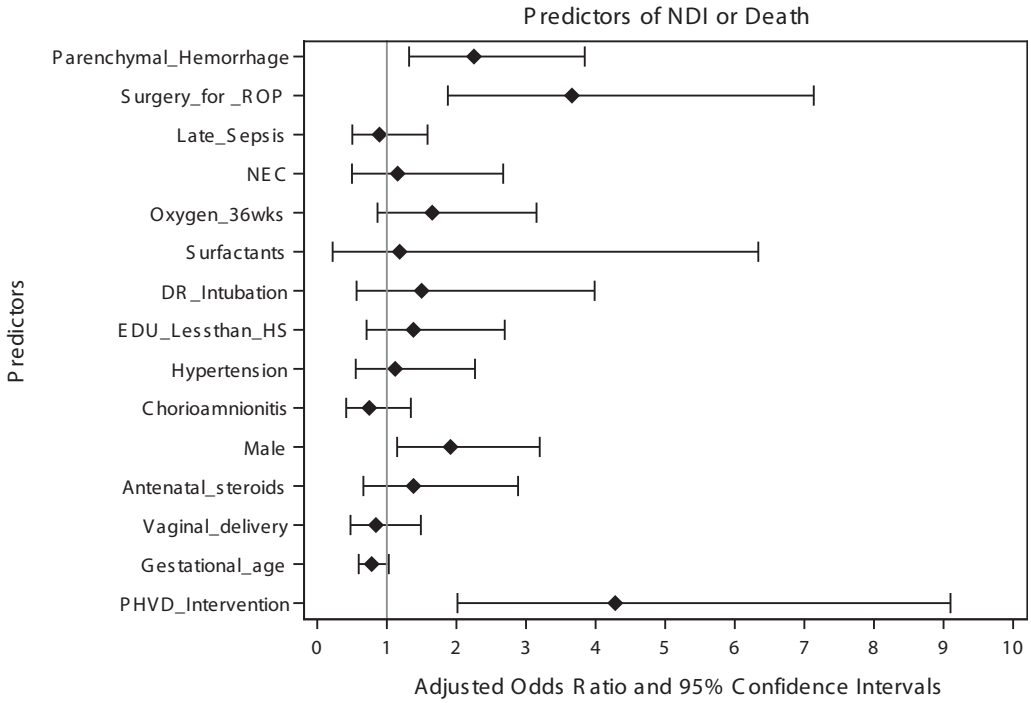

Figure 2. Factors associated with death or neurodevelopmental impairment after PHVD among infants of extremely low gestational age. *DR*, delivery room; *EDU*, education; *HS*, high school; *NDI*, neurodevelopmental impairment; *NEC*, necrotizing enterocolitis; *ROP*, retinopathy of prematurity.

Table I. Maternal and neonatal characteristics of infants seen in follow-up vs those lost to follow-up

Characteristics	Seen in follow-up N = 3069	Lost to follow-up N = 288	*P* value*
Maternal variables			
Age of mother, y, mean (SD)	N = 3068 28.32 (6.21)	27.04 (5.80)	<.01
Antenatal steroids, n (%)	2756/3065 (89.9)	259/287 (90.2)	.86
Complete, n (%)	2098/2747 (76.4)	200/259 (77.2)	.76
Partial, n (%)	649/2747 (23.6)	59/259 (22.8)	.82
Delivery mode: vaginal, n (%)	1076/3069 (35.1)	107/288 (37.2)	.48
Histologic chorioamnionitis, n (%)	1599/2739 (58.4)	152/255 (59.6)	.70
Hypertension/preeclampsia, n (%)	676/3064 (22.1)	53/287 (18.5)	.16
Maternal education < high school, n (%)	462/2437 (19.0)	40/214 (18.7)	.92
Race			
Black, n (%)	1310/2977 (44.0)	120/282 (42.6)	.64
White, n (%)	1502/2977 (50.5)	140/282 (49.7)	.80
Other, n (%)	165/2977 (5.5)	22/282 (7.80)	.12
Neonatal variables			
Outborn, n (%)	106/3069 (3.5)	8/288 (2.8)	.54
Gestational age, wk, mean (SD)	24.91 (1.04)	25.05 (1.02)	.02
Birth weight g, mean (SD)	757.09 (159.92)	776.27 (160.33)	.07
Male, n (%)	1554/3065 (50.7)	143/288 (49.7)	.73
Delivery room intubation, n (%)	2420/3069 (78.9)	226/288 (78.5)	.88
Surfactant use, n (%)	2784/3069 (90.7)	261/288 (90.6)	.96
Postnatal steroids, n (%)	688/2808 (24.5)	56/264 (21.2)	.23
Intraventricular hemorrhage, n (%)	490/3059 (16.0)	40/287 (13.9)	.36
Parenchymal hemorrhage, n (%)	254/3059 (8.30)	24/28 7 (8.36)	.97
Oxygen at 36 wk, n (%)	1921/3067 (62.6)	171/288 (59.4)	.27
Necrotizing enterocolitis > stage 2, n (%)	267/3069 (8.70)	24/288 (8.33)	.83
Late-onset sepsis, n (%)	805/3069 (26.2)	69/288 (24.0)	.40
Retinopathy of prematurity requiring therapy, n (%)	425/3040 (14.0)	32/279 (11.5)	.24

**P* values obtained using the χ^2 test or Fisher exact test for categorical and the nonparametric Wilcoxon test for continuous outcomes.