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ORIGINAL COMMUNICATION

Risk factors for in-hospital and follow-up mortality after childhood arterial ischemic stroke

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Abstract

Objectives To explore risk factors contributing to 30-day and long-term survival in children with a first episode of arterial ischemic stroke (AIS).

Study design Single center prospective observational study including 119 children aged between 30 days and 18 years, with a first episode of AIS between 2003 and 2015. Diagnosis was confirmed with magnetic resonance images. Outcomes included 30-day mortality and survival up to 8 years of follow-up. Demographic (e.g., gender, age), clinical (e.g., stroke severity measured by the Pediatric National Institute of Health Stroke Scale (NIHSS), clinical presentation, underlying conditions), radiological (e.g., involved circulation, location), and stroke recurrence data, were used to predict outcomes. Data analyses included logistic and Cox regression multivariate models with Firth's bias correction.

Results 30-day mortality was 11.7% ($n = 14$). A total of 23 (19.3%) children died during the follow-up. 30-day mortality was only predicted by stroke severity (OR = 1.11, 95% CI = 1.02–1.26) in children > 2 years. Survival was predicted by stroke severity (HR = 1.05, 95% CI = 1.01–1.09), congenital heart disease (HR = 3.62, 95% CI = 1.33–10.93), prothrombotic states (HR = 3.51, 95% CI = 1.25–9.32), and anterior plus posterior circulation stroke (HR = 2.43, 95% CI = 1.42–4.61, p 0.026). Stroke recurrence (n= 23; 19.3%) was not a significant predictor of follow-up mortality.

Conclusions This study identified groups with greater acute and long-term mortality after a first episode of AIS in childhood. Specific interventions focused on these risk groups may decrease mortality rates. Further studies need to confirm our findings by adding children from other centers.

Keywords Childhood stroke · Stroke mortality · Hispanic ethnicity · Cohort study · Stroke outcomes

Introduction

Arterial ischemic stroke (AIS) is a rare condition with an annual incidence of 1.2–8 per 100,000 children beyond neonatal age [1–3]; however, prior studies found a higher frequency in males, black patients, and infants under one year of age [4]. Etiologies of childhood AIS are varied and differ substantially from those in adults, among whom atherosclerotic disease is the leading cause of AIS. According to the International Pediatric Stroke Study (IPSS), the most common risk factors for AIS are the central nervous system (CNS) arteriopathies, cardiac diseases, and chronic prothrombotic states (PS) [5].

Despite the lower incidence of AIS compared to other childhood neurological disorders, functional impairment, morbidity, and mortality are quite significant [6]. Although research has revealed a decrease in mortality among children with AIS throughout the last two decades [7, 8], pediatric cerebrovascular diseases still be an important cause of death, at least in developed countries [9].

A recent retrospective analysis of the IPSS registry conducted by Beslow et al. [10] studying 2273 children aged between 28 days and 19 years diagnosed with an AIS (January 2003 through July 2014) revealed that Hispanic ethnicity, congenital heart disease (CHD), and posterior plus anterior circulation stroke are risk factors for mortality during hospitalization. Even though this work determined predictors

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for in-hospital mortality following AIS, there is a paucity of studies focused on death beyond hospital discharge.

In a previous report, we found an association between cumulative mortality at five years of AIS and chronic illness (cardiopathy and head and neck disorders, specifically), but radiological features of stroke were not analyzed [11]. An improved understanding of variables associated with mortality in children following a stroke may improve supportive care and specific intervention to decrease adverse outcomes in risk groups. Therefore, in this study, we sought to explore potential clinical and stroke-related risk factors for both 30 days in-hospital mortality and mortality in a long-term follow-up in a single-center cohort of predominantly Hispanic children from Chile who were suffering a first-ever AIS.

Methods

Study design and patients

This was a prospective, observational cohort study conducted at a single-center, tertiary referral university hospital. All children aged 30 days–18 years with radiologically confirmed first-ever AIS [defined as acute neurological symptoms or signs secondary to acute focal cerebral infarction in an arterial distribution on magnetic resonance images (MRI)] occurring between January 2003 and December 2015 and admitted to the Pontifical Catholic University of Chile's Clinical Hospital were consecutively enrolled and evaluated.

All information was corrected according to a review of medical and neuroimaging records and prospectively registered in a database according to institutional protocols [11]. In all children older than two years at diagnosis, we measured initial stroke severity using the Pediatric National Institute of Health Stroke Scale (NIHSS) score. In patients enrolled before December 2012, the score was estimated by reviewing their clinical records from the database, while in children admitted after that date, the score was calculated at the time of the stroke [12]. To avoid additional factors affecting mortality, we excluded patients with previous childhood stroke (including suspected perinatal stroke), moderate to severe hypoxic-ischemic encephalopathy, cerebral sinovenous and venous thrombosis, intracranial hemorrhage (not attributable to hemorrhagic transformation), prematurity (less than thirty-seven weeks of gestation at birth), cranial surgery, intracranial tumor-related stroke, and concomitant moderate to severe traumatic brain injuries.

Definitions and data collection

A pediatric neurologist obtained imaging and clinical data of acute events during the hospital stay. The clinical variables examined were age at stroke, sex, initial stroke severity measured as Pediatric NIHSS score, decreased level of consciousness (defined as Glasgow Coma Score less than twelve points), headache in the prior twelve hours, acute symptomatic seizures (defined as any clinical seizure occurring within seven days of stroke [13]), status epilepticus within twenty-four hours of stroke, focal deficits at onset (including motor, visual, or language impairment), CHD, CNS arteriopathy (including vasculitis, dissection, Moyamoya, focal cerebral, and unspecified arteriopathies), acute infections (including CNS infections, mild systemic infections, and upper respiratory infections), PS (including antiphospholipid antibodies, factor V Leiden, antithrombin III deficit, protein C or S deficit, lupus anticoagulant antibodies, elevated lipoprotein a, and thrombocytopenia), anemia (defined as a hemoglobin level that is two standard deviations (SD) below the mean for age; although types and causes of anemia were not studied, we did not find patients with sickle cell disease), and neoplasms (hematological and solid tumors).

Eighty-six children had MRI with vascular imaging (67 by magnetic resonance angiography), and 33 children only had MRI showing an acute cerebral infarction in a typical arterial distribution. As a previous work, a radiologist evaluated all MRI sequences and posteriorly were reviewed by an experienced neuroradiologist and a pediatric neurologist together [14]. Stroke-related variables examined were circulation involved (anterior, posterior, and anterior plus posterior), structure involved (classified as lobar only: cortical and with matter infarction, thalamus/basal ganglia only, brainstem/cerebellum only, and multiple structures), infarct number (unique or multiple), infarct laterality (left hemisphere, right hemisphere, and bilateral), infarct hemorrhagic transformation, and presence of an acute subdural hematoma. Stroke recurrence was defined as any new acute neurological deficit with further brain infarction occurred after two weeks of the index stroke.

We used death certificates from studied children between January 01, 2003 and July 30, 2017 (follow-up period ranged from 0.1 to 184 months) to obtain date of death and cause of death (classified as due to stroke: intracranial hemorrhage, brain death or herniation, due to a cardiopathy, or due to multisystemic failure). We categorized all children who died during the first thirty days of the onset of the stroke as in-hospital mortality group ($N = 119$); likewise, we classified all children who died after this period in follow-up mortality group ($N = 105$).

Statistical analysis

All analyses were conducted using the IBM SPSS Statistics version 20 (IBM Corp., Somers, NY) and R 3.3.3 version software. Continuous variables were expressed as median and interquartile range (IQR) or mean and SD, and discrete variables as both absolute and relative frequencies.

To account for the lack of deaths in this cohort, we used regression models with penalized likelihood method. First, a univariate analysis was performed comparing differences in in-hospital and follow-up mortality for each dependent variable using logistic regression and Cox regression, respectively.

We performed a multivariate Firth logistic regression model to determine risk factors for in-hospital mortality, including all variables with a p value < 0.1 in the univariate analysis [significance set at 5%; results presented as Odds ratios (OR) with 95% confidence intervals (CI)].

In addition, we performed a multivariate Cox proportional-hazards regression model with Firth's bias correction method to assess hazard ratios (HRs) and 95% CI of risk factors for mortality during follow-up, including all variables with a p value < 0.1 in the univariate analysis (significance set at 5%).

Results

Among the 129 patients who had met the study criteria, ten (7.8%) were lost or declined to participate. A total of 119 children who suffer a first-ever AIS after neonatal age were included in the final study cohort. The median age at stroke onset was 1.42 (IQR 0.41–6.11) years. The number of months from stroke onset to death was available in all children; the mean follow-up time was 82.56 (SD 58.63; min: 2, max: 97) months. Patient characteristics, including demographics, clinical manifestations, underlying conditions, stroke-related characteristics, and stroke recurrences are summarized in Table 1.

This study identified a mortality rate of 31.1% ($n = 37$). Fourteen (11.8%) children died before hospital discharge (< 30 days), and 23 (19.3%) died after the first month following the stroke. Causes of death among children who died before hospital discharge were due to stroke in eight (57.1%), due to a cardiopathy in two (14.3%), and due to multisystemic failure in four (28.6%) (Fig. 1). Meanwhile, the causes of death among children who died during follow-up was stroke in three (13.1%), cardiopathy in 11 (47.8%), and multisystemic failure in nine (39.1%).

Univariate logistic regression revealed that initial stroke severity and absence of focal deficits at onset were positively associated with in-hospital mortality (Table 2). After the multivariate model, only initial stroke severity was positively associated with in-hospital mortality (OR = 1.11, 95% CI = 1.02–1.26, $p < 0.001$).

Table 1 Characteristics for children with a first-ever arterial ischemic stroke diagnosed at a tertiary referral university hospital of Santiago, Chile, 2003–2015 ($N = 119$)

Variables	*N*	(%)
Demographics		
Age in years (median (IQR))	1.42	(0.41–6.11)
Aged < 2 years at onset	63	(52.9)
Male sex	74	(62.2)
Follow-up in months (mean (SD))	82.6	(58.6)
Clinical manifestations		
Pediatric NIHSS score[a] (median (IQR))	6	(3.25–24.25)
GCS < 12	83	(69.7)
Focal deficits	58	(48.7)
Headache	17	(14.3)
Acute symptomatic seizures	69	(58)
Status epilepticus	22	(18.5)
Underlying conditions		
Congenital heart disease	48	(40.3)
CNS arteriopathy	37	(31.1)
Infections	41	(34.5)
CNS infections	10	(8.4)
Prothrombotic states	34	(28.6)
Anemia	21	(17.6)
Neoplasms	7	(5.9)
Circulation involved		
Anterior	79	(58.8)
Posterior	15	(12.6)
Anterior plus posterior	34	(28.6)
Structure involved		
Lobar only	42	(35.3)
Cortical only	19	(16)
White matter only	23	(19.3)
Thalamus/basal ganglia only	22	(18.5)
Brainstem/cerebellum only	3	(2.5)
Multiple	52	(43.7)
Other stroke characteristics		
Multifocal infarction	75	(63)
Bilateral infarction	63	(52.9)
Left hemisphere infarction	30	(25.2)
Right hemisphere infarction	26	(21.8)
Hemorrhagic transformation	26	(21.8)
Acute subdural hematoma	7	(5.9)
Stroke recurrence		
Yes	23	(19.3)

[a]Pediatric NIHSS was applied exclusively to children older than 2 years ($N = 56$)

[b]Percentage of children older than 2 years with Pediatric NIHSS score > 15

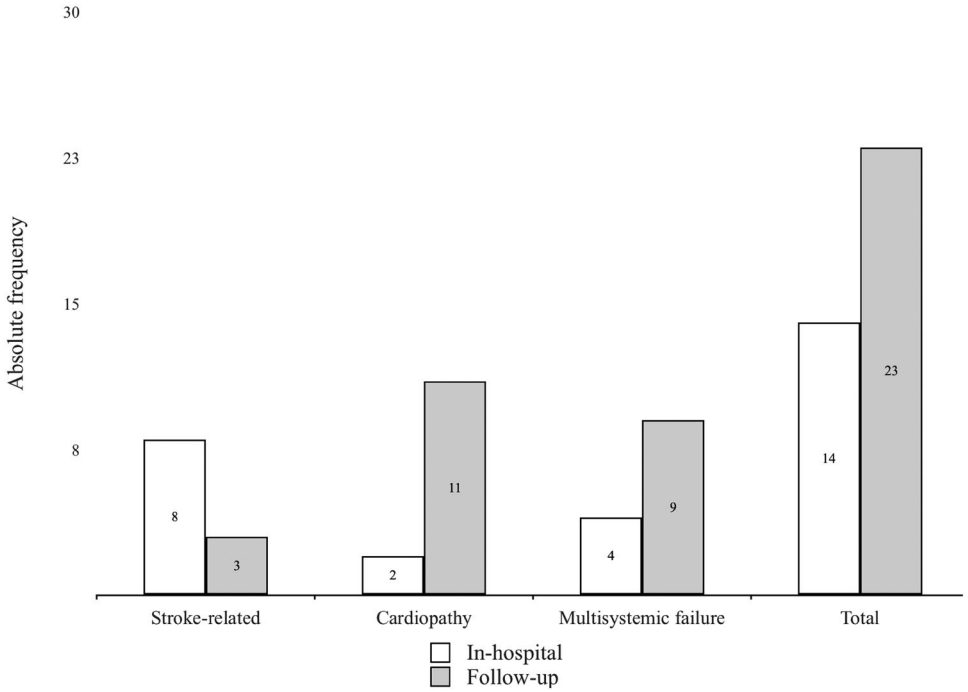

Fig. 1 Causes of death for children with a first-ever arterial ischemic stroke 2003–2015 (Microsoft Excel® was used to create the artwork)

While on univariate Cox regression analysis, CHD, PS, neoplasms, anterior plus posterior stroke, thalamus/basal ganglia only infarct, and initial stroke severity were the factors decreasing the survival rate in the follow-up (Table 3). Multivariate analysis showed that CHD (HR = 3.62, 95% CI = 1.33–10.93, $p = 0.011$), PS (HR = 3.51, 95% CI = 1.25–9.32, $p = 0.017$), initial stroke severity (HR = 1.05, 95% CI = 1.01–1.09, $p = 0.019$), and anterior plus posterior stroke (HR = 2.43, 95% CI = 1.42–4.61, p 0.026) were independent factors influencing the follow-up mortality.

Discussion

The goal of this study was to explore the risk factors for mortality following a first-ever AIS in childhood. We analyzed data from 119 patients, 14 of whom died within one month of stroke, and 23 died during the follow-up period. The major finding of our study is that stroke severity, circulation, and some chronic illnesses are significant determinants in long-term mortality following a childhood stroke. After multivariate analysis, mortality during follow-up was higher in children with higher initial stroke severity (Pediatric NIHSS score), CHD, PS, and anterior plus posterior circulation involvement. Although, according to the IPSS data, both CHD and anterior plus posterior circulation stroke are predictors for in-hospital mortality, till date, no studies are evaluating these factors as risk factors for long-term survival.

Also, our data showed a significant association between higher initial stroke severity and increased 30-day in-hospital mortality. This finding is comparable to a previous multicenter study in the pediatric population and confirms that the most consistent predictor of early mortality after childhood AIS is stroke severity [10]. However, in contrast with this study, neither CHD nor stroke-related features are influencing mortality during hospitalization.

The mortality rate experienced in this cohort of children are higher than those in contemporaneous studies carried out in Asia, Europe, and North America [1, 3, 15]. These elevated figures are probably due to the high proportion of children coursing a CHD in our study group and to the prolonged follow-up in some cases. Hispanic ethnicity has been indicated to be associated with adverse survival outcomes after a childhood AIS [10]. Although ethnic disparities in mortality rates might be related to differences on the geographical distribution of stroke risk factors and socioeconomic determinants, studies from hemorrhage stroke and adult population coincide, in that there are higher figures of mortality in the Hispanic community [16, 17]. Thus, ethnicity appears as a feasible risk factor for adverse survival outcomes after pediatric stroke.

The cause of death of the majority of children who died before hospital discharge was directly related to the stroke, finding consistency with previous studies in which the stroke itself was the cause of death in 55–65% of the cases [10, 18]. In contrast, most children who died during the follow-up did so due to CHD or multisystemic failure related to chronic illness, including PS. Studies

Table 2 Univariate analysis for risk factors of in-hospital mortality for children with a first-ever arterial ischemic stroke, 2003–2015 ($N = 119$, total deaths = 14)

Variable	With variable (death/total)	Without variable (death/total)	OR	95% CI	*p* value**
Age (years)	N/A	N/A	0.17	0.79–1.06	0.331
Male sex	8/74	6/45	1.28	0.41–3.84	0.652
Pediatric NIHSS score[b]	N/A	N/A	1.12	1.05–1.25	< 0.001[a]
GCS < 12	12/83	2/36	2.41	0.67–12.85	0.189
Focal deficits	3/58	11/61	0.27	0.06–0.89	0.031[a]
Headache	1/17	13/102	0.60	0.06–2.75	0.553
Acute symptomatic seizures	7/69	7/50	0.69	0.23–2.09	0.512
Status epilepticus	5/33	9/97	2.92	0.86–9.27	0.083
Congenital heart disease	7/48	7/71	1.55	0.51–4.68	0.426
CNS arteriopathy	2/37	12/82	0.39	0.07–1.42	0.167
Infections	6/42	8/78	1.51	0.48–4.54	0.459
CNS infections	1/10	13/109	1.12	0.11–5.54	0.897
Prothrombotic states	5/34	9/85	1.50	0.45–4.56	0.488
Anemia	3/21	11/98	1.43	0.34–4.89	0.591
Neoplasms	0/7	14/112	1	N/A	N/A
Anterior circulation	8/70	6/49	0.91	0.30–2.82	0.866
Posterior circulation	0/15	14/104	1	N/A	N/A
Anterior plus posterior circulation	6/34	8/85	2.07	0.66–6.29	0.202
Lobar only	4/42	10/77	0.75	0.21–2.31	0.628
Cortical only	1/19	13/100	0.52	0.05–2.37	0.484
White matter only	3/23	11/96	1.26	0.30–4.27	0.721
Thalamus/basal ganglia only	5/22	9/97	2.92	0.86–9.27	0.083
Brainstem/cerebellum only	0/3	14/116	1	N/A	N/A
Multiple	5/52	9/67	0.71	0.21–2.13	0.549
Multifocal infarction	10/75	4/44	1.44	0.46–5.15	0.532
Bilateral infarction	9/63	5/56	1.63	0.54–5.32	0.383
Left hemisphere infarction	3/30	11/89	0.86	0.20–2.86	0.826
Right hemisphere infarction	2/26	12/93	0.66	0.12–2.43	0.563
Hemorrhagic transformation	4/26	10/23	1.59	0.43–5.04	0.458
Acute subdural hematoma	2/7	12/112	3.65	0.60–17.16	0.142

N/A not applicable

***p* value of likelihood ratio test

[a]Statistically significant in multivariable analysis

[b]OR for Pediatric NIHSS is per 1-point increase in score. Pediatric NIHSS was applied exclusively to children older than 2 years ($N = 56$)

on long-term survival outcome and its predictors after an AIS in childhood are limited and sparse. Brush et al. [19] confirmed an association between hypertension and 1-year mortality in childhood ischemic stroke; however, they included venous infarcts and did not evaluate the radiological features of the stroke. A prospective analysis of the Hong Kong Children's Stroke Registry conducted by Chung and Wong, including short-term and long-term mortality, suggests that decreased levels of consciousness, hematologic causes (such as asparaginase therapy, thalassemia, aplastic anemia, and hemophilia), and hemorrhagic transformation of infarct might be positively associated with high mortality rates [20]. Research from the adult population has demonstrated that the principal risk factors of death within 1–5 years after AIS are increasing age, cardiac diseases, atherothrombotic disease, and stroke severity [21]. Similarly to the observed results in adults, our findings emphasize the fact that the chronic conditions, particularly heart diseases and prothrombotic illness, and initial stroke severity are the main predictors of mortality after hospital discharge in children with an AIS.

Our results showed that AIS is more common in boys and infants than girls and older children, but there are no differences in mortality rates between the sexes or age. These findings contrast with previous reports that found that the risk of death was higher in infants and boys [4] but are similar to

Table 3 Univariate analysis for risk factors of follow-up mortality for children with a first-ever arterial ischemic stroke, 2003–2015 ($N = 105$, total deaths = 23)

Variable	With variable (death/total)	Without variable (death/total)	HR	95% CI	*p* value**
Age (years)	N/A	N/A	1.01	0.93–1.09	0.706
Male sex	10/39	13/66	1.35	0.58–3.01	0.469
Pediatric NIHSS score[b]	N/A	N/A	1.05	1.01–1.09	0.019[a]
GCS < 12	17/71	6/34	1.32	0.56–3.52	0.381
Focal deficits	12/55	11/50	0.94	0.42–2.13	0.883
Headache	5/16	18/89	1.51	0.52–3.68	0.410
Acute symptomatic seizures	13/62	10/43	0.84	0.37–1.93	0.678
Status epilepticus	6/17	17/88	1.97	0.74–4.65	0.161
Congenital heart disease	14/41	9/64	3.21	1.42–7.59	0.005[a]
CNS arteriopathy	5/35	18/70	0.51	0.17–1.25	0.149
Infections	4/35	19/70	0.40	0.12–1.03	0.059
CNS infections	0/9	23/96	1.00	N/A	N/A
Prothrombotic states	12/29	11/76	3.14	1.40–7.11	0.005[a]
Anemia	6/18	17/87	1.84	0.69–4.32	0.206
Neoplasms	5/7	18/98	5.20	1.80–12.76	0.004
Anterior circulation	12/62	11/43	0.70	0.31–1.60	0.399
Posterior circulation	1/15	22/90	0.34	1.33–2.16	0.141
Anterior plus posterior circulation	10/28	13/77	2.56	1.11–5.75	0.027[a]
Lobar only	7/38	16/67	0.79	0.31–1.83	0.607
Cortical only	3/18	20/87	0.75	0.19–2.07	0.611
White matter only	4/20	19/85	1.07	0.33–2.73	0.897
Thalamus/basal ganglia only	7/17	16/88	2.74	1.07–6.38	0.035
Brainstem/cerebellum only	0/3	23/102	1.00	N/A	N/A
Multiple	9/47	14/58	0.75	0.32–1.70	0.501
Multifocal infarction	16/65	7/40	1.47	0.64–3.71	0.370
Bilateral infarction	15/54	8/51	1.88	0.83–4.57	0.127
Left hemisphere infarction	4/27	19/78	0.63	0.19–1.62	0.364
Right hemisphere infarction	4/24	19/81	0.72	0.22–1.84	0.519
Hemorrhagic transformation	7/22	16/83	2.01	0.79–4.64	0.132
Acute subdural hematoma	1/5	22/100	1.45	0.16–5.65	0.672
Stroke recurrence	8/23	15/82	1.77	0.73–4.02	0.192

N/A not applicable

***p* value of likelihood ratio test

[a]Statistically significant in multivariable analysis

[b] HR for Pediatric NIHSS is per 1-point increase in score. Pediatric NIHSS was applied exclusively to children older than 2 years ($N = 49$)

the recent findings of a multicenter study conducted by the IPSS group [10].

Long-term outcomes of pediatric stroke are difficult to obtain due to the low incidence and the required follow-up. Additionally, given the significant acute and long-term mortality surrounding pediatric stroke, the knowledge of risk groups for adverse survival outcomes might improve monitoring and targeted therapeutic interventions. To our knowledge, this is the first study conducted in predominantly Hispanic children that evaluated the influence of clinical and radiological characteristics on mortality in a long-term follow-up.

This study has several limitations. We only recruited children in a single-center tertiary care with a high proportion of children aged less than 2 years, and we did not analyze either the socioeconomic status or the geographic location of residence. This limitation might alter the distribution of stroke risk factors and increase the proportion of high initial severity stroke; thus, our results should be carefully extrapolated to the ambulatory setting and national population. We did not record initial stroke size, the timing of hemorrhagic transformation of infarction, and the apparition of new medical problems during the follow-up, each one a possible relevant variable for the outcome. Finally, we did not

analyze the impact of cardiovascular modifiable risk factors such as hypertension, smoking, and hyperlipidemia, which might be significant in the case of mortality, particularly in adolescents.

The Major strengths of our study are clear selection criteria controlled for confounding variables, the prospective nature of the data collection, homogeneous evaluations, the cause of death being available for all participants, and scarce losses to follow-up.

Conclusion

In summary, our analyses showed that factors associated with impaired survival during a long-term follow-up after a first-ever AIS in children beyond neonatal age include multiple characteristics of the stroke at diagnosis. These findings warrant future studies collecting clinical and radiological data from multiple centers for further understanding of risk factors for long-term mortality after an AIS in childhood.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical standard The institution's ethics committee approved this study.

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