Title Page

Title: **Imaging Predictors of Neurologic Outcome after Pediatric Arterial Ischemic Stroke**

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Appendix

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Abstract:

Background and Purpose: To assess whether initial imaging characteristics independently predict one-year neurological outcomes in childhood arterial ischemic stroke (AIS) patients.

Methods: We used prospectively collected demographic and clinical data, imaging data, and one-year outcomes from the Vascular effects of Infection in Pediatric Stroke (VIPS) study. In 288 patients with first-time stroke, we measured infarct volume and location on the acute magnetic resonance imaging (MRI) studies, and hemorrhagic transformation on brain imaging studies during the acute presentation. Neurological outcome was assessed with the Pediatric Stroke Outcome Measure (PSOM). We used univariate and multivariable ordinal logistic regression models to test the association between imaging characteristics and outcome.

Results: Univariate analysis demonstrated that infarcts involving uncinate fasciculus, angular gyrus, insular cortex, or that extended from cortex to the subcortical nuclei were significantly associated with poorer outcomes with odds ratios ranging from 1.95 to 3.95. All locations except the insular cortex remained significant predictors of poor outcome on multivariable analysis. When infarct volume was added to the model, the locations did not remain significant. Larger infarct volumes and younger age at stroke onset were significantly associated with poorer outcome, but the strength of the relationships was weak. Hemorrhagic transformation did not predict outcome.

Conclusion: In the largest pediatric AIS cohort collected to date, we showed that larger infarct volume and younger age at stroke were associated with poorer outcomes. We made the novel observation that the strength of these associations was modest and limits the ability to use these characteristics to predict outcome in children. Infarcts affecting specific locations were significantly associated with poorer outcomes in univariate and multivariable analyses, but lost

significance when adjusted for infarct volume. Our findings suggest that infarcts which disrupt critical networks have a disproportionate impact upon outcome after childhood AIS.

Non-standard Abbreviations and Acronyms: Acute Ischemic Stroke (AIS); Vascular effects of Infection in Pediatric Stroke (VIPS); Pediatric Stroke Outcome Measure (PSOM); Percentage Infarct Volume (PIV)

Introduction

Childhood stroke can be associated with severe neurological deficits, long-term disability and poor quality of life. Overall estimates of the annual incidence of childhood arterial ischemic stroke (AIS) in the US range around 4.6~6.4 for every 100,000 children.[1] This figure has remained stable in comparison to the decreasing incidence of stroke in adults over the past 17 years[2]. Because of the highly variable outcome of childhood AIS, it is crucial that practitioners can accurately identify children at greater risk for poor outcomes in a timely manner. The ability to better target earlier therapeutic interventions would maximize the chance of a better outcome. Outcome prediction in childhood AIS can be challenging not only because of the large number of clinical and imaging factors that must be considered, but also because injury to the immature nervous system perturbs subsequent development.

In adults, studies have demonstrated that larger acute infarct volume, specific locations, and hemorrhagic transformation predict poorer outcome. In one study involving 107 adults, smaller final infarct volume following thrombolysis was significantly correlated with both 90-day good outcomes and survival[3]. Infarcts affecting certain locations including uncinate fasciculus, precuneus, and angular gyrus of the left hemisphere and parietal lobe, and putamen of the right hemisphere were associated with poorer functional outcome[4] in patients enrolled in the Echoplanar Imaging Thrombolytic Evaluation Trial (EPITHET)[5] and Diffusion and Perfusion Imaging Evaluation for Understanding Stroke Evolution (DEFUSE)[6] studies. Parenchymal hematoma was associated with early neurological deterioration and increased mortality in a cohort of adults with AIS from the European Cooperative Acute Stroke Study I (ECASS I)[7]. While infarct volume was examined as a predictor of clinical or functional outcome after childhood AIS in small studies[8-11],

the evidence for the relationship between other infarct characteristics and neurological outcome is limited and lacks scientific rigor.

Age at stroke onset has been examined in several studies, and young age at stroke onset has been reported to predict poorer outcome. This relationship has been strongly linked with perinatal stroke[12-15], but the link between age and outcome after the neonatal period is inconclusive[12-14, 16-18]. In an earlier analysis of the Vascular effects of Infection in Pediatric Stroke (VIPS) study cohort we found that children ages 4-7 years at the time of stroke tended to have poorer outcomes in a multivariable analysis adjusted for race and family income[15]. Studies that examined cognitive outcomes have reported conflicting results, with younger age either being associated with poorer cognitive outcomes[16] or not[19]. Other studies examining overall neurological outcomes found that younger age at onset was associated with poorer outcomes[12, 16] after the neonatal period.

Most previous childhood AIS studies have been relatively small, of retrospective design, and without systematic data collection. We addressed these limitations by examining the largest prospective cohort of childhood AIS cases to date, the VIPS study cohort. We previously published demographic predictors of 12-month post-stroke outcomes in this cohort. We hypothesized that the initial imaging characteristics of the infarct (infarct location, volume, and hemorrhagic transformation) would independently predict the one-year outcome in children after AIS. Hence, we performed additional review of the brain imaging collected for the VIPS cohort to measure these imaging characteristics.

Materials and Methods:

In accordance with the NIH-approved data sharing policy for the VIPS study, the data supporting this study are available from the corresponding author upon request. We analyzed patient data from the Vascular effects of Infection in Pediatric Stroke (VIPS) study. The VIPS study enrolled 355 children with arterial ischemic stroke after the neonatal period (ages 29 days to 18 years) at 37 international sites from 1/2010-3/2014. The methods have been previously reported[20]. Detailed clinical data were collected at stroke onset, and outcomes were measured at one year post-stroke[15]. Clinical magnetic resonance imaging (MRI) was required for patient inclusion. In addition, vascular imaging was a requirement for inclusion in the VIPS study.[21] All images were centrally reviewed to confirm arterial ischemic stroke as part of the VIPS study. Ethical committee approvals were obtained at all participating centers. Written informed consent was obtained from all guardians of patients participating in the study.

For this study, we selected patients who had MRI imaging that was suitable for volumetric analysis and who had outcome data at one year after the incident stroke. Imaging studies were obtained as standard of care and did not follow a standardized research imaging protocol. The slice thickness, resolution, and magnet strength varied from site to site. The minimum imaging protocol for inclusion in the study was diffusion weighted imaging (DWI) (2-5mm slice thickness, 0-1mm gap) with the coverage from skull base to vertex. We excluded children who had evidence of prior brain infarction to the index stroke that led to VIPS enrollment. Children who had multiple infarcts at presentation were included. Hemorrhagic transformation was evaluated on SWI or GRE sequences obtained during the initial hospital stay (typically a follow-up MRI 24-72 hours after admission).

Imaging Review

A board certified neuroradiologist (MW) recorded the infarct volume, laterality, location, brain volume, and the presence of hemorrhagic transformation without knowing the outcome. To calculate the infarct and the brain volumes, semi-automated measurements were performed on the axial DWI images using the OSIRIX (https://www.osirix-viewer.com/resources/certifications/). The reviewer manually segmented the border of the diffusion restricted area (infarct contour) and the whole brain contour on the DWI images. ADC maps were visually compared to remove T2 shine through. Tracing was initiated when the brain appeared on the image, and continuously traced on each slice until the foramen magnum, although a subsampling methodology by progressively selecting one of every x slices permits reliable estimation in brain volume[22]. Taking into account slice thickness and gap between slices, infarct and brain volume were automatically calculated in three dimensions. Percentage infarct volume (PIV), defined as infarct volume divided by total brain volume x 100, was used because children's brain volumes change with age. Volumetric, voxel-based analysis was not possible because thin sliced volumetric acquisition was not part of the routine imaging protocol at most sites, primarily because patients were acutely ill children and it was necessary to reduce the scan time in these unstable patients.

The anatomical location of the infarct was classified in seven categories based upon previous descriptions in the literature[8, 23]: 1) cortex only (only superficial grey matter), 2) subcortical white matter only, 3) cortex-subcortical white matter (both grey and white matter involved), 4) subcortical nuclei (only basal ganglia and/or thalamus involved), 5) cortex-subcortical white matter-subcortical nuclei, 6) brainstem, and 7) cerebellum. The neuroradiologist annotated the involvement of the above-mentioned seven locations on DWI images. The T1WI and T2WI FLAIR sequences were compared as an anatomical reference. Wallerian degeneration with DWI changes in internal capsule, thalamus, and brainstem was not recorded as true infarction.

Because studies in adults linked infarcts involving the uncinate fasciculus, precuneus, angular gyrus, internal capsule and insular cortex with poorer outcomes[4, 24], we also coded whether infarcts involved these specific regions. Laterality (left, right, bilateral) was coded for each of the above-mentioned cerebral regions. Hemorrhagic transformation was coded using the European Cooperative Acute Stroke Study (ECASS) classification system[7, 25].

Outcome assessment

Neurological outcome 12 ± 3 months post-stroke was assessed with the Pediatric Stroke Outcome Measure (PSOM) for patients who could be examined in person[15]. The PSOM is a standardized, validated instrument that is the most widely used pediatric AIS outcome measure[26]. The PSOM uses five subscales: left sensorimotor, right sensorimotor, language comprehension, language production, and cognitive/behavioral function. Subscale scoring involves four levels (0, 0.5, 1, 2) ranging from normal to severely affected. The total PSOM score can range from 0 (normal) to 10 (severely impaired or dead). Participants who could not be evaluated in person were assessed by telephone interview with the Recovery and Recurrence Questionnaire (RRQ)[27], a validated scoring system based upon the PSOM. Children who were deemed fully recovered at year 1 did not undergo a full exam for a PSOM and were assigned a total PSOM of 0 as in our previous analysis of the cohort.[28] We examined total PSOM scores with categories as used in our two recent studies of the VIPS cohort[15, 29] as follows: 0-1 (normal to mild), 1.5-3 (mild to moderate), 3.5-6 (moderate to severe), and 6.5 to 10 (very severe or death). This allowed for a more granular analysis than in earlier studies, which dichotomized outcome as good or poor.

Statistical Analysis

Demographics, imaging and clinical characteristics of the cohort were summarized as counts and percentages for categorical characteristics, and as medians and interquartile ranges (IQR) for

continuous characteristics. We first examined infarct location, volume, and hemorrhagic transformation as potential predictors of the categorical PSOM score using univariate ordinal logistic regression models to accommodate our ordinal outcomes. We conducted a Brant test for each model to validate the assumptions specific to ordinal logistic regression models[15]. Multivariable ordinal logistic regression models were then conducted that included all the location markers that were found to be significant at the $\alpha = 0.05$ level in univariate analysis, adjusted only for age. To examine the relationship of PIV relative to infarct location on outcome we then further adjusted our multivariable model for percent infarct volume. All analyses were completed using Stata version 15 (College Station, Texas)[30]; a $p<0.05$ was considered statistically significant.

Results

From 2010 to 2014, the VIPS study enrolled 355 patients with childhood AIS. Of these, 311 had brain images of sufficient quality to measure acute infarct volumes and PSOM/RRQ scores at one-year. Because prior infarcts would complicate the interpretation of outcome, 23 patients with prior infarcts were excluded, leaving 288 patients for this study. Demographics, major risk factors, and PSOM score distribution are summarized in Table 1. The median (IQR) age at onset was 7.77 (2.78, 14.4) years (range: 0.08, 18.9); 56.3% were males. The most common stroke etiologies were definite arteriopathy (35%), idiopathic (27%), and cardioembolic (22%). Demographic and clinical characteristics generally did not differ between the original cohort (n=355), the patients included in this study (n=288), and excluded patients (n=67), except the percentages of patients with congenital heart disease in the original cohort and the study group were higher than in the excluded patients. We note that of 23 children reported as having had a prior thromboembolic event 14 had definite arteriopathy, while only 2 were classified as cardioembolic. (Supplementary On-line Table I).

For the one-year outcome, 190 patients were evaluated with PSOM, 84 with the RRQ, and 14 who were deceased were assigned a score of 10. Most patients (84.4%) had normal/mild or moderate neurological impairment (PSOM 0-1 and PSOM 1.5-3,), 8.3% had moderate to severe impairments (PSOM 3.5-6), and 7.3% had very severe impairments or died (PSOM 6.5-10).

Association of Infarct Location with One-year Outcome

Infarcts that involved the combination of cortex-subcortical white matter-subcortical nuclei structures were associated with worse outcome at one year on univariate analysis (Table 2). The odds of a worse outcome were 3.29 (95% CI= [1.84, 5.87]) when compared with patients whose infarcts did not involve this combination of structures. Unilateral infarcts involving other less extensive structures (only cortex, subcortical nuclei, or subcortical white matter) were not significantly associated with worse outcomes, nor were bilateral infarcts involving cortex or cerebellum. Other bilateral infarcts occurred so infrequently that we lacked sufficient power to analyze them. (Table 2) We examined whether outcomes were worse when the precuneus, uncinate fasciculus, angular gyrus, internal capsule, or insular cortex were involved. When infarcts involved the uncinate fasciculus, angular gyrus, or insular cortex, the odds of a worse outcome were 3.95, 2.90, and 1.95 times greater, respectively, when compared with infarcts not involving these structures.

We examined if there was a difference between involvement of the left versus right side. Overall there were no marked differences based upon laterality. While infarcts involving the left uncinate fasciculus, angular gyrus, and insular cortex were associated with slightly higher odds of poorer outcomes, the differences were modest (Supplementary On-line Table II).

When we conducted a multivariable analysis including the four infarct locations that were significantly associated with worse outcome in univariate analysis (cortex-subcortical white matter-subcortical nuclei, uncinate fasciculus, angular gyrus, and insular cortex), we found that infarcts involving the cortex-subcortical white matter-subcortical nuclei, uncinate fasciculus, and angular gyrus remained independently associated with worse outcomes (Table 3).

The assessment of language and cognition/behavior is difficult in children younger than 2 years old. We tested whether the relationship between infarct location and outcome remained in patients older than 2 years when language and cognition/behavior could be assessed more confidently. In these older patients, the associations between worse outcomes and infarcts involving the cortex-subcortical white matter-subcortical nuclei, uncinate fasciculus, and angular gyrus remained significant, although the association with insular cortex did not.

Infarct Volume and Age at Stroke and One-year Outcome

We used PIV instead of infarct volume in these analyses since the brain volume increases during childhood. The median PIV overall was 1.4% (IQR 0.3% - 5.4%). The median PIV for normal, mild, and moderate outcome groups increased from 0.9% to 3.1% and 7.8% but dropped to 3.4% for severe outcomes. It is noteworthy that only 5/21 children in this last group were alive at one year. A graph of PIV by outcome category demonstrates the substantial overlap in the range of PIV across the four outcome categories (Figure 1). Despite this, there was a significant association between increasing PIV and worse outcome (OR=1.11, 95% CI= [1.07, 1.15], $p<0.001$), although the strength of the relationship was modest.

To examine the relationship of PIV relative to infarct location on outcome we adjusted for it in the logistic regression model containing the significantly associated infarct locations for PIV. In

this multivariable analysis, PIV was significantly associated with poorer outcome (OR=1.08, 95% CI= [1.04, 1.13], $p<0.001$), but the specific regions – cortex-subcortical white matter-nuclei, uncinate fasciculus and angular gyrus – were no longer significant. (Table 4) Again the strength of the association between PIV and outcome was modest. Since the specific locations lost significance when PIV was added to the model, we examined whether the volumes of infarcts involving these regions were large. Indeed, the PIV for infarcts involving the four regions we identified as associated with outcome were substantially larger than the median PIV for the cohort overall. (Table 5) The association between poor outcome and these locations may be partially explained by the fact that they have larger volumes, and those with larger volumes do worse.

Age at Stroke and One-year Outcome

Patient age was inversely correlated with poorer outcome (OR=0.96, 95% CI= [0.92, 0.995], $p=0.03$). As above, we examined if the relationship between age and outcome in children < 2 years differed from that in children ≥ 2 years; we found no differences in their total PSOM scores (p=0.66, χ^2 test). When we limited our analysis to children ages 2 years and older, the association between age and outcomes for the whole group was slightly attenuated but more strongly significant (OR=0.92, 95% CI= [0.87-0.97], p=0.003). Lastly, to explore the possibility that there may have been domain specific differences in outcomes, we performed domain-based analyses that examined the combined left/right sensorimotor subscales, the combined language production/comprehension subscales, and the cognitive/behavior subscale. There was a tendency for poorer outcomes in these three overall domains in the younger age group, but we found no significant associations, likely due to the small sample size (data not shown).

Hemorrhagic Transformation and One-year Outcome

Since hemorrhagic transformation is associated with poor outcomes in adults,[7] we asked whether it was associated with poorer outcomes in children. Follow-up imaging during the acute admission that would allow for the detection of hemorrhagic transformation was available in 152 patients. HT was detected in 27 patients (Supplementary On-line Table III). The median outcome score in children with hemorrhagic transformation (0.5; IQR= 0-2) was similar to the median outcome score of children without hemorrhagic transformation (1; IQR= 0-2) and did not differ between the two groups (OR=0.85, 95% CI= [0.36, 2.01], p=0.71). Although the sample size was small, no hemorrhagic transformation subtype showed any correlation with outcome.

Discussion

This study adds new information that while infarct volumes and younger age at stroke onset are associated with poorer outcomes, the strength of these relationships is weak. As a consequence, it is difficult to use these two factors to predict the outcome of childhood AIS. In addition, we showed that infarcts involving the angular gyrus or uncinate fasciculus are associated with significantly worse outcomes, similar to what has been reported in adults[4, 24], and infarcts extending from the cortex to the subcortical nuclei also are associated with worse outcomes. When the effect of location was adjusted for infarct volume, only volume remained significant.

The VIPS cohort previously has been analyzed for imaging predictors of outcome. That earlier analysis identified children with focal cerebral arteriopathy (FCA) and developed a severity score for the arteriopathy, the FCASS score.[29] The maximum FCASS score correlated with outcome at

1 year, higher FCASS scores significantly correlating with poorer outcome. We did not include this arteriopathy score in the present study, rather we restricted the analysis in the current study to infarct characteristics.

A small number of studies have examined the relationship of infarct volume to outcome in childhood stroke, but these were limited because they were retrospective, much smaller in sample size, and the results were inconsistent [8, 9, 10, 11]. Ganesan[9] et al. measured chronic infarct volume in 38 children, and found no significant relationship between infarct size and clinical outcome. In 40 children with childhood AIS[8], acute infarct volumes were compared with neurologic functional outcomes assessed by the Glasgow Outcome Scale. When PIV was >10%, poor outcome was a significantly greater risk. In a study limited by small samples, Lo et al.,[10] found that larger PIV correlated with worse PSOM scores, lower IQ and poorer social participation. Long et al.,[11] reported an association between worse executive performance with large lesion size. Our results support the idea[8, 10, 11] that larger infarct volume is associated with worse outcome; however, we show that the strength of this relationship is modest with an odds ratio of only 1.11. The substantial overlap of the distribution of infarct volumes across the different outcome categories showed that using a specific infarct volume to predict outcome is quite difficult. Even defining a specific threshold infarct volume that can consistently predict one-year outcome is challenging.

Earlier studies showed an association between younger age at pediatric AIS and poor outcomes, typically when stroke occurred in the neonatal period, but the evidence in older children is conflicting. In a prospective study of 145 children with subcortical infarcts[23], the perinatal group did not perform as well as the older groups in cognition domains, but no significant difference in cognitive outcomes was observed between the two groups with stroke occurring at 1 month~5

years and at 6~16 years. In a recent study of 96 children[16], younger age at stroke onset, acute seizures, and the severity of neurological impairment predicted impaired cognitive function. Another prospective study of 99 children with childhood AIS showed a tendency toward poorer neurological function in children who had strokes at a younger age when compared with those who had strokes at a later age[31]. Our earlier VIPS paper[15], which addressed the socioeconomic determinants of outcome after childhood AIS, found that increasing age for the whole cohort (320 patients) was correlated with better PSOM scores (OR=0.95, 95%CI=0.92~0.99, p=0.02) in univariate analysis. However, in multivariable analysis adjusted for race and family income this association was no longer statistically significant. In the current study of children with childhood AIS occurring after the neonatal period, we found that younger age at stroke onset was significantly associated with worse neurological outcome, but as with infarct volume and outcome, the strength of the association was modest with an odds ratio of only 0.96. This makes age a weak predictor of outcome at best. We performed a domain-based analysis to see if domains and age were associated with outcome, but we found no significant associations. The sample size and the ordinal nature of the domain scores (0, 0.5, 1, 2) likely limited this more granular analysis.

To date, few studies have examined the relationship between infarct location and outcome in pediatric AIS. Westmacott et al. [23] categorized infarct locations as cortical, subcortical (i.e., subcortical nuclei; basal ganglia and thalamus), or combined cortico-subcortical, which is similar to the cortex-subcortical white matter-subcortical nuclei category in the current study. In their study, combined cortico-subcortical infarcts were associated with poorer IQ scores, while no IQ differences were observed in children with subcortical infarcts versus cortical infarcts. Our univariate analysis results were consistent with this earlier result. Furthermore, infarcts involving the uncinate fasciculus and angular gyrus were also significantly associated with worse outcomes.

These findings are consistent with what is known about the uncinate fasciculus and angular gyrus, for they serve important functions in connecting or receiving input from other regions[19, 32-34]. When infarct volume was added to the model, these locations were no longer significantly associated with outcome even though the magnitude of the infarct volume effect was modest. Exploring this further, we found that infarcts were substantially larger when they involved those locations identified as adversely affecting long-term outcome in children. This suggests when an infarct is large enough to damage structures that connect other regions, those larger infarcts have a disproportionately greater impact and result in poorer long-term outcome in children.

Few pediatric stroke studies have examined the link between hemorrhagic transformation and outcome. Beslow et al. [35] reported that in a registry of 63 patients, 19 had hemorrhagic transformation. These were associated with large infarct volumes and showed a tendency toward worse outcomes that did not reach significance (p=0.07). In the VIPS cohort we did not find a significant association between hemorrhagic transformation and poorer outcome, which differs from both the earlier pediatric report and data on the adult experience[7].

Our study has a number of limitations. We could not perform a voxel-based brain topography analysis since the images were clinically acquired outside of a standardized research imaging protocol. We lacked data to characterize the amount or intensity of rehabilitation/treatment that participants received; this may have affected outcomes. Although this is the largest prospective study of childhood AIS to date, our sample size was too small to allow us to test the simultaneous effect of risk factors, age at onset, and infarct characteristics upon outcomes. The PSOM/RRQ do not measure fine details of motor, speech or cognitive function, and are harder to measure in younger children. Our study, however, has many strengths compared with earlier studies because

of the VIPS study characteristics: 1) standardized prospective collection of acute MRI images, clinical information, and outcomes; 2) centralized image review to ensure radiological diagnostic accuracy; and 3) the largest cohort of post-neonatal childhood AIS patients studied to date.

Summary

Our results support the findings of previous studies that larger infarct volume and younger age at stroke onset are associated with worse outcome. Our study adds new information by demonstrating that the strength of these associations, while significant, is quite modest. This new data helps explain why it is difficult to predict outcome based solely upon infarct volume or patient age. In addition, we found that specific infarct locations are associated with worse outcome. This finding suggests the hypothesis that infarcts which damage structures that connect other regions and serve a network function have a disproportionate effect upon function. Future studies of pediatric AIS should examine the effect of network disruption upon outcomes.

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Disclosure:

Dr. Jordan reported personal fees from expert testimony outside the submitted work. Besides, she served as a consultant for a company trying to cure Sickle Cell Disease with gene therapy: Bluebird Bio (for 2 hours one day in 2019). Those 2 hours resulted in modest compensation for the time.

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The other authors report no disclosures relevant to the manuscript.

Supplementary Materials: Supplementary On-line Table I-III

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Table 1. Demographic and clinical characteristics comparing 288 patients enrolled in study to those excluded.

Characteristics	Total cohort (n=355)	Included (n=288)	Excluded[a] (n=67)	*P* value[b]
Demographic characteristics				
Age in years, median (IQR)	7.6(2.8,14.3)	7.77(2.78,14.4)	7.5(3.3,14.3)	0.86[c]
Male gender, n (%)	199(56.1)	162 (56.3)	37(55.2)	0.88
Race, n (%)				0.58
White	234(65.9)	191 (66.3)	43(64.2)	
Black	39(11.0)	34 (11.8)	5(7.5)	
Asian	35(9.9)	27 (9.4)	8(11.9)	
other	47(13.2)	36 (12.5)	11(16.4)	
Clinical characteristics, n (%)				
Congenital heart disease	64(18.0)	59(20.5)	5(7.5)	0.01
Sickle-cell disease	13(3.7)	10(3.5)	3(4.5)	0.72[f]
Trauma	28(7.9)	24(8.3)	4(6.0)	0.62[f]
Hypercoagulable state	9(2.5)	6(2.1)	3(4.5)	0.38
Infection within prior week	64(18.0)	54(18.8)	10(14.9)	0.46
Stroke classifications, n (%)				0.32
Idiopathic	90(25.4)	78 (27.1)	12(17.9)	
Cardioembolic (spontaneous/iatrogenic)	65(18.3)	64 (22.2)	11(16.4)	
Definite Arteriopathy	127(35.8)	100(34.7)	27(40.3)	
Other[d]	73(20.6)	56 (18.4)	17(25.4)	
Outcome-PSOM at one year, n (%)				0.29[f]
Missing[e]	35(9.9)	0	35(9.9)	
0–1	207(58.3)	190/288(66.0)	17(25.4)	
1.5–3	60(16.9)	53/288(18.4)	7(10.4)	
3.5–6	27(7.6)	24/288(8.3)	3(4.5)	
6.5–10	26(7.3)	21/288(7.3)	5(7.5)	

[a] Subjects excluded = those without either PSOM/MRI data (n=44); those with prior strokes (n=23)

[b] p-values calculated using chi-square test unless otherwise indicated

[c] p-value calculated using Wilcoxon rank sum test

[d] includes: Iatrogenic cardioembolic (n=10); hypercoagulable state (n=6) and "other" (n=17) idiopathic; possible arteriopathy (n=23)

[e] PSOM scores at 1 year were not available for all children in VIPS

f p-value calculated using Fisher's exact test

Table 2. Univariate analysis of association between infarct location and worse outcomes after one year.

	Total Cohort (n=288)			Only children ≥ 2 years old(n=231)		
Location	N (%)	OR (95%CI)	p-value*	n (%)	OR (95% CI)	p-value*
Cortex						
No involvement	196 (68.1)	Ref		161 (69.7)	Ref	
Unilateral	70 (24.3)	1.21 (0.69, 2.11)	0.51	54 (23.4)	1.17 (0.62, 2.20)	0.63
Bilateral	22 (7.6)	1.81 (0.77, 4.24)	0.18	16 (6.9)	1.59 (0.58, 4.32)	0.37
Subcortical white matter						
No involvement	243 (84.4)	Ref		197 (85.3)	Ref	
Unilateral	36 (12.5)	0.86 (0.41, 1.81)	0.69	29 (12.6)	0.87 (0.38, 1.98)	0.74
Bilateral	9 (3.1)	2.09 (0.63, 6.96)	0.23	5 (2.2)	3.78 (0.84, 17.0)	0.08
Cortex-subcortical white matter						
No involvement	220(76.4)	Ref		187 (81.0)	Ref	
Unilateral	60(20.8)	1.29 (0.72, 2.31)	0.40	39 (16.9)	1.27 (0.63, 2.55)	0.50
Bilateral	8 (2.8)	1.88 (0.58, 6.13)	0.3	5 (2.2)	1.03 (0.19, 5.64)	0.97
Subcortical nuclei						
No involvement	181 (62.8)	Ref		145 (62.8)	Ref	
Unilateral	98 (34.0)	0.68 (0.40, 1.15)	0.15	79 (34.2)	0.79 (0.44, 1.39)	0.41
Bilateral	9 (3.1)	2.53 (0.74, 8.73)	0.14	7 (3.0)	2.88 (0.70, 11.8)	0.14
Cortex-subcortical white matter -subcortical nuclei						
No involvement	236 (81.9)	Ref		186 (80.5)	Ref	
Unilateral	50 (17.4)	3.29 (1.84, 5.87)	<0.001	43 (18.6)	2.53 (1.34, 4.77)	0.004
Bilateral	2 (0.7)	<0.001(0, .)	1	2 (0.9)	<0.001(0, .)	0.98
Combined cerebellum						
No involvement	249 (86.5)	Ref		199 (86.1)	Ref	
Unilateral	25 (8.7)	0.84 (0.36, 1.98)	0.69	21 (9.1)	0.84 (0.33, 2.13)	0.72
Bilateral	14 (4.9)	0.64(0.20, 2.02)	0.44	11 (4.8)	0.37 (0.08, 1.72)	0.20
Brainstem						
No involvement	249 (86.5)	Ref		200 (86.6)	Ref	
Unilateral	31 (10.8)	0.71(0.31, 1.66)	0.43	23 (10.0)	0.51 (0.18, 1.44)	0.21
Bilateral	8 (2.8)	1.28(0.30, 5.37)	0.74	8 (3.5)	1.25 (0.29, 5.32)	0.76
Internal capsule						
No involvement	254 (88.2)	Ref		211 (91.3)	Ref	
Unilateral	33 (11.5)	1.46(0.70, 3.04)	0.31	20 (8.7)	1.35 (0.54, 3.36)	0.52
Bilateral	1 (0.3)	<0.001(0, .)	0.99	0	n/a	
Uncinate fasciculus						
No involvement	246 (85.4)	Ref		200 (86.6)	Ref	
Unilateral	40 (13.9)	3.95(2.10, 7.43)	<0.001	31 (13.4)	3.4 (1.67, 6.90)	0.001
Bilateral	2 (0.7)	6.98(0.86, 56.9)	0.07	0	n/a	
Precuneus						
No involvement	267 (92.7)	Ref		216 (93.5)	Ref	
Unilateral	20 (6.9)	1.79(0.74, 4.33)	0.20	15 (6.5)	2.72 (0.99, 7.43)	0.05
Bilateral	1 (0.3)	8.9(0.51, 155)	0.13	0	n/a	
Angular gyrus						
No involvement	233 (80.9)	Ref		194 (84.0)	Ref	
Unilateral	53 (18.4)	2.9(1.63, 5.18)	<0.001	37 (16.0)	2.78 (1.41, 5.46)	0.003
Bilateral	2 (0.7)	15.1(1.14, 199)	0.04	0	n/a	
Insular cortex						
No involvement	206 (71.5)	Ref		162 (70.1)	Ref	
Unilateral	79 (27.4)	1.95(1.16, 3.28)	0.01	66 (28.6)	1.73 (0.97, 3.07)	0.06
Bilateral	3 (1.0)	8.57(1.24, 59.0)	0.03	3 (1.3)	8.8 (1.25, 61.8)	0.03

*P-values calculated using ordinal logistic regression

Table 3: Multivariable analysis of association between infarct location and worse outcomes at 1-year.

Locations	OR (95% CI)	*p*-value*
Cortex-subcortical white matter -subcortical nuclei	2.19(1.01, 4.75)	**0.046**
Uncinate fasciculus	2.45(1.15, 5.21)	**0.02**
Angular gyrus	2.51(1.38, 4.57)	**0.003**
Insular cortex	0.84(0.43, 1.63)	0.60

**p*-value calculated using ordinal logistic regression

Table 4: Multivariable analysis of infarct location adjusted for percentage of infarct volume (PIV) on worse 1-year outcome.

PIV and Locations	OR (95% CI)	*p*-value*
Cortex-subcortical white matter -subcortical nuclei	1.41(0.69, 2.90)	0.35
Uncinate fasciculus	1.25 (0.55, 2.85)	0.58
Angular gyrus	1.39 (0.72, 2.68)	0.32
Percentage infarct volume (PIV)	1.08 (1.04, 1.13)	**<0.001**

**p*-value calculated using ordinal logistic regression

Table 5: Percent Infarct Volume for Specific Locations

	Patients with infarct in location		Size of infarct as % of total volume	
Location	n	(%)	Median (%)	IQR
Cortex-subcortical white matter-subcortical nuclei	52	(18.1)	11.9	(3.71, 17.0)
Uncinate fasciculus	42	(14.0)	13.5	(7.23, 18.9)
Angular gyrus	55	(19.1)	9.57	(4.72, 15.2)
Insular cortex	82	(28.5)	7.21	(2.27, 14.2)

Figure legend:

Figure1: Boxplot of percentage infarct volume (PIV) in predicting one-year worse outcome (n=288) demonstrated the significant association between increasing PIV and worse outcome. It is noteworthy that there was substantial overlap in the distribution of PIVs across the four outcome categories.