Mortality After Pediatric Arterial Ischemic Stroke

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abstract

OBJECTIVES: Cerebrovascular disease is among the top 10 causes of death in US children, but risk factors for mortality are poorly understood. Within an international registry, we identify predictors of in-hospital mortality after pediatric arterial ischemic stroke (AIS).

METHODS: Neonates (0–28 days) and children (29 days–<19 years) with AIS were enrolled from January 2003 to July 2014 in a multinational stroke registry. Death during hospitalization and cause of death were ascertained from medical records. Logistic regression was used to analyze associations between risk factors and in-hospital mortality.

RESULTS: Fourteen of 915 neonates (1.5%) and 70 of 2273 children (3.1%) died during hospitalization. Of 48 cases with reported causes of death, 31 (64.6%) were stroke-related, with remaining deaths attributed to medical disease. In multivariable analysis, congenital heart disease (odds ratio [OR]: 3.88; 95% confidence interval [CI]: 1.23–12.29; $P = .021$), posterior plus anterior circulation stroke (OR: 5.36; 95% CI: 1.70–16.85; $P = .004$), and stroke presentation without seizures (OR: 3.95; 95% CI: 1.26–12.37; $P = .019$) were associated with in-hospital mortality for neonates. Hispanic ethnicity (OR: 3.12; 95% CI: 1.56–6.24; $P = .001$), congenital heart disease (OR: 3.14; 95% CI: 1.75–5.61; $P < .001$), and posterior plus anterior circulation stroke (OR: 2.71; 95% CI: 1.40–5.25; $P = .003$) were associated with in-hospital mortality for children.

CONCLUSIONS: In-hospital mortality occurred in 2.6% of pediatric AIS cases. Most deaths were attributable to stroke. Risk factors for in-hospital mortality included congenital heart disease and posterior plus anterior circulation stroke. Presentation without seizures and Hispanic ethnicity were also associated with mortality for neonates and children, respectively. Awareness and study of risk factors for mortality represent opportunities to increase survival.

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WHAT'S KNOWN ON THIS SUBJECT: Stroke is among the top 10 causes of death among children according to administrative data in the United States, with differences in mortality possibly associated with geographic location, sex, and race.

WHAT THIS STUDY ADDS: In this study, we add to our understanding of mortality rates among neonates and children with arterial ischemic stroke and identify both demographic and stroke-related risk factors for in-hospital mortality.

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Childhood arterial ischemic stroke (AIS) affects ~1.2 to 2.4 per 100 000 children per year in developed countries.[1–3] In one study, researchers used death certificates from children in the United States between 1979 and 1998 to demonstrate a decline in mortality due to all stroke subtypes during that period, including in AIS.[4] This finding was supported by the Global Burden of Disease Study, which revealed a global trend toward a decrease in mortality among children with ischemic stroke between 1990 and 2013.[5] However, in 2015, childhood cerebrovascular disease remained among the top 10 causes of death among children in the United States (1–19 years),[6] demonstrating that despite overall decreases in mortality, stroke remains an important cause of pediatric deaths.

Given differing stroke definitions and case ascertainment methods among studies, risk factors for mortality remain poorly understood. In the United States, Black race and living in certain geographic regions (southeastern "stroke belt" states) have been reported as mortality risk factors after childhood AIS.[4,7] Geographic region was also important in the Global Burden of Disease Study; an estimated 4043 children aged 0 to 19 years died of ischemic stroke in 2013 globally (0.2 per 100 000), with 3948 deaths in developing countries (30–60-fold higher mortality than in developed countries).[5]

The Global Burden of Disease Study also showed a trend toward higher mortality among male children with ischemic stroke globally,[5] a finding not present in a previous report from the United States.[4] The authors of most reports on mortality after pediatric AIS have not examined specific stroke risk factors or stroke severity; however, recent work from Chile revealed that cardiac disease and chronic head and/or neck conditions were associated with mortality.[8] We explored potential risk factors for mortality in a large multinational cohort of children and neonates with AIS.

METHODS

Subjects and Study Design

The International Pediatric Stroke Study (IPSS) is a multinational cohort study of children aged 0 to <19 years with AIS or cerebral sinovenous thrombosis. IPSS participation was approved by the institutional review board of each contributing center. Informed consent and assent, when appropriate, was obtained for each enrolled subject. This study is a retrospective analysis of the IPSS registry and includes children >28 days to <19 years and neonates 0 to 28 days of life diagnosed with AIS between January 1, 2003, and July 31, 2014. Subjects with concomitant cerebral sinovenous thrombosis were excluded.

Data Abstraction

Enrolling institutions recorded medical, laboratory, and imaging data on a standardized IPSS data collection form that included demographics, clinical presentation, stroke risk factors, imaging results, laboratory data, treatment, and outcome at discharge (normal, death, neurologic deficit). Race and ethnicity were based on National Institutes of Health definitions and assigned by the enrolling investigator. For those who died during hospitalization, centers were recontacted to obtain date of death and cause of death. Causes of death included those directly related to stroke (brain death, herniation, hemorrhagic transformation, intracerebral hemorrhage, or other) or those related to an underlying medical illness (treatment-related, surgery- and/or procedure-related, complication, disease progression, ventricular assist device, extracorporeal membrane oxygenation, or other). Information regarding withdrawal of care included whether withdrawal was entirely or in part due to stroke deficit severity or to an underlying medical illness. Cause of death was then classified as due to stroke, due to a combination of underlying medical disease and stroke, or due to underlying medical disease.

Statistical Analysis

Descriptive statistics included counts and percentages for categorical variables, means with SD for normally distributed continuous variables, and medians with interquartile range (IQR) for nonnormally distributed continuous variables. A nonparametric test of trend was used to determine whether mortality changed during the study period. Logistic regression was used to analyze associations between possible risk factors and odds of in-hospital mortality. The following factors were hypothesized to be associated with mortality: age at stroke, congenital heart disease, clinical stroke severity (Pediatric National Institutes of Health Stroke Scale [PedNIHSS] score),[9] Black race, Hispanic ethnicity, and birth in a low- or middle- income (LAMI) country. Only variables with <15% missing data were evaluated, with the exception of the PedNIHSS because it has previously been validated as a predictor of functional outcome.[10] LAMI countries were defined by the World Bank.[11] Subjects from 3 countries (Chile, Estonia, and Poland) whose LAMI status changed to high income during the study period were assigned LAMI status on the basis of whether the birth country was LAMI at the date of stroke ictus. Sites from the United States were categorized as "stroke belt" states if located in the South versus other regions as in previous work.[5] Multivariable logistic regression adjusted for possible risk factors that reached the $P < .05$ level in univariable analyses

TABLE 1 LAMI Country Status (N = 3188), Race and Ethnicity (N = 2567)

	n/N (%)
LAMI country[a]	447/3188 (14.0)
White	1475/2567 (57.4)
Hispanic	396/2567 (15.4)
Black[b]	196/2567 (7.6)
East Indian, South Asian	174/2567 (6.8)
Other	167/2576 (6.5)
Southeast Asian	83/2576 (3.2)
North American First Nations	38/2567 (1.5)
Middle Eastern	34/2576 (1.3)
Pacific Islander	4/2576 (0.2)

[a] Argentina, Brazil, Chile, Egypt, Estonia, China, Georgia, India, Malaysia, Poland, Romania, Serbia, Thailand.
[b] Black, African American, African Canadian, African, Caribbean.

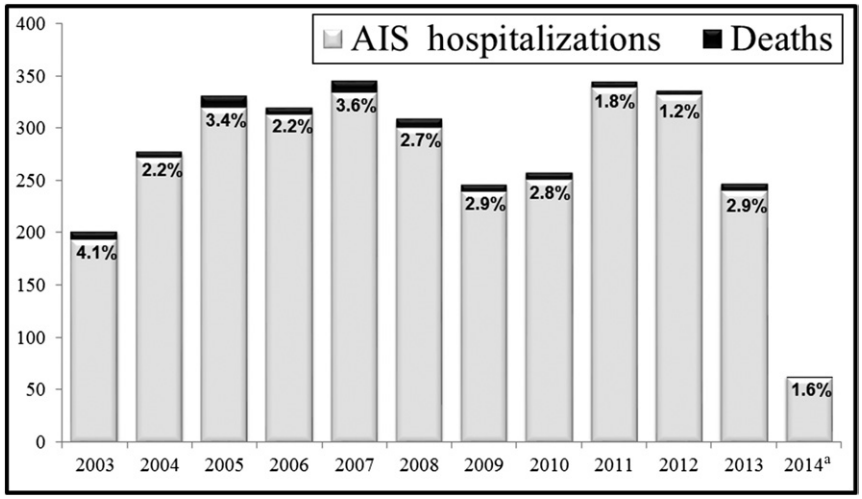

FIGURE 1
In-hospital deaths by year (neonates and children). Percent indicates the mortality rate in study year.
[a] Enrollment through July 31, 2014.

with the exception of the PedNIHSS score because too few subjects had this score recorded. Neonatal and childhood stroke cases were analyzed separately because of differences in underlying stroke risk factors. A P value of $\leq .05$ was considered statistically significant. Stata Version 12.0 (Stata Corp, College Station, TX) was used for all analyses.

RESULTS

In total, 915 neonates (541 male patients, 59.1%) and 2273 children (1322 male patients, 58.2%) with AIS from 87 hospitals in 24 countries were included. Median age of the children was 5.7 years (IQR 1.6–12.3 years). Race and ethnicity information, available for 2567 of 3188 participants (80.5%), and LAMI data are presented in Table 1.

Eighty-four of 3188 (2.6%) subjects died during the hospitalization. In-hospital mortality during each study year is presented in Fig 1. Stroke deaths did not differ by year of stroke ictus, P = .11, test of trend. The average yearly in-hospital mortality was 2.7 deaths per 100 stroke admissions. Children were more likely to die during hospitalization than neonates (odds ratio [OR]: 2.04; 95% confidence interval [CI]: 1.15–3.65; P = .015); 14 neonates (1.5%) and 70 children (3.1%) died. Among children, there was no increased risk of death with increasing age (OR: 0.97 per 1 year of age; 95% CI: 0.93–1.01; P = .16). When age at AIS was categorized as previously defined by the National Center for Health Statistics,[6] 34 of 1332 patients who were <1 year old died (2.6%), 19 of 643 patients who were 1 to 4 years old died (3.0%), 9 of 480 patients who were 5 to 9 years old died (1.9%), 14 of 432 patients who were 10 to 14 years old died (3.2%), and 8 of 301 patients who were 15 to <19 years old died (2.7%), P = .82, test of trend. Univariable mortality risk factors for neonates and children are found in Tables 2 and 3, respectively. In multivariable analysis for neonates, congenital heart disease (OR: 3.88; 95% CI: 1.23–12.22; P = .021), posterior plus anterior circulation stroke (OR: 5.36; 95% CI: 1.70–16.85; P = .004), and stroke presentation without seizures (OR: 3.95; 95% CI: 1.26–12.37; P = .019) were associated with in-hospital mortality. In multivariable analysis among children, Hispanic ethnicity (OR: 3.12; 95% CI: 1.56–6.24; P = .001), congenital heart disease (OR: 3.14; 95% CI: 1.75–5.61; P < .001), and posterior plus anterior circulation stroke (OR: 2.71; 95% CI: 1.40–5.25; P = .003) remained associated with in-hospital mortality. In children, neither seizures at presentation nor residence in stroke belt states versus other US regions was associated with mortality.

Cause of death was available in 9 of 14 neonates (64.3%, Table 4) and 39 of 70 children (55.7%, Table 5). Number of days from stroke onset to death was available in 9 of 14 neonates (64.3%; median 26 days, IQR 15–65 days) and in 40 of 70 children (57.1%; median 11 days, IQR 5–26.5 days). Of 48 cases with reported causes of death, 31 (64.6%) were stroke-related or due to stroke plus medical causes, with remaining deaths attributed to medical disease.

DISCUSSION

In this multinational cohort, 2.6% of pediatric patients with AIS died during hospitalization, and nearly 65% of deaths with a known cause were related to the stroke and/or subsequent deficits. Risk factors for in-hospital mortality in neonates and children included congenital heart disease and stroke in the posterior plus anterior circulations, with the additional risk factor of Hispanic ethnicity for children. Also, neonates presenting without seizures had

TABLE 2 Univariable Predictors of In-Hospital Mortality in Neonates (0–28 Days), 14 Total Deaths and 915 Total Neonates

Risk Factor	*N* With Mortality/*N* With Variable	*N* With Mortality/*N* Without Variable	OR	95% CI	*P*
Male sex	12/541	2/374	4.22	0.94–18.96	.06
LAMI country	3/112	11/803	1.98	0.54–7.21	.30
Southern United States (versus Western, Northeastern, Midwestern United States)	2/67	3/284	2.88	0.47–17.60	.25
Hispanic ethnicity	3/125	11/790	1.74	0.49–6.33	.40
Black race	0/30	14/885	1	NA	NA
Presentation without seizure	8/243	6/652	3.67	1.26–10.67	.017[a]
Sickle cell anemia[b]	0/0	14/915	NA	NA	NA
Prothrombotic abnormality	2/94	12/821	1.47	0.32–6.65	.62
Congenital heart disease	6/125	7/707	5.04	1.67–15.26	.004[a]
Arteriopathy (vasculopathy)	0/16	10/770	1	NA	NA
Anterior and posterior circulation (reference group isolated anterior circulation)	7/104	Anterior only 7/632; posterior only 0/71	6.44	2.21–18.77	.001[a]

NA, not applicable.
[a] Also statistically significant in multivariable analysis.
[b] No neonate was diagnosed with sickle cell anemia.

TABLE 3 Univariable Predictors of In-Hospital Mortality in Children (29 Days—<19 Years), 70 Total Deaths and 2273 Total Children

Risk Factor	*N* With Mortality/*N* With Variable	*N* With Mortality/*N* Without Variable	OR	95% CI	*P*
Male	42/1322	28/951	1.08	0.67–1.76	.75
LAMI country	22/335	48/1938	2.77	1.65–4.65	<.001
Southern United States (versus Western, Northeastern, Midwestern United States)	12/355	21/767	1.24	0.60–2.56	.55
Hispanic ethnicity	22/271	48/2002	3.60	2.14–6.06	<.001[a]
Black race	3/166	67/2107	0.56	0.17–1.80	.33
Presentation without seizure	45/1570	24/632	0.75	0.45–1.24	.26
Sickle cell anemia	0/98	70/2175	NA	NA	NA
Prothrombotic disorder	3/173	67/2100	0.54	0.17–1.72	.29
Congenital heart disease	28/397	42/1784	3.15	1.93–5.14	<.001[a]
Arteriopathy (vasculopathy)	11/679	52/1383	0.42	0.22–0.81	.01
Anterior and posterior circulation (reference group isolated anterior circulation)	18/221	Anterior only 34/1298; posterior only 11/434	3.30	1.83–5.95	<.001[a]
PedNIHSS median (IQR)	20.5 (12.5–28) of 12 with PedNIHSS scores who died	6.5 (3–12) of 342 with PedNIHSS scores who did not die	1.13[b]	1.08–1.19	<.001

NA, not applicable.
[a] Also statistically significant in multivariable analysis.
[b] OR for PedNIHSS is per 1-point increase in score.

TABLE 4 Causes of Death Among Neonates

Stroke-Related (*N* = 2)	Stroke-Related Plus Medical Cause (*N* = 4)	Medical Cause (*N* = 3)
Care withdrawn because of deficits (2)	Congenital heart disease plus support withdrawn because of stroke-related deficits (2)	Air leak syndrome related to congenital heart disease (1)
	Pneumothorax plus support withdrawn because of stroke-related deficits (2)	Acute renal failure (1)
	Neurologic respiratory arrest plus severity of underlying disease (1)	Meningitis (1)

an increased risk of in-hospital mortality. A major strength of the IPSS registry and the current report is that children from 24 countries, including 13 LAMI nations, were included.

In a previous cross-sectional analysis of critical care usage in a California cohort of childhood stroke (age >28 days–19 years), 4 of 124 ischemic stroke patients (3.2%) died,[12] which is similar to our finding of an in-hospital mortality rate of 3.1% among children. The overall in-hospital mortality rate of 2.6% we report is lower than the in-hospital mortality rate of 6.5% reported in a Canadian cohort of 1129 pediatric AIS patients presenting between 1992 and 2001.[13] In that study, 35 of 74 in-hospital deaths (47.3%) were stroke-related.[13] Although not directly comparable because in-hospital mortality was not reported, our in-hospital mortality rate appears lower than the mortality

TABLE 5 Causes of Death Among Children

Stroke-Related ($N = 14$)	Stroke-Related Plus Medical Cause ($N = 11$)	Medical Cause ($N = 14$)
Brain death (6)[a,b]	Congenital heart disease plus support withdrawn due to stroke-related deficits (9)	Bronchopneumonia (1)
Herniation (6)[a,c,d]	Severe pertussis, support withdrawn due to medical severity and stroke-related deficits (1)	Congenital heart disease (7)
Hemorrhagic transformation (4)[b,d]	Human immunodeficiency and unspecified stroke-related cause (1)	Acquired cardiomyopathy (2)
Care withdrawn because of deficits (4)[c,d]		Chronic renal failure and renal transplant rejection (1)
Neurologic respiratory failure (1)		Malaria (1)
		Tuberculosis meningitis (1)
		Juvenile idiopathic arthritis with acquired pulmonary hypertension leading to fatal arrhythmia (1)

[a] One child with brain death after herniation.
[b] One child with brain death after hemorrhagic transformation.
[c] One child with herniation leading to withdrawal of care.
[d] Two children with herniation after hemorrhagic transformation leading to withdrawal of care.

rate among Chilean children with AIS, among whom 26.5% died.[8]

Geographic, sex, and racial disparities in childhood stroke mortality have been found in several studies.[1,5,7] In the Global Burden of Disease Study, there was excess mortality in children with ischemic stroke from developing nations compared with those from developed countries as well as a trend toward increased mortality in male patients.[5] Although living in a LAMI country was a risk factor for death in children in univariable analysis, living in a LAMI country was not a risk factor for neonatal mortality or for childhood mortality in multivariable analysis. However, it is possible that the lack of association between LAMI countries and mortality in this cohort was because only 14% of participants were from LAMI countries. Although not statistically significant, the *P* value for in-hospital mortality for male sex among neonates with stroke was .06. Given that only 14 deaths occurred among neonatal stroke subjects, it is possible that male sex would emerge as a risk factor for in-hospital mortality among neonates if the sample size were larger. In contrast to work by Fullerton et al,[7] which revealed that stroke in the southern United States compared with other United States regions was a risk for mortality for both ischemic and hemorrhagic stroke, we did not demonstrate an increased risk of in-hospital mortality in southern states among the neonatal or childhood stroke groups.

Black race was not a risk factor for in-hospital mortality in the current cohort, whereas Black race was a mortality risk factor in previous work.[4] Several reasons could account for these differences, including enrollment period. The study by Fullerton et al[4] included subjects from 1979 to 1998, whereas our cohort presented between 2003 and 2014. In 1998, the landmark Stroke Prevention Trial in Sickle Cell Anemia was published,[14] and subsequent work has shown that ischemic stroke mortality decreased among Black children in the time period between 1998 and 2007 compared with between 1988 and 1997.[15] Therefore, access to improved preventive stroke measures like transfusion therapy in children with sickle cell disease may be in part responsible for the lack of association between Black race and in-hospital mortality in the current cohort. However, in the work by Fullerton et al,[4] the excess mortality risk among Black children was not fully explained by sickle cell anemia, and the authors concluded that other factors could play a role. In the current study, 6.8% of participants were Black, compared with 15% in the work by Fullerton et al,[4] so our cohort could have been underpowered to demonstrate a difference. Although Black race was not a risk factor for in-hospital mortality in the current study, an interesting finding was that Hispanic ethnicity was a risk factor for in-hospital mortality among children with AIS, even when controlling for LAMI country status. The reasons for this finding are not known, but similar results have been found in childhood intracerebral hemorrhage and in adult stroke.[16,17] Among 1172 children with spontaneous intracerebral hemorrhage from the Kids' Inpatient Database, 150 (12.8%) died, and Hispanic ethnicity was a risk factor for death.[16] Among adults with ischemic stroke in the United States, stroke mortality rates have increased among Hispanics since 2013.[18] In future research efforts, investigators should explore whether ethnic differences in mortality rates are related to disparities in care.

Previous outcome studies have been primarily small single-site studies, studies from large administrative data sets in which examining individual data was not possible, or have assessed predictors of combined neurologic and mortality outcomes. Therefore, few previous studies have examined risk factors

for mortality. We found that stroke cause was associated with mortality. Congenital heart disease was a risk factor for in-hospital mortality among neonates and children. Among those with congenital heart disease, the cause of death was stroke-related or in part stroke-related in 65.2% of cases, indicating that the strokes themselves are an important cause of mortality in this group. Our finding supports the conclusions of López-Espejo and Hernández-Chávez[8] from a Chilean cohort. Both studies indicate that children with cardiac stroke may warrant additional monitoring for neurologic deterioration. Although not significant in multivariable analysis, children with arteriopathic stroke seemed to have decreased mortality.

Seizures at presentation have been associated with poor outcome and more severe stroke in the pediatric population.[19–22] In our cohort of neonates, presentation without seizures was associated with in-hospital mortality. One possible explanation for our finding is that neonates who presented with seizures may have been diagnosed and treated more quickly for their strokes. Moreover, although seizures are associated with cortical strokes,[23] deep strokes in neonates are associated both with nonseizure presentations (persistent altered consciousness, diffuse hypotonia) and with worse outcomes.[13,24]

Children who were critically ill or moribund after stroke may not have been included because of the reluctance of clinicians to approach distressed parents for consent. This problem may have been especially true in neonates for whom redirection of care was a common mechanism of mortality. Therefore, we consider our mortality rate to be a minimum estimate. Furthermore, additional information is needed on stroke-related deaths after hospitalization. Imaging was not available for central review or for infarct volume quantification. Despite this limitation, our results suggest that increased stroke severity is a risk factor for mortality. Both neonates and children with strokes that affected the posterior and anterior circulations were at increased risk for mortality compared with those with isolated anterior circulation stroke, a finding that may indicate that larger strokes are associated with death. Also, among children for whom the PedNIHSS was scored (n = 354), the median score among those who died was 20.5 compared with 6.5 among those who survived hospitalization. Although these results are not surprising and are consistent with the adult literature,[17] children with larger or more clinically severe strokes may also benefit from especially vigilant monitoring.

Another study limitation is that cause of death was not available for 36 of 84 participants (42.9%) who died. Cause of death was collected retrospectively, and in some cases additional details were not available. Certain sites deidentified data and were not able to relink study identification numbers to patient names to collect additional information. We also do not have information about timing of complications like hemorrhagic transformation of infarction. Our registry did not collect information about seizures after presentation or EEG results. Electrographic-only seizures are common in critically ill children,[25] so it is possible that the number of neonates with seizures was underestimated. Finally, although congenital heart disease was a risk factor for death among neonates and children, the IPSS did not collect information regarding heart lesion type and use of ventricular assist devices or extracorporeal membrane oxygenation. Therefore, we were not able to analyze whether specific congenital heart diseases (eg, cyanotic vs acyanotic lesions) or specific procedures or support devices were related to mortality.

Mortality cause was not available in nearly 43% of the subjects who died, so it is difficult to draw firm conclusions about reasons for death. However, among those for whom cause of death was known, the stroke itself was the cause or contributed to the cause of death in 64.6% of cases, a finding consistent with work by Fox et al[12] in which 6 of 11 childhood stroke deaths (54.5%) were due to the stroke itself. Importantly, 12 of 14 stroke-related deaths were due to progression to brain death or herniation, indicating that malignant cerebral edema is a likely mechanism. It is critical for pediatric intensivists and other medical personnel to recognize malignant middle cerebral artery syndrome and herniation syndromes because these fatal conditions can be treated with lifesaving and function-sparing hemicraniectomy when recognized quickly.[22,26] The fact that the strokes or their direct sequelae are responsible for more than half of pediatric stroke deaths indicates that improved stroke recognition, earlier supportive care, more rapid intervention, and neuroprotective treatments are critical for decreasing mortality after stroke in the pediatric population.

CONCLUSIONS

In-hospital mortality occurred in 2.6% of pediatric patients with AIS in a multinational prospective cohort from both LAMI and non-LAMI countries, indicating that stroke remains an important cause of death in neonates and children. We leverage one of the largest prospective pediatric stroke registries available and have confirmed risk factors for mortality found in single-site studies as well as identified risk factors for in-hospital mortality that have

not previously been reported. Risk factors for mortality among neonates and children included congenital heart disease and stroke affecting both the anterior and posterior circulation. Additional risk factors included Hispanic ethnicity (among children) and presentation without seizures (among neonates). Physicians including neonatologists, pediatric intensivists, and hospitalist pediatricians who care for pediatric patients with AIS may use the information in this report to aid recognition of those who may be at high risk for deterioration and death. Additional studies are needed to understand reasons for ethnic disparities and to develop improved neuroprotective strategies for children with severe AIS.

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ABBREVIATIONS

AIS: arterial ischemic stroke
CI: confidence interval
IPSS: International Pediatric Stroke Study
IQR: interquartile range
LAMI: low- and middle- income
OR: odds ratio
PedNIHSS: Pediatric National Institutes of Health Stroke Scale

Dr Beslow designed the study, designed the data collection instrument regarding cause of death, collected the data, performed all statistical analyses, and drafted the manuscript; Dr Dowling conceptualized the study, designed the study, designed the data collection instrument regarding cause of death, and collected the data; Drs Hassanein, Lynch, Titomanlio, Kolk, Biller, Grabowski, Abdalla, and Mackay designed the data collection instrument regarding cause of death and collected the data; Drs Zafeiriou, Sun, Kopyta, and Chan reviewed the study design, designed the data collection instrument regarding cause of death, and collected the data; Dr deVeber designed the study, designed the data collection instrument regarding cause of death, collected the data, and coordinated and supervised the data collection process and analysis plan; and all authors critically reviewed, revised, and edited the manuscript, approved the final manuscript as submitted, and agree to be accountable for all aspects of the work.

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