Neurologic Outcome Predictors in Pediatric Intracerebral Hemorrhage

A Prospective Study

Giulia S. Porcari, BA; Lauren A. Beslow, MD, MSCE; Rebecca N. Ichord, MD; Daniel J. Licht, MD; Jonathan T. Kleinman, MD; Lori C. Jordan, MD, PhD

Background and Purpose—Intracerebral hemorrhage is a considerable source of morbidity and mortality. This 3-center study describes outcomes of pediatric intracerebral hemorrhage and identifies 2-year neurological outcome predictors.

Methods—Children 29 days to 18 years of age presenting with intracerebral hemorrhage from March 2007 to May 2015 were enrolled prospectively. Exclusion criteria included trauma; intracranial tumor; hemorrhagic transformation of arterial ischemic stroke or cerebral sinovenous thrombosis; isolated subdural, epidural, or subarachnoid hemorrhage; and abnormal baseline neurological function. Intracerebral hemorrhage and total brain volumes were measured on neuroimaging. The Pediatric Stroke Outcome Measure assessed outcomes.

Results—Sixty-nine children were included (median age: 9.7 years; interquartile range: 2.2–14). Six children (9%) died during hospitalization. Outcomes in survivors were assessed at early follow-up in 98% (median 3.1 months; interquartile range: 3.1–3.8) and at later follow-up in 94% (median: 2.1 years; interquartile range: 1.3–2.8). Over a third had a significant disability at 2 years (Pediatric Stroke Outcome Measure >2). Total Pediatric Stroke Outcome Measure score improved over time (P=0.0003), paralleling improvements in the sensorimotor subscore (P=0.0004). Altered mental status (odds ratio, 13; 95% confidence interval, 3.9–46; P<0.001), hemorrhage volume ≥4% of total brain volume (odds ratio, 17; 95% confidence interval, 1.9–156; P=0.01), and intensive care unit length of stay (odds ratio, 1.1; 95% confidence interval, 1.0–1.2; P=0.002) were significantly associated with poor 2-year outcome.

Conclusions—Over one third of children experienced significant disability at 2 years. Improvements in outcomes were driven by recovery of sensorimotor function. Altered mental status, hemorrhage volume ≥4% of total brain volume, and intensive care unit length of stay were independent predictors of significant disability at 2 years. **(*Stroke*. 2018;49:1755-1758. DOI: 10.1161/STROKEAHA.118.021845.)**

Key Words: brain ■ central nervous system vascular malformations ■ cerebral hemorrhage ■ neuroimaging ■ pediatrics

Although approximately half of pediatric strokes are hemorrhagic, studies of pediatric intracerebral hemorrhage (ICH) have rarely examined outcome predictors, and retrospective studies are limited by the inadequacy of *International Classification of Diseases, Ninth Revision*, code-based case identification.[1] Prospective studies have been small or have focused on short-term outcomes (<1 year).[2,3] Study aims were to describe the spectrum of outcomes of pediatric spontaneous ICH prospectively at 3 pediatric centers and to identify predictors of poor 2-year neurological outcome.

Methods

Case Identification and Clinical Data

All children presenting with ICH from March 2007 to May 2015 were included. The Institutional Review Board approved the study at each site; informed consent was obtained. Inclusion criteria were age 29 days to 18 years, spontaneous ICH confirmed by computed tomograpy or magnetic resonance imaging. Exclusion criteria included trauma, intracranial tumor, hemorrhagic transformation of arterial ischemic stroke or cerebral sinovenous thrombosis, isolated epidural/subdural/subarachnoid hemorrhage, and abnormal baseline neurological function. Data supporting the study findings are available from the corresponding author upon request.

Pediatric stroke neurologists collected data via parental interview, medical record abstraction, and at follow-up stroke clinic visits. Glasgow Coma Score ≤9 was not obtained consistently. Thus, we defined altered mental status (AMS) as obtunded, comatose, or unresponsive on initial physician examination, or if Glasgow Coma Score ≤9, when recorded.

Hemorrhage Analysis

Cause was determined by medical history, imaging review, intraoperative observation, and surgical pathology. Parenchymal hemorrhage

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volume was measured as previously described and expressed as a percentage of total brain volume (TBV).[4] Cutoffs of 2% of TBV and 4% of TBV defined large and very large hemorrhage. Children with isolated intraventricular hemorrhage were excluded from volumetric analyses.

Outcomes

Outcomes were assessed at 3-month and 2-year clinic visits using the Pediatric Stroke Outcome Measure (PSOM), a standardized score of neurological function commonly used in pediatric ischemic and hemorrhagic stroke.[2,4,5] Scores are assigned from 0 to 2 for 5 domains (right and left sensorimotor, expressive and receptive language, cognitive/behavioral) and are summed for a total PSOM score. A total score of >2 or death represented "poor" outcome. A score >2 reflects a deficit in >1 domain and was chosen to distinguish between children with residual disability but a good degree of function and children at risk of long-term dependence. A short parent survey regarding the child's level of functioning, which is included in the most recent International Pediatric Stroke Study PSOM Short Neuro Exam form, was also administered at these visits.[6]

Statistical Analyses

Wilcoxon signed-rank tests and Stuart–Maxwell tests compared equality of distributions and differences in proportions over time. Univariable logistic regressions evaluated associations between possible predictors and poor outcome at 2-year follow-up. The multivariable logistic regression model included the 3 most significant predictors on univariable analysis, adjusting for age. Analyses were conducted in STATA 15.0.

Results

Patient Characteristics

Sixty-nine children met inclusion criteria, median age 9.7 years (interquartile range [IQR]: 2.2–14; range: 30 days–18 years). Table I in the online-only Data Supplement summarizes patient characteristics. Known medical risk factors were present in 20%, including cardiac, hematologic, immunologic, or genetic diagnoses. A precipitating factor for ICH was present in 19%, including hypertension (3%), infection (13%), surgery within 1 month (3%), coagulopathy (13%), and multiple factors (69%).

Hemorrhage was isolated parenchymal in 45%, isolated intraventricular in 9%, and involved >1 compartment in 46%. ICH volume could be calculated in 61 children (88%) and was <2% TBV in 54%, 2% to <4% TBV in 25%, and ≥4% TBV in 10%. Vascular malformations accounted for 63% of hemorrhages and coagulopathy for 17%. Cause could not be determined in 19%, although vascular malformations were suspected in one third of these cases. Children were carefully evaluated for ICH cause (online-only Data Supplement). Median hospital length of stay was 15 days (IQR: 9–22); median intensive care unit stay was 11 days (IQR: 5–18). Six children died during hospitalization (9%). Most children were discharged to inpatient rehabilitation (52%) or home with outpatient rehabilitation (27%).

Outcomes

Outcomes were assessed at a median of 3.1 months (IQR: 2.8–3.8) in 98% and again at 2.1 years (IQR: 1.3–2.8 years) in 94%. Median total 3-month PSOM was 1.5 (IQR: 0.5–3) and 2-year PSOM was 1 (IQR: 0–2.5). Overall, 38% and 34% of children had poor outcomes, respectively (Figure 1). Although total PSOM scores improved over time (median: 1.5 at 3 months–1.0 at 2 years; P=0.0003), this was largely because of improvements in sensorimotor subscores (median: 1.0 at 3 months–0.5 at 2 years; P=0.0004), whereas language and cognitive/behavioral subscores did not change significantly. Figure 2 shows direction of change for these subscores. From a functional standpoint, at 2 years 76% of parents reported that their children had not made a complete recovery, with 20% also noting the need for extra help with day-to-day activities compared with peers and 19% an impact on emotional state, behavior, and self-esteem.

Outcome Predictors

In univariable analyses, AMS and hemorrhage ≥4% of TBV were strongly associated with poor 2-year outcome (odds ratio, 13; 95% confidence interval, 3.9–46; P<0.001 and odds ratio, 17; 95% confidence interval, 1.9–156; P=0.01; Table I in the online-only Data Supplement). Longer hospital and intensive care unit (ICU) stay were significantly associated with poor outcomes (odds ratio, 1.1; 95% confidence interval, 1.0–1.1; P=0.005 and odds ratio, 1.1; 95% confidence interval, 1.0–1.2; P=0.002). Other associations with poor 2-year outcome included male sex, hemiparesis, hydrocephalus, and herniation. The 3 strongest outcome predictors (AMS, ICH volume ≥4% of TBV, and ICU length of stay) remained significantly associated with poor outcome in multivariable regression adjusted for age (Table I in the online-only Data Supplement). In univariable logistic regression, death was significantly associated with AMS, hemorrhage volume ≥4% of TBV, and coagulopathy (Table II in the

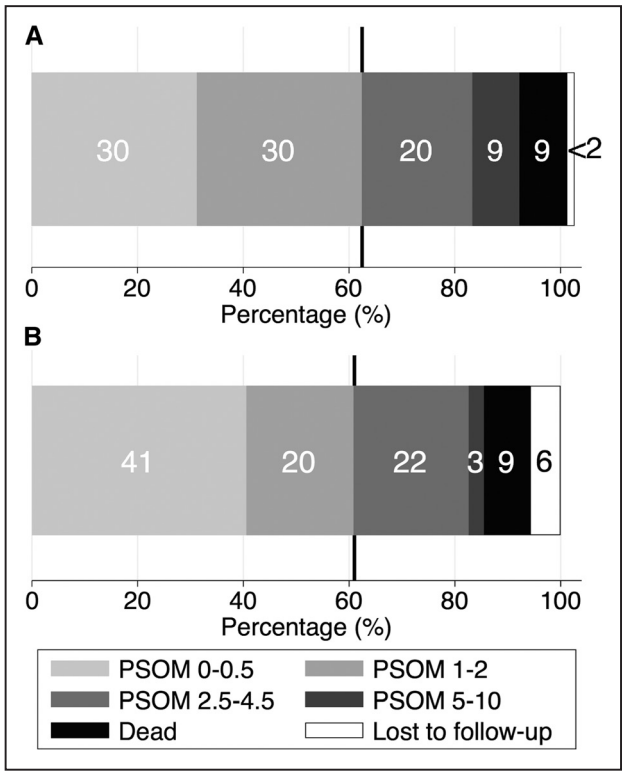

Figure 1. Total Pediatric Stroke Outcome Measure (PSOM) score distributions at: 3 months (**A**) and 2 years (**B**; labeled with % in each category).

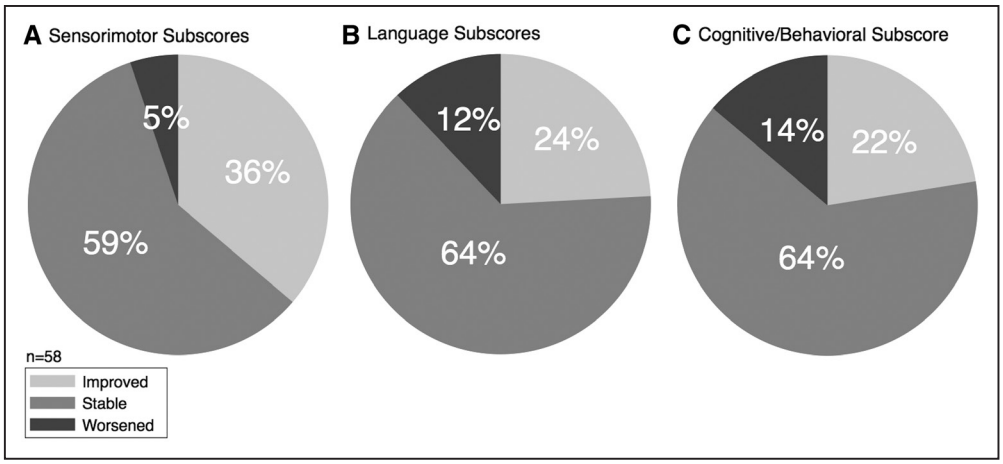

Figure 2. Direction of change over time of Pediatric Stroke Outcome Measure sensorimotor (**A**), language (**B**), and cognitive/behavioral subscores (**C**).

online-only Data Supplement); hemorrhage volume ≥2% of TBV, edema, hydrocephalus, and herniation syndrome were not.

Discussion

In this multicenter prospective study, we describe outcomes of pediatric spontaneous ICH over time and identify 2-year outcome predictors. Over one third of children had a poor 2-year outcome measured by dichotomized PSOM scores. Four prior studies have examined outcomes of pediatric ICH after 1 year.[3,7–9] Comparing studies is challenging because of the use of different outcome assessments, study designs, and inclusion criteria. Studies show widely divergent outcomes, with 10% to 75% of children experiencing clinically significant deficits, variably defined (Table III in the online-only Data Supplement). Mortality ranged from 4.5% to 39%.[2–4,7–9] Lower mortality (9%) in our study may reflect exclusion of children with intracranial tumors, management by dedicated stroke teams, and improvements in neurocritical care, including aggressive neurosurgical management.

AMS, hemorrhage volume, and ICU length of stay were strongly associated with poor 2-year outcome on age-adjusted multivariable analysis. Prolonged ICU stay may reflect underlying medical complexity, hemorrhage severity, treatment complications, or a combination. The association of poor 2-year outcome with AMS at presentation and hemorrhage volume ≥4% of TBV is consistent with previous studies assessing short-term outcomes and confirms its importance as a predictor in a larger prospective study.[2–4] AMS has not been a predictor in other pediatric studies, possibly because of differences in mental status assessment. Consistent with others' findings, we did not observe an association between poor functional outcome and infratentorial location, intraventricular extension, or coagulopathy.[2] Coagulopathy was associated with mortality along with AMS and hemorrhage volume ≥4% of TBV. Consistent with other reports, volume ≥2% of TBV was not associated with death, which suggests a threshold effect.[3]

The improvements in sensorimotor subscores, without change in language and cognitive/behavioral subscores, are consistent with evidence in both pediatric hemorrhagic and ischemic stroke that cognitive and language deficits are increasingly observed over time, perhaps because of poor sensitivity of assessment measures at young ages or emerging deficits as cognitive demands children face increase.[3,10]

Study limitations include lack of a specific outcome measure validated for pediatric ICH. We chose the PSOM over other metrics because it was developed and validated for pediatric ischemic stroke, relies on a detailed physical examination, and correlates with results from standardized neuropsychological measures.[5,11,12] The PSOM, however, is limited in its ability to capture functional impairments. Sample size is a weakness of pediatric ICH studies because of low incidence. Our study is one of the largest prospective studies of pediatric ICH to have followed children beyond 1 year. Its prospective and multicenter nature are important strengths given difficulties with ascertainment and bias in single-center or retrospective studies, providing wider generalizability of results.

Conclusions

Over one third of children had significant functional disability at 2 years, with a 9% mortality rate. Better outcomes over time were driven by improvements in the sensorimotor domain, compared with the language and cognitive/behavioral domains where deficits may emerge/become more evident with age. AMS, large hemorrhage volume, and ICU length of stay were associated with significant functional disability at 2 years. Improved understanding of outcomes after pediatric ICH and factors that affect long-term outcomes will allow physicians to counsel families on prognosis.

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Disclosures

None.

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ONLINE SUPPLEMENTAL MATERIAL

Neurologic Outcome Predictors in Pediatric Intracerebral Hemorrhage: A Prospective Study

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Supplemental Methods
Pediatric Intracerebral Hemorrhage Standard Acute Evaluation

Given the observational nature of this study, a specific protocol was not created to guide the care of enrolled children. Practices across the institutions, however, varied minimally. A standard evaluation is described here for a more thorough presentation of methodology.

Case ascertainment was facilitated by prior implementation of a protocol for children suspected to have an intracerebral hemorrhage (ICH), with activation of a code stroke and evaluation by pediatric neurology, neurosurgery, and critical care teams. There are strong connections between these departments at all three institutions allowing for a team approach during initial diagnosis and management.

All patients with suspected ICH were evaluated, at a minimum, with a CBC with differential and PT/PTT/INR, which was followed up by further coagulopathy testing (factor deficiencies and thrombophilias) as appropriate. Vitals were obtained as part of clinical care for all patients, but the presence of hypertension was not determined in each case, as establishing hypertension in pediatric patients requires conversion to percentiles based on age, sex, and height, the latter of which is challenging to measure during acute hospitalizations. Hypertension was only noted as a possible precipitating factor when it pre-dated ICH, was considered to play a role in the acute decompensation of the child, and required treatment due to severe elevation. Otherwise, a permissive approach was used as distress and elevated ICP can both contribute to mild-moderate blood pressure elevations in this population.

Imaging was obtained for all children presenting with a concern for stroke upon arrival, with the exception of transfers requiring emergent surgical intervention and for whom neuroimaging performed at the referring center was available for review. Children typically had an initial head CT/CTA and, if stable, a brain MRI/MRA following. MRI was the first neuroimaging study in rare cases. If initial imaging revealed an obvious cerebral cavernous malformation, digital subtraction angiography (DSA) was not done. If, however, the cause of ICH remained unclear, DSA was completed as soon as possible and always within the initial hospital stay. Most children also had follow-up DSA first at 6 weeks to 3 months post-ICH if their ICH was idiopathic and then again at 1 year post-ICH. Angiography was not performed in infants (<12 months of age) in the acute period unless a vascular lesion was strongly suspected.

ICH etiology was successfully determined in all but 19% of cases with this work-up. Those whose cause was ultimately determined to be idiopathic received extensive neuroimaging with the following during their initial admission: CT (100%), MRI brain (100%), MRA brain (77%), MRV brain in 38%, and conventional angiography (90% of children ≥12 months of age & 70% overall). Further imaging (MRI/MRA/angiogram) was

completed during follow-up in 69% of cases without further clarification of etiology. Thrombophilia evaluations were undertaken in 23% and 8% of cases in the pre and post-discharge setting respectively, without notable findings. Overall, despite an extensive work-up, 19% of cases were felt to have had an idiopathic event, which consistent with what has been reported in prior studies[1].

Medical and neurosurgical interventions were at the discretion of the treating teams. Overall, hematoma evacuation occurred if the patient was not clinically stable and had a large hematoma (clinical estimate) amenable to surgical evacuation. Children were admitted to the intensive care unit (ICU) for at least 1 night for observation and transferred to the floor when clinically stable. Direct admission to the floor was considered acceptable for clinically stable children with a Glasgow coma scale of 15 when ICU beds were not available.

Physical, occupational, and speech therapists were consulted during the admission for all children with a functional deficit. They played an active role in initial inpatient rehabilitation and in discharge planning. Receipt of therapy and services was assessed at follow-up visits, but was not quantified and thus not objectively evaluated as part of this study.

Supplemental Tables and Figures

Supplemental Table I. Patient characteristics and associations (univariable and multivariable logistic regressions) with poor 2-year outcome (N=69), *p<0.05, **p<0.005.

Univariable	N (%)	OR	95% CI	p-value
Demographics				
Age, years (median, IQR)	9.7 (2.2–14)	1.0	0.9–1.1	0.7
Male	39 (57)	3.4	1.1–10	0.03*
Caucasian (reference)	45 (65)			
African-American	24 (35)	2.2	0.7–6.3	0.2
Hispanic	4 (5.8)			
Pertinent history#				
Cardiac	7 (10)	1.4	0.3–7.0	0.7
Hematologic	4 (5.8)	0.6	0.06–6.0	0.7
Rheumatologic	1 (1.4)			
Genetic	3 (4.3)	0.9	0.08–11	0.9
Clinical presentation				
Hemiparesis	36 (52)	3.7	1.0–14	0.04*
Vision deficit	6 (8.7)	0.3	0.03–2.5	0.2
Speech deficit	17 (25)	0.8	0.2–2.5	0.7
Ataxia	2 (2.9)	1.5	0.09–26	0.8
Seizure	23 (33)	1.5	0.5–4.5	0.4
Abnormal tone	10 (14)	2.2	0.6–8.6	0.3
AMS	26 (39)	13	3.9–46	<0.001**
Emesis	36 (52)	1.2	0.5–2.9	0.7
Headache	36 (52)	1.1	0.7–1.8	0.6
Hemorrhage characteristics				
Volume (% TBV)				
<2	37 (54)			
≥2	24 (35)	4.8	1.5–16	0.009**
≥4	7 (10)	17	1.9–156	0.01*
Location				
Supratentorial (reference)	63 (91)			
Infratentorial	6 (8.7)	0.9	0.2–5.4	0.9
Hemorrhage pattern				
Isolated IVH	6 (8.7)			
Isolated ICH	31 (45)			
ICH + IVH	32 (46)			
Complicating findings				
Edema	48 (70)	0.8	0.3–2.2	0.6
Hydrocephalus	24 (35)	5.4	1.7–17	0.004**
Herniation syndrome	25 (36)	7.8	2.4–25	0.001**

Etiology				
AVM	27 (39)	1.4	0.5–3.9	0.5
Idiopathic	13 (19)	0.3	0.06–1.5	0.1
Coagulopathy	12 (17)	1.1	0.3–4.1	0.9
Cavernoma	9 (13)	0.5	0.09–2.5	0.4
Aneurysm	7 (10)	5.6	1.0–31	0.05*
DVA	1 (1.4)			
Treatment and Hospital Course				
Interventions				
Mannitol/hyperosmolar saline	27 (39)			
Transfusion	13 (19)			
Hemicraniectomy	14 (20)			
Hematoma evacuation	24 (35)			
Ventriculostomy	25 (36)			
Anomaly resection/repair	28 (41)			
Length of stay (median, IQR)				
Overall	15 (9–22)	1.1	1.0–1.1	0.005*
ICU	11 (5–18)	1.1	1.0–1.2	0.002*
Multivariable		**OR**	**95% CI**	**p-value**
AMS		9.6	1.6–56	0.01*
Hemorrhage volume ≥4%		17	1.3–225	0.03*
Days in the ICU		1.2	1.0–1.3	0.006*
Age		0.9	0.8–1.1	0.3

#: Cardiac – congenital heart disease, cardiopulmonary arrest, post-infectious valvular disease; Hematologic – sickle cell disease, hemophilia B, G6PD deficiency; Rheumatologic – macrophage activating syndrome; Genetic – hereditary hemorrhagic telengiactasia

AMS: altered mental status, TBV: total brain volume, IVH: intraventricular hemorrhage, ICH: intracerebral hemorrhage, AVM: arteriovenous malformation, DVA: developmental venous anomaly, PSOM: Pediatric Stroke Outcome Measure, ICU: intensive care unit.

Supplemental Table II. Summary of cohort characteristics and univariable associations with death (N=6),*p<0.05, and **p<0.005.

	N (%)	OR	95% CI	p-value
Demographics				
Age, years (median and IQR)	11.2 (7.7–15)	1.1	0.9–1.2	0.5
Male sex	3 (50)	0.8	0.1–4.0	0.7
Race & Ethnicity				
Caucasian	4 (67)			
African American	2 (33)	0.9	0.2–5.5	0.9
Hispanic	1 (17)			
Clinical presentation				
Hemiparesis	2 (33)	0.4	0.05–2.3	0.3
Speech deficit	1 (17)	0.6	0.06–5.4	0.6
Seizure	2 (33)	1.0	0.2–5.8	1.0
Abnormal tone	1 (17)	1.1	0.1–10.7	0.9
AMS	5 (83)	9.5	1.0–87	0.05*
Emesis	3 (50)	3.4	0.9–13	0.08
Headache	2 (33)	2.0	0.9–4.2	0.08
Pertinent past medical history				
Cardiac	2 (33)	5.8	0.8–40	0.07
Hemorrhage characteristics				
Volume				
<2% TBV	2 (33)			
≥2% TBV	3 (50)	2.5	0.4–16	0.3
≥4% TBV	3 (50)	19	2.5–153	0.005**
Supratentorial	6 (100)			
Hemorrhage pattern				
Isolated IVH	1 (17)			
Isolated ICH	1 (17)			
ICH + IVH	4 (67)			
Complicating findings on imaging				
Edema	4 (67)	0.9	0.1–5.1	0.9
Hydrocephalus	4 (67)	4.2	0.7–25	0.1
Herniation syndrome	4 (67)	4.0	0.7–24	0.1
Etiology				
AVM	3 (50)	1.6	0.3–8.7	0.6
Coagulopathy	3 (50)	6.0	1.0–34	0.04*

Supplemental Table III. Comparison of studies reporting long-term outcomes (> 1 year) in non-traumatic pediatric ICH.

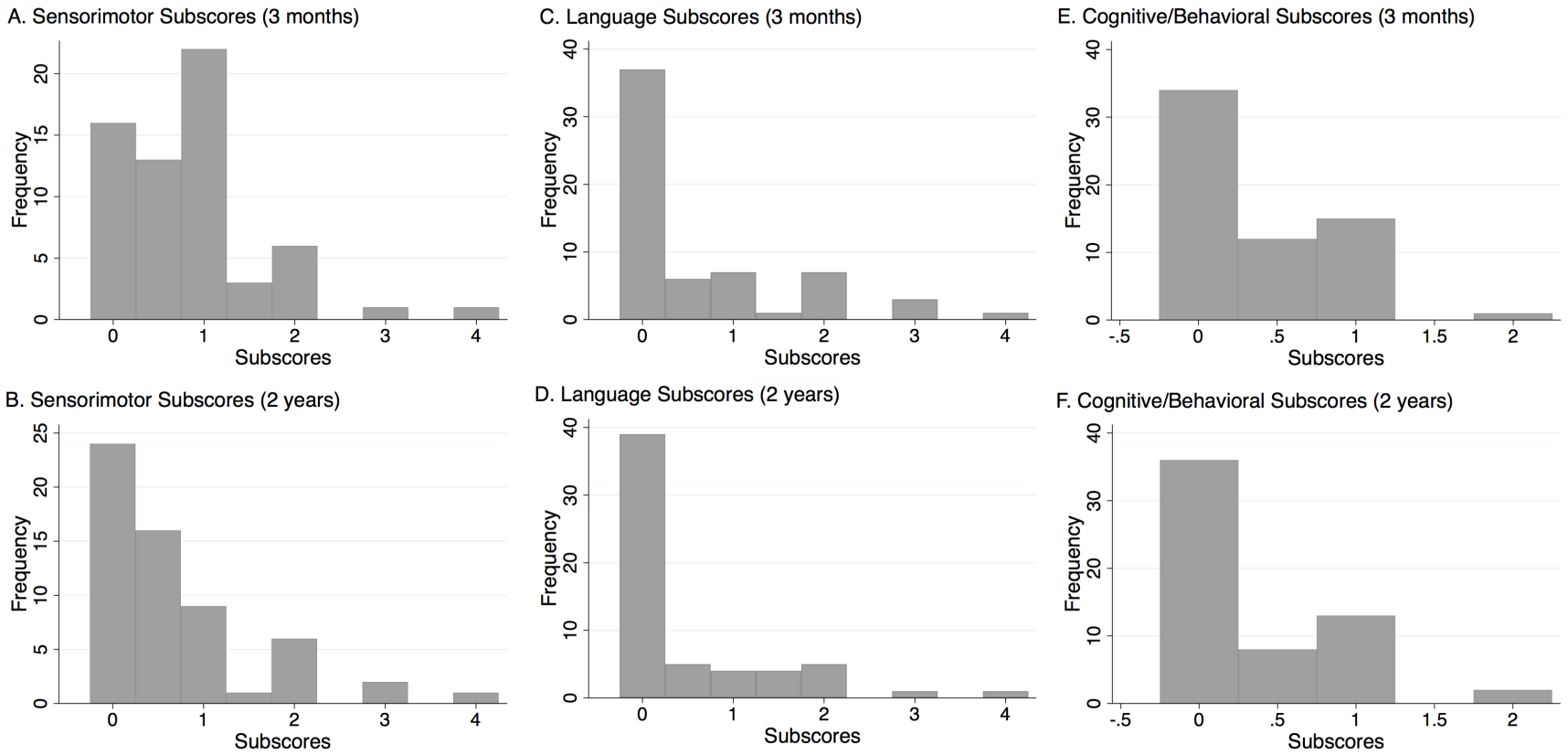
Study	N	Age range	Population	Follow-up	Outcome measures	Results
Blom[2]	31	1 mo-16 yrs	Intracranial hemorrhages (identified by ICD9 codes), including primary IVH and intracranial malignancy, excluding primary subdural or epidural hemorrhages	11 yrs (median)	- Physical exam - Neuropsychological assessment battery - Modified Rankin Scale (mRS) - Quality of life questionnaires (Short Form Health Survey, Child- and Parent-completed Child Health Questionnaires)	- Physical or cognitive impairment in 75% - No deficit in 45% (mRS 0) and no dependent patients (mRS 4-5) - Low self-esteem, behavioral, or emotional problems in majority - 36% cohort mortality rate
Meyer-Heim[3]	32	1 mo-17 yrs	Intracranial hemorrhages (identified retrospectively), including intracranial malignancy, excluding primary subdural and intraventricular hemorrhages	3 yrs (mean)	- Pediatric Clinical Scale or Glasgow Outcome Scale (based on age) -Neuropsychological assessment battery	- Good recovery in 31%, mild impairment in 22%, and severe neurological deficit in 22% - Minimal deficits in attention, memory, and behavior - 25% cohort mortality rate
Lo[4]	48*	7 d-17 yrs	Intracranial hemorrhages (identified by ICD9 codes & term search of radiology reports), including primary IVH and intracranial malignancy	25 mo (median)	- Pediatric Stroke Outcome Measure (modified for telephone)	- No deficit (PSOM 0) in 54% and poor outcome (PSOM≥5) in 10% - 34% cohort mortality rate

Lo[5]	19*	1 mo-18 yrs	Intracerebral and subarachnoid hemorrhages (identified as above), including primary IVH and intracranial malignancy, excluding isolated subarachnoid hemorrhage	5 yrs (median)	- Recovery and Recurrence Questionnaire (RRQ) - King's Outcome Scale for Childhood Head Injury (KOSCHI) - Pediatric Quality of Life Inventory - Caregiver Strain Questionnaire	- Median RRQ 1 (mild-moderate degree of impairment), with IQR 0-4 and range 0-6 - Median KOSCHI 5A (minimal impairment with daily function), with IQR 4B-5B and range 3-5B - Lower parent and patient-rated school quality of life and patient-rated physical quality of life; increased caregiver internalized stress - 34% cohort mortality rate

* Case overlap reported

ICD9 – International Classification of Diseases, Ninth Revision; IVH – Intraventricular hemorrhage

Supplemental Figure I. Distribution of domain subscores at 3-month and 2-year follow-up. A) Sensorimotor Subscores*, B) Language Subscores*, C) Cognitive/Behavioral Subscore.
*note: Left/Right Sensorimotor subscores are combined, as well as Expressive/Receptive Language subscores



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