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Factors Associated with Increased In-Hospital Mortality Among Children with Intracerebral Hemorrhage

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Abstract

We assessed factors associated with mortality and potential targets for intervention in a large national sample of children with nontraumatic intracerebral hemorrhage. Using Healthcare Cost and Utilization Project Kids' Inpatient Database ICD-9-CM code 431 identified children 1–18 years with nontraumatic intracerebral hemorrhage in 2003, 2006 and 2009. Intracerebral hemorrhage was the primary diagnosis for 1172 children (ages 1–18 years) over the 3-year sample. Factors associated with mortality based on multivariable logistic regression included Hispanic ethnicity (OR 1.9, 95% CI 1.1–3.3), older age (11–18 versus 1–10 years, OR 2.5, 95% CI 1.3–5.0), coagulopathy (OR 3.0, 95% CI 1.6–6.0), and coma (OR 9.0, 95% CI 3.2–24.6). From 2003 to 2009 there was a non-significant decrease in mortality with a significant increase in length of stay from 9 to 11 days ($P < .003$). In children with intracerebral hemorrhage, coma and coagulopathy had the strongest association with mortality; coagulopathy is a potentially modifiable risk factor.

Keywords

intracerebral hemorrhage; mortality; child

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Malik M. Adil, MD: wrote the first draft of the manuscript, performed statistical analysis, and critically revised the manuscript

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Lori C. Jordan, MD, PhD: study design, interpreted data, wrote and critically revised the manuscript

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Introduction

In contrast to adults, approximately half of strokes in childhood are hemorrhagic. Collectively, studies provide consistent estimates that hemorrhagic stroke accounts for between 39% and 54% of all childhood stroke.^{1–3} In a study from a northern California health system, intracerebral hemorrhage had an incidence of 1.4 per 100,000 person-years in children >28 days of age.⁴ Much is known about predictors of outcome after intracerebral hemorrhage in adults, but in children factors associated with outcome are poorly understood. Prior reports have noted intracerebral hemorrhage volume and altered mental status within 6 hours of hospital arrival to be predictors of poor outcome in children.⁵ However, there is less information about predictors of death in children after intracerebral hemorrhage. We aimed to assess factors associated with mortality and potential targets for intervention in a large national sample of children with nontraumatic intracerebral hemorrhage.

Methods

We used the Kids' Inpatient Database, years 2003, 2006, and 2009, part of the Healthcare Cost and Utilization Project, for our analysis. A comprehensive synopsis of the Kids' Inpatient Database is available at <http://www.hcup-us.ahrq.gov/kidoverview.jsp>. Nonfederal, short-term, non-rehabilitation, community general, and specialty hospitals are included in the Kids' Inpatient Database. National estimates were obtained by the use of discharge weights that were developed using the American Hospital Association as the standard.

For the current study, we included children 1 to 18 years of age. The International Classification of Disease, 9th Revision, Clinical Modification (ICD-9-CM) primary diagnosis code 431 was used to identify children admitted with intracerebral hemorrhage. Children with ICD-9 codes for trauma (830s) were excluded. We searched the KID for traditional vascular risk factors for adult hemorrhagic and ischemic stroke (diabetes, hypertension) as well as known risk factors for pediatric intracerebral hemorrhage like coagulopathy, pediatric cancer, and vascular malformations. Study variables included age, sex, race/ethnicity, and comorbidities obtained from Agency for Healthcare Research and Quality's comorbidity data files including hypertension, diabetes, iron deficiency anemia, coagulopathy, chronic lung disease, renal failure, obesity, lymphoma, metastatic cancers, and solid tumors without metastasis. ICD-9-CM secondary diagnosis codes identified secondary diagnoses in children with intracerebral hemorrhage like hypertension (401, 405), elevated blood pressure (796.2), diabetes (249, 250), congenital heart disease (745–747), subarachnoid hemorrhage (430), anomalies of the cerebrovascular system including arteriovenous malformations of the brain and other congenital anomalies of cerebral vessels (747.81), coma (780.01), fever (780.60), seizure (345), altered mental status (780.97), nicotine dependence (305), and sickle cell disease (282.6). Subarachnoid hemorrhage was included as a secondary diagnosis code as it can occur together with intracerebral hemorrhage, particularly with brain arteriovenous malformations. In children, most subarachnoid hemorrhage is traumatic; therefore we did not include it as a primary code, hoping to avoid hemorrhages due to trauma. ICD-9-CM procedure codes were used to estimate the percentage of children with intracerebral hemorrhage who underwent hemorrhage-related procedures like cerebral angiography (88.41), craniotomy (01.20, 01.25

and 01.24), gastrostomy (431), mechanical ventilation (96.72), intubation (96.04), and transfusion (99.04). ICD-9-CM secondary diagnosis codes were used to identify those with intracerebral hemorrhage-associated complications like pneumonia (486, 481, 482.8, and 482.3), urinary tract infection (599.0, 590.9), deep vein thrombosis (451.1, 451.2, 451.81, 451.9, 453.1, 453.2, 453.8, and 453.9), and sepsis (995.91, 996.64, 038, 995.92, and 999.3). Length of stay was recorded. This study was considered exempt by the institutional review board.

Statistical analysis

Logistic regression was used to identify associations between patient characteristics (demographics, comorbidities, secondary diagnoses), which were all independent variables, and in-hospital mortality. All variables that were significantly associated with mortality in the univariate analysis were added as “predictor variables” to a backward step-wise logistic regression model. Variables were included in the final model if they were associated with mortality and if the *P* value was $<.05$. The Cochran-Armitage trend test was used to determine the change in annual average mortality and length of stay from 2003 to 2009. SAS 9.3 software (SAS Institute, Cary, NC) was used to perform the analyses.

Results

Intracerebral hemorrhage was the primary diagnosis for 1172 children (age 1–18 years) over the 3-year sample (Table 1). Fifty-seven percent were male. The most common comorbid conditions included coagulopathy (10.7%), brain arteriovenous malformations (17.6%), hypertension (11.4%), seizure (4.8%), deficiency anemia (4.1%), renal failure (2.7%) and congenital heart disease (1.9%). The most common in-hospital complications were urinary tract infection (4.1%), pneumonia (2.7%) and sepsis (1.1%). The most common procedures performed were cerebral angiography (39.2%), intubation (18.7%), transfusion (10.1%) and craniotomy (5%). Overall, 12.8% died in the hospital, and 21% were discharged to a rehabilitation or nursing facility.

Univariate analyses are shown in Table 2. Factors associated with mortality in multivariate analysis included Hispanic ethnicity (Odds ratio (OR) 1.9, 95% CI 1.1–3.3, $P = .01$), older age (11–18 years versus 1–10 years, OR 2.5, 95% CI 1.3–5.0, $P = .008$), coagulopathy (OR 3.0, 95% CI 1.6–6.0, $P = .0001$), coma (OR 9.0, 95% CI 3.2–24.6, $P < .0001$), and transfusion (OR 2.7, 95% CI 1.2–6.4, $P = .001$). Mortality decreased in a non-significant fashion from 15.4% in 2003 to 12.8% in 2009 ($P < .1$). Mean length of stay increased from 9 days (95% CI 7–11 days) in 2003 to 11 days (95% CI 9–13 days) in 2009 ($P < .003$).

Discussion

Prior studies have noted intracerebral hemorrhage volume and altered mental status within 6 hours of hospital arrival to be associated with poor outcome in children,^{5,6} but few have addressed factors associated with mortality, primarily due to the fact that most studies had samples of less than 150 children and mortality less than 10%.^{5,7} In the present study, in a 3-year sample of more than 1100 children hospitalized with a primary diagnosis of intracerebral hemorrhage, Hispanic ethnicity, older age (11–18 years), coagulopathy,

transfusion, and coma were factors associated with mortality in children with intracerebral hemorrhage. Comparing the mortality rate of 12% in the current study to other studies, in a prospective series of 22 children with intracerebral hemorrhage by Beslow et al., 4.5% of the children died.⁵ In a retrospective cohort study of 132 children with hemorrhagic stroke (identified via ICD-9 codes 430 and 431 and confirmed via chart review), mortality was 4%.⁷ In a series by Lo et al., that utilized a wider ICD-9 code search [(430 (subarachnoid hemorrhage), 431 (intracerebral hemorrhage), 432.0 (nontraumatic extradural hemorrhage), 432.1 (nontraumatic subdural hemorrhage), 432.9 (unspecified intracerebral hemorrhage)] and chart review, of 85 children with intracranial hemorrhage, 34% died.⁸

Hypertension was present in 20% of children that died and 10% of survivors, but this was not statistically significant (Table 2). We found that overall, 11% of children have hypertension as a diagnosis in the setting of intracerebral hemorrhage. This is a higher prevalence of hypertension than is reported in US children (0.3 %)⁹ or Swiss children (2.2 %).¹⁰ Hypertension in this acute setting probably reflects a combination of factors: true hypertension and elevated blood pressure due to pain, stress, or increased intracranial pressure.

In terms of factors associated with mortality, Hispanic children had a higher mortality compared to prior studies where African American children had a higher mortality than white children.^{1,6} The larger sample size in the current study allowed us to identify several factors associated with mortality including older age, coagulopathy, and coma in children with intracerebral hemorrhage. While a prospective study of 22 children with intracerebral hemorrhage did find a trend towards clinically significant disability in older versus younger children in univariate analysis ($P = .06$),⁵ no studies report the association of older age in children with in-hospital mortality. Since coagulopathy is a potentially modifiable risk factor, it may be an important target for intervention. We found that 10.7%, 17.6%, and 11.4% had a secondary diagnosis of coagulopathy, arteriovenous malformation and hypertension respectively. These data support the findings of a single center study that reported that arteriovenous malformations (17%), coagulopathy (13%), and hypertension (10%) were the most common reasons for parenchymal hemorrhage.⁶ However, this is in contrast to the findings in another single center cohort where over 90% of childhood intracerebral hemorrhage was due to vascular malformations.⁵ The differences in risk factors among studies may be due to differences in study inclusion criteria. Other reasons for risk factor differences include tertiary care center “bias” because complicated vascular malformations may be referred more frequently, small sample sizes in prior single center studies, or due to incomplete or inconsistent diagnostic work-ups among the Kids’ Inpatient Database centers. Finally, vascular malformations may not always be visualized in the acute setting and are therefore often found when the hematoma resolves weeks or months later. Of note, brain arteriovenous malformations were recorded in 17.6% of children, though only 5% had a craniotomy. Two factors may be important here. Not all arteriovenous malformations are surgically resectable and some may have been treated with stereotactic radiosurgery. Probably more important is the fact that most arteriovenous malformations are resected during a subsequent admission, particularly if the patient is stable after intracerebral hemorrhage and does not require urgent craniotomy related to elevated intracranial pressure.

Subsequent craniotomy would not have been captured as the Kids' Inpatient Database only allows analysis of a single hospital stay. As shown in Table 2, brain arteriovenous malformations were associated with decreased mortality after intracerebral hemorrhage in univariate analysis, OR 0.3, 95% CI 0.1–0.8, $P = .02$) when compared to children with other causes of intracerebral hemorrhage which also supported delayed treatment. Finally, approximately 6% of children with ICH had cancer, either solid tumors or metastatic cancer (Table 1). Cancer was not significantly associated with mortality, however absolute numbers were small.

Other significant findings included a higher frequency of intubation, mechanical ventilation, blood transfusion and a longer length of stay in the hospital for children with intracerebral hemorrhage who died compared with those who survived (Table 2). The higher frequency of these procedures points to the fact that children with intracerebral hemorrhage who died were sicker than those who survived. Similarly, children who died after intracerebral hemorrhage had significantly fewer angiograms (11.8%) compared to those who lived (43.3%), probably because moribund children did not undergo cerebral angiography.

There was a non-significant decrease in mortality from 2003 to 2009 from 15% to 12% along with a significant increase in length of stay in the hospital from 9 to 11 days. Coma was present in only 3.5% while mortality was 12%. While this seems difficult to reconcile, this may be because intracerebral hemorrhage was not the primary cause of death. In prior pediatric series, in many cases the cause of death is the underlying illness (congenital heart disease, cancer, multi-organ failure) not intracerebral hemorrhage.^{6,7} It also may reflect the limitations of coding a condition, such as coma, in a database. Lastly, coagulopathy may be congenital, pharmacologic, or acquired (related to sepsis leading to disseminated intravascular coagulation). The first two might be manageable, but coagulopathy acquired in the setting of critical illness may not be fully treatable.

This study has limitations inherent to the Kids' Inpatient Database data set, namely the accuracy of the diagnoses and the procedure codes listed in the discharge summaries. For adults with intracerebral hemorrhage, the sensitivity, specificity, and positive predictive values of ICD-9 codes were 85%, 96%, and 89%, respectively.¹¹ In children with intracerebral hemorrhage, Lo et al. raised concerns about the accuracy of ICD-9 codes, particularly for traumatic versus nontraumatic hemorrhage.⁸ While mortality should be coded accurately, other discharge outcome coding might be less accurate, and detailed neurological examinations upon discharge or at follow-up intervals are not available. Prior work in a Northern Californian healthcare plan has documented lesser disability in children with hemorrhagic versus ischemic stroke but significant deficits at discharge were recorded in nearly 50% with hemorrhagic stroke.⁷ The lack of information on hemorrhage volume, a predictor of functional outcome in children, is a substantial limitation of the Kids' Inpatient Database data set. The Kids' Inpatient Database, like the California discharge database and many other large databases used for research, is anonymized so verification of the accuracy of the diagnoses or the procedures via chart review was not possible. Similarly, as this is a discharge database, it is not possible to assess temporal relationships between diagnoses and comorbidities or to test the relationship of one condition “predicting” another. The value of large dataset analyses is to find associations that might not be apparent in smaller samples

that then may guide further study of uncommon conditions. In children with intracerebral hemorrhage, coma and coagulopathy had the strongest association with mortality. Coagulopathy is a potentially modifiable risk factor that warrants further study.

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Table 1

Demographics, clinical characteristics and outcomes of children admitted with intracerebral hemorrhage to hospitals in the United States. (Kids' Inpatient Database: 2003, 2006, and 2009; N=1172)

	n (%)
Demographics	
Age (years), median (IQR)	12 (7–16)
Male	670 (57.4)
White	451 (48.8)
African American	145 (15.6)
Hispanic	200 (23.8)
Other	109 (11.8)
Co-morbid conditions	
Brain arteriovenous malformation	206 (17.6)
Hypertension	134 (11.4)
Coagulopathy	126 (10.7)
Chronic pulmonary disease	68 (5.8)
Seizure	56 (4.8)
Deficiency anemia [†]	48 (4.1)
Coma	42 (3.5)
Metastatic cancer	38 (3.2)
Solid tumor without metastasis	37 (3.1)
Renal failure	32 (2.7)
Fever	26 (2.2)
Congenital heart disease	22 (1.9)
Nicotine dependence	22 (1.9)
Obesity	15 (1.3)
Sickle cell disease	13 (1.1)
Diabetes	12 (1.0)
In-hospital complications	
Urinary tract infection	48 (4.1)
Pneumonia	32 (2.7)
Sepsis	13 (1.1)
Deep vein thrombosis	11 (0.9)
In-hospital procedures	
Cerebral angiography	460 (39.2)
Intubation	220 (18.7)
Mechanical ventilation	128 (10.9)
Transfusion	119 (10.1)
Craniotomy	59 (5.0)
Gastrostomy	28 (2.4)
Length of stay, median (IQR)	5 (3–11)
Discharge disposition/outcome	

	n (%)
Home	776 (66.1)
Nursing/rehabilitation facilities	245 (21.0)
Other*	1 (0.1)
In-hospital mortality	150 (12.8)

[†]The Kids' Inpatient Database uses the term deficiency anemia which includes iron, B12, and folate.

* Other discharge disposition/outcome refers to: missing, left against medical advice, and unknown.

Table 2

Univariate analysis of demographics, clinical characteristics and outcomes of children admitted with intracerebral hemorrhage that died versus were discharged alive from hospitals in the United States. (Kids' Inpatient Database: 2003, 2006 and 2009; N=1172)

	Died (Total n=150) n (%)	Alive (Total n=1022) n (%)	P value
Demographics			
Age (years), median (IQR)	12 (8–16)	12 (7–16)	.7
Male	89 (59.1)	580 (57.1)	.6
White	41 (34.8)	408 (50.7)	.01*
African American	23 (19.2)	122 (15.2)	.4
Hispanic	47 (39.6)	173 (21.5)	.002*
Other	7 (6.4)	101 (12.6)	.04
Co-morbid conditions			
Diabetes	2 (1.6)	10 (1.0)	.9
Hypertension	30 (20.0)	104 (10.1)	.003*
Deficiency anemia [†]	5 (3.2)	43 (4.2)	.6
Congenital heart disease	3 (2.1)	19 (1.8)	.8
Chronic pulmonary disease	13 (9.0)	55 (5.3)	.3
Coagulopathy	42 (28.2)	84 (8.1)	<.0001*
Sickle cell disease	5 (3.2)	8 (0.8)	.2
Renal failure	8 (5.3)	24 (2.3)	.2
Arteriovenous malformation	8 (5.3)	198 (19.4)	<.0001*
Coma	26 (17.0)	16 (1.6)	<.0001*
Fever	4 (2.8)	21 (2.1)	.6
Seizure	4 (2.8)	52 (5.1)	.2
Metastatic cancer	5 (3.5)	33 (3.2)	.8
Solid tumor without metastasis	10 (6.6)	27 (2.6)	.1
Obesity	5 (3.1)	10 (1.0)	.3
Nicotine dependence	2 (1.6)	20 (2.0)	.5
In-hospital complications			
Pneumonia	6 (4.1)	26 (2.5)	.4
Sepsis	4 (2.8)	9 (0.8)	.2
Urinary tract infection	2 (1.6)	46 (4.5)	.03
Deep vein thrombosis	2 (1.6)	9 (0.9)	.8
In-hospital procedures			
Cerebral angiography	18 (11.8)	442 (43.3)	<.0001*
Craniotomy	13 (8.5)	46 (4.5)	.2
Gastrostomy	0 (0)	28 (2.8)	-
Mechanical ventilation	29 (19.5)	99 (9.6)	.04
Intubation	77 (51.3)	143 (14.0)	<.0001*

	Died (Total n=150) n (%)	Alive (Total n=1022) n (%)	P value
Transfusion	40 (26.5)	79 (7.7)	.001 *
Length of stay, median (IQR)	2 (1–4)	6 (3–12),	.001 *

[†]The Kids' Inpatient Database uses the term deficiency anemia which includes iron, B12, and folate.

* Variables with a *P*-value <.05 were included in multivariate analysis.