Published Ahead of Print on August 13, 2021 as 10.1212/WNL.0000000000012558

Neurology®

The most widely read and highly cited peer-reviewed neurology journal
The Official Journal of the American Academy of Neurology

AMERICAN ACADEMY OF NEUROLOGY®

Neurology Publish Ahead of Print
DOI: 10.1212/WNL.0000000000012558

Association of Pediatric ASPECTS and NIH Stroke Scale, Hemorrhagic Transformation, and 12-Month Outcome in Children With Acute Ischemic Stroke

Author(s):
Lauren A. Beslow, MD MSCE[1]; Arastoo Vossough, MD PhD[2]; Rebecca N. Ichord, MD[1]; Nedelina Slavova, MD[3]; Maggie L.Y. Yau, MBBS[4]; Jay Gajera, MD[5]; Belinda Stojanovski, BSc[6]; Malik M. Adil, MD[7]; Jake Breimann, BA[1]; Alexandra Kimmel, BA[1]; Mark T. Mackay, MBBS PhD[6,8]

Corresponding Author:
Lauren A. Beslow
beslow@email.chop.edu

Affiliation Information for All Authors: 1. Departments of Neurology and Pediatrics, Perelman School of Medicine at the University of Pennsylvania, Division of Neurology, Children s Hospital of Philadelphia, Philadelphia, Pennsylvania, USA; 2. Department of Radiology, Perelman School of Medicine at the University of Pennsylvania, Division of Neuroradiology, Children s Hospital of Philadelphia; 3. Department of Diagnostic, Interventional and Pediatric Radiology, Inselspital, Bern University Hospital, Bern, Switzerland; 4. Department of Pediatrics, Prince of Wales Hospital, Hong Kong SAR, Department of Pediatrics, The Chinese University of Hong Kong, Hong Kong SAR; 5. Department of Surgery, The Alfred Hospital Melbourne, Victoria, Australia; 6. Department of Neurology, Royal Children s Hospital, Melbourne, Victoria, Australia; 7. Department of Neurology, Johns Hopkins University School of Medicine; 8. Murdoch Children s Research Institute, Melbourne, Victoria, Australia, Department of Pediatrics, University of Melbourne, Victoria, Australia

Contributions:

Lauren A. Beslow: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data; Study concept or design; Analysis or interpretation of data; Additional contributions: Figure preparation

Arastoo Vossough: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data; Analysis or interpretation of data; Additional contributions: Figure preparation

Rebecca N. Ichord: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data; Study concept or design

Nedelina Slavova: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data

Maggie L.Y. Yau: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data

Jay Gajera: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data

Belinda Stojanovski: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data

Malik M. Adil: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data; Analysis or interpretation of data; Additional contributions: Figure preparation

Jake Breimann: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data

Alexandra Kimmel: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data

Mark T. Mackay: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data; Study concept or design; Analysis or interpretation of data

Number of characters in title: 140

Abstract Word count: 290

Word count of main text: 3280

References: 29

Figures: 3

Tables: 2

Supplemental: STROBE Checklist

Statistical Analysis performed by: Lauren A. Beslow, MD MSCE and Malik M. Adil, MD

Search Terms: [10] Childhood stroke, [120] MRI, [128] DWI, [322] Class II, [293] Pediatric stroke; see Cerebrovascular Disease/ Childhood stroke (S)

Acknowledgements: None

Study Funding: The authors report no targeted funding

Disclosures: The authors report no disclosures relevant to the manuscript.

ABSTRACT

OBJECTIVE We aimed to determine whether a modified pediatric Alberta Stroke Program Early CT Score (modASPECTS) is associated with clinical stroke severity, hemorrhagic transformation, and 12-month functional outcomes in children with acute AIS.

METHODS Children (29 days to <18 years) with acute AIS enrolled in two institutional prospective stroke registries at Children's Hospital of Philadelphia and Royal Children's Hospital Melbourne, Australia were retrospectively analyzed to determine whether modASPECTS, in which higher scores are worse, correlated with acute Pediatric NIH Stroke Scale (PedNIHSS) scores (children ≥2 years of age), was associated with hemorrhagic transformation on acute MRI, and correlated with 12-month functional outcome on the Pediatric Stroke Outcome Measure (PSOM).

RESULTS 131 children were included; 91 were ≥2 years of age. Median days from stroke to MRI was 1 (interquartile range [IQR] 0-1). Median modASPECTS was 4 (IQR 3-7).

ModASPECTS correlated with PedNIHSS (rho=0.40, P=0.0001). ModASPECTS was associated with hemorrhagic transformation (OR 1.13 95% CI 1.02-1.25, P=0.018). Among children with follow-up (N=128, median 12.2 months, IQR 9.5-15.4 months), worse outcomes were associated with higher modASPECTS (common OR 1.14, 95%CI 1.04-1.24, P=0.005). The association between modASPECTS and outcome persisted when we adjusted for age at stroke ictus and the presence of tumor or meningitis as stroke risk factors (common OR 1.14, 95%CI 1.03-1.25, P=0.008).

CONCLUSIONS ModASPECTS correlates with PedNIHSS scores, hemorrhagic transformation, and 12-month functional outcome in children with acute AIS. Future pediatric studies should evaluate its usefulness in predicting symptomatic intracranial hemorrhage and outcome after acute revascularization therapies.

CLASSIFICATION of EVIDENCE This study provides Class II evidence that the modified pediatric ASPECTS on MRI is associated with stroke severity (as measured by the baseline pediatric NIH Stroke Scale), hemorrhagic transformation, and 12-month outcome in children with acute supratentorial ischemic stroke.

INTRODUCTION

The Alberta Stroke Program Early CT Score (ASPECTS) assesses early ischemic changes in adult middle cerebral artery infarction and predicts 3-month functional outcome after thrombolytic therapy.[1] Several practice-changing adult endovascular treatment trials that demonstrated benefit of mechanical thrombectomy for anterior circulation large vessel occlusion used ASPECTS for patient selection.[2-4] The 2019 American Heart Association guidelines suggest use of ASPECTS for patients presenting within 6 hours of onset of large vessel occlusion when determining eligibility for mechanical thrombectomy without perfusion imaging.[5] Pediatric mechanical thrombectomy trials have not been done, but small cohort studies of feasibility,

safety, and outcomes of pediatric endovascular therapies have been published.[6, 7] ASPECTS was not used to determine eligibility for mechanical thrombectomy for children, but adult ASPECTS was retrospectively determined at admission and post-procedure in one study.[7] A modified pediatric ASPECTS (modASPECTS) correlates with infarct volume.[8, 9] ModASPECTS is performed on diffusion-weighted imaging (DWI), includes anterior and posterior cerebral artery regions, and higher scores indicate more areas of infarction. ModASPECTS predicts epilepsy, cerebral palsy, and neurological impairment after perinatal arterial ischemic stroke (AIS)[8, 10] and functional outcome in children with AIS due to focal cerebral arteriopathy.[11, 12] However, modASPECTS' relationship to outcome in a broader cohort of childhood AIS with varied risk factors has not been evaluated. We aimed to determine whether modASPECTS correlates with clinical stroke severity, hemorrhagic transformation, and 12-month outcome in a childhood AIS cohort to provide information that may be helpful in determining whether modASPECTS can be used for eligibility determination for hyperacute therapies.

MATERIAL AND METHODS

Study Design

This is a retrospective analysis of subjects from two prospectively enrolled pediatric stroke registries. The primary research question was to determine whether modASPECTS can differentiate between severe AIS and less severe strokes by determining the score's associations with clinical stroke severity, hemorrhagic transformation, and 12-month functional outcomes in children with acute AIS. The analyses in this study provide Class II evidence.

Subjects

The study subjects were identified from stroke registries enrolled at two tertiary-care centers, Children's Hospital of Philadelphia (Philadelphia, Pennsylvania, United States) and Royal

Children's Hospital (Melbourne, Australia). Children's Hospital of Philadelphia (CHOP) subjects were enrolled from January 2005 to November 2008. Royal Children's Hospital (RCH) subjects were enrolled from January 2003 to November 2017. Inclusion criteria were MRI-confirmed diagnosis of acute AIS on DWI, age 29 days to <18 years of age at stroke ictus, supratentorial AIS, and availability of MRI with DWI for modASPECTS scoring.

Standard Protocol Approvals, Registrations, and Patient Consents This study was reviewed and approved by the Children's Hospital of Philadelphia and Royal Children's Hospital Institutional Review Boards. Written informed consent and assent, when appropriate, were obtained at the time of enrollment in the stroke registries.

Data Availability Anonymized data will be shared by request from a qualified investigator.

Modified Pediatrics ASPECTS (modASPECTS) Scoring and Hemorrhagic Transformation All modASPECTS raters had previous experience with the score and were blinded to clinical stroke severity and outcomes. Children's Hospital of Philadelphia cohort modASPECTS were scored by A.V., a pediatric neuroradiologist. Royal Children's Hospital cohort modASPECTS were scored by consensus by M.M. and N.S., a pediatric stroke neurologist and a pediatric neuroradiologist. ModASPECTS were scored on clinically acquired axial DWI sequences on 1.5 or 3.0 Tesla MRI scanners from each institution as previously described.[9] The MRIs were performed using several different scanners at each hospital or at the referring center. ModASPECTS is scored on axial DWI (DWI with apparent diffusion coefficient map) in the following fifteen regions in the left and in the right hemispheres: seven cortical middle cerebral artery regions (M1-M6 and insula), two cortical anterior cerebral artery regions (A1 and A2), two cortical posterior cerebral artery regions (P1 and P2), and four subcortical regions (caudate,

lentiform nucleus, internal capsule, and thalamus. If there is diffusion restriction in any portion of a region, that region is scored as 1. Areas without infarction are scored as 0. The total modASPECTS is additive and ranges from 0, indicating no infarction, to a score of 30 indicating infarction in all scored areas. Parental consent was not obtained for image transfer at the time of enrollment into the cohorts, so modASPECTS was performed independently at each institution. ModASPECTS' interrater reliability was excellent, 0.94, among a pediatric neuroradiologist, pediatric stroke neurologist, and pediatric neuroradiology fellow, in its original validation study.[9] The same neuroradiologists and pediatric stroke neurologist recorded the presence or absence of hemorrhagic transformation on initial MRI on which modASPECTS was scored. Hemorrhagic transformation was considered areas of hypointensity on T2* gradient echo, echoplanar-spin echo-T2, or susceptibility-weighted imaging. The exact time of stroke ictus was not recorded in the majority of charts, so time to MRI and therefore modASPECTS is presented as the number of days from stroke ictus.

Clinical Stroke Severity and Outcome Measurement

Clinical stroke severity was scored either prospectively or retrospectively with the Pediatric NIH Stroke Scale (PedNIHSS) score in children aged 2 years or older for whom the score is validated.[13, 14] The PedNIHSS ranges from 0 (no deficits scored) to 42 (maximal deficits in all scored areas). The exact time that the PedNIHSS score or neurological examination was performed was not recorded in the majority of charts, so time to PedNIHSS is presented as the number of days from stroke ictus. Stroke subtypes were classified using the Childhood AIS Standardized Classification and Diagnostic Evaluation (CASCADE) criteria.[15] Neurological outcome was determined at 12 +/- 6 months, and presence of epilepsy was determined at the last follow-up appointment available for each subject. The Pediatric Stroke Outcome Measures (PSOM) characterized deficits and their severity in 5 domains: left sensorimotor, right

sensorimotor, expressive language, receptive language, and cognitive/behavioral.[16] Each domain is scored at 0 (no deficit), 0.5 (mild deficit not interfering with function), 1 (moderate deficit interfering with function), and 2 (severe deficit with loss of function). The total PSOM score ranges from 0 to 10. Epilepsy was defined as 2 or more unprovoked remote symptomatic seizures more than 24 hours apart.[17]

Statistical Analysis

Stata 12.0 was used for all analyses (StataCorp, College Station, TX, USA). Descriptive statistics were used to characterize baseline demographic data, PedNIHSS scores, modASPECTS, and follow-up time and included counts and percentages for categorical variables and medians with interquartile range (IQR) for continuous variables. Spearman's rank-order correlation coefficient (rho) was used to determine the relationship between modASPECTS and PedNIHSS scores. Logistic regression was used to determine whether modASPECTS was associated with development of epilepsy at last follow-up. Assessment of the relationship of modASPECTS and outcome on PSOM was assessed in several ways to allow comparison with other published studies. Spearman's rank-order correlation coefficient (rho) was used to evaluate the correlation between total modASPECTS and total PSOM scores at follow-up. Wilcoxon rank-sum was used to determine whether the modASPECTS distribution was different among those with poor outcomes versus those with good outcomes, with poor outcomes defined as in previous work as those with a total PSOM of ≥1 or who died.[11, 13] Generalized ordered logistic regression was also used to evaluate the relationship between modASPECTS and outcome with PSOM scores categorized more granularly as previously done with score categories 0 to 1, 1.5 to 3, 3.5 to 6, 6.5 to 10.[18] Children who died were included in the worst outcome category (6.5 to 10). A multivariable generalized ordered logistic regression included age at stroke ictus and tumor or meningitis as a stroke risk factor. A Wald test was used to ensure that the regression model did

not violate the assumption of parallel lines. A 2-sided P-value of ≤0.05 was considered statistically significant.

RESULTS

Subject Characteristics

A flow diagram of subject inclusion is presented in Figure 1. Sixty children (45.8%) were female. Median age at stroke ictus was 4.1 years (IQR 1.4-11.5 years). Racial distribution of the children included the following: 106 White (80.9%), 12 Black (9.2%), 9 Asian (6.9%), 2 Native Peoples or Pacific Islanders (1.5%), and 2 other races (1.5%). Stroke CASCADE classification and arterial territories infarcted are in Table 1.

ModASPECTS and Stroke Severity, Hemorrhagic Transformation, and Outcome

ModASPECTS, hemorrhagic transformation, PedNIHSS, and PSOM summary statistics are found in Table 2. Figure 2 provides two examples of modASPECTS scoring. In the entire cohort of 131 children, median modASPECTS was 4 (IQR 3-7), and median number of days from stroke ictus to MRI was 1 (IQR 0-1 day). ModASPECTS was associated with the presence of hemorrhagic transformation (OR 1.13, 95% CI 1.02-1.25, P=0.018); however, when limiting the analysis to a subset of 48 children aged 2 years or older with isolated anterior circulation infarction and PedNIHSS on the day of stroke ictus, the association of modASPECTS and hemorrhagic transformation was not significant (OR 0.82, 95% CI 0.54-1.25, P=0.36). Among 89 children aged 2 years or older, rho between modASPECTS and PedNIHSS was 0.40, P=0.0001 (Figure 3A). Among 48 children aged 2 years or older with isolated anterior circulation stroke and PedNIHSS score on the day of stroke ictus, rho between modASPECTS and PedNIHSS score was 0.44, P=0.017. Among 29 children (31.9%) age 2 years or older who had both an MRI and a neurological examination on the day of stroke ictus, rho between modASPECTS and PedNIHSS score was 0.47, P=0.0098.

Twelve-month follow-up was available in 128 of 131 children (97.7%) at a median of 12.2 months post-stroke (IQR 9.5 months to 15.4 months). Only four subjects' last follow-up was prior to 6 months from stroke ictus. Children with poor outcomes had higher modASPECTS scores than those with good outcomes (median modASPECTS 6 [IQR 3-8] versus median modASPECTS 3 [IQR 2-5], P=0.0008, rank-sum). There was a correlation between modASPECTS and 12-month PSOM (rho=0.35, P<0.0001; Figure 3B). In an analysis of 48 children aged 2 years or older at stroke ictus with isolated anterior circulation infarction and PedNIHSS on the day of stroke ictus, rho between modASPECTS and PSOM was 0.32, P=0.027. For every 1-point increase in modASPECTS, the common odds ratio (cOR) for an outcome in the next PSOM severity category was 1.14 (95% CI 1.04-1.24, P=0.005). When adjusting for both age at stroke ictus and the presence of tumor or meningitis, two stroke risk factors that are independently associated with poor outcome, the cOR was 1.14 (95% CI 1.03-1.24, P=0.008).

DISCUSSION

In this retrospective analysis of prospectively enrolled pediatric AIS cases at two tertiary care hospitals, we found that modASPECTS was associated with 12-month functional outcome. The association of modASPECTS and outcome persisted when adjusting for stroke risk factors that may have independent associations with poor outcome and age at stroke ictus as well as in a subgroup of children with anterior circulation stroke who were older than age 2 years at stroke ictus with PedNIHSS scores available from the day of the stroke. ModASPECTS also correlated with PedNIHSS scores and was associated with hemorrhagic transformation on acute MRI, although the latter association was no longer significant when analysis was confined to children aged 2 years or older with anterior circulation stroke who had PedNIHSS on the day of stroke

ictus. PedNIHSS and modASPECTS correlated in a previous study, although the actual correlation coefficient was not presented.[19] The modest correlation between modASPECTS and PedNIHSS could indicate that an imaging-clinical mismatch exists in some patients but also could be indicative of the fact that certain stroke locations, for example the basal ganglia, that are common regions of infarction in pediatrics stroke can have relatively low modASPECTS scores with significant deficits and thus high PedNIHSS scores. Our rho of 0.40 was similar to the rho of -0.31 in adult studies that compared ASPECTS and an electronic ASPECTS to NIHSS scores.[20, 21] In the present study, more than half of MRIs were performed one or more days after stroke ictus, which is not surprising given diagnostic delays that are well described in pediatric stroke.[22, 23] The value of the acute adult ASPECTS is to identify and quantify early ischemic changes that may reflect irreversibly damaged tissue or conversely, salvageable tissue. [1] These imaging changes are dynamic and may vary as time from stroke ictus increases.[24] In this pediatric cohort, the correlation between modASPECTS and PedNIHSS improved among the subset of children with both MRI and PedNIHSS on the day of stroke ictus and in a subset with isolated anterior circulation stroke in whom PedNIHSS was available from the day of stroke ictus, suggesting that modASPECTS may be more informative among children who present in the therapeutic window for hyperacute therapies. Future studies should address whether modASPECTS can differentiate which children will benefit from hyperacute therapies like endovascular thrombectomy.

Additionally, the correlation of modASPECTS with outcome on the PSOM was previously reported by two groups at follow-up durations of 1-year and 2-years, respectively.[11, 12] These latter studies limited participants to those with focal cerebral arteriopathy of childhood. The current study's findings are applicable to children with AIS due to other common risk factors like cardioembolic stroke and arteriopathy subtypes in addition to focal cerebral arteriopathy.

The correlation of modASPECTS and outcomes was less striking than in both previous studies (rho=0.35 in current study versus 0.74 in previous report for 1-year outcomes[11] and 0.66 for 2-year outcomes[12]). The less robust correlation in the current study is possibly explained by the restriction to focal cerebral arteriopathy cases in the previous works. ModASPECTS was not associated with later seizures as it is in the setting of neonatal AIS,[8, 10] possibly because only 11 subjects developed epilepsy in our study. The finding that supratentorial infarct volume was associated with hemorrhagic transformation has already been demonstrated in a cohort with 38 overlapping subjects,[18] so the result that modASPECTS is associated with hemorrhagic transformation of childhood AIS on acute MRI is not surprising.

While we found that modASPECTS is associated with functional outcome and hemorrhagic transformation on acute MRI, its usefulness for outcome prediction or hemorrhagic transformation after endovascular therapy or tPA for childhood AIS is yet unknown. In three of 5 treatment trials for endovascular therapy published in 2015, ASPECTS was an inclusion criterion.[2-4] In a meta-analysis of 5 endovascular treatment trials, those with high (good) and moderate baseline ASPECTS had benefit with endovascular therapy.[25] Those in the endovascular treatment arm with low ASPECTS did not have improved functional outcomes, but the authors concluded that further study was required to determine if some with very large strokes would have some benefit. In a pooled analysis of 7 prospective registries that examined patients with low ASPECTS of 0-5 who underwent mechanical thrombectomy, those who achieved reperfusion had improved functional outcomes, decreased mortality, and decreased risk of symptomatic intracranial hemorrhage.[26] In a meta-analysis of 7 clinical endovascular trials, treatment effect favored endovascular therapy with the exception of very low ASPECTS of 0-2.[27] Treatment was also associated with higher rates of symptomatic hemorrhage in patients with ASPECTS scores of 0-4. In a retrospective analysis of 73 children who underwent endovascular

therapy, the median adult ASPECTS was 8 (IQR 7-9) before treatment among 63 with available imaging for scoring and 7 (IQR 5-8) after treatment among 58 with imaging available for scoring.[7] Only 1 child in this previous study had a symptomatic intracerebral hemorrhage, so evaluation of ASPECTS with regard to symptomatic hemorrhagic transformation risk was not possible. In a study of 26 children who received intravenous tPA, 15 had pre-treatment adult ASPECTS, and all scores were moderate to high (8-10).[28] None of the 26 children had a symptomatic intracranial hemorrhage.[28] Our finding that modASPECTS is associated with hemorrhagic transformation on acute stage MRI may indicate that the score could help risk stratify children eligible for hyperacute therapy. However, future studies with longitudinal imaging acquisition for identification of hemorrhagic transformation is required to determine whether modASPECTS on acute MRI can identify those at highest risk for post-therapy hemorrhagic transformation.

The current study has several limitations many of which are related to the retrospective design. The study was observational, so follow-up time was not uniform. Some limitations demonstrate that important metrics are often not recorded in the setting of pediatric stroke. For example, exact times of stroke onset and neurological examination, and therefore PedNIHSS scores were not recorded in the majority of cases. Therefore, precise times from stroke ictus to PedNIHSS scores or MRIs could not be assessed beyond whether these were performed on the same calendar date as stroke ictus. It should be noted that most of the cohort presented before hyperacute therapies like intravenous alteplase and endovascular thrombectomy were common considerations for children with stroke, so the recording of information about timing may not have been a focus of the acute care. While 131 subjects represent a large sample for childhood AIS studies, there was still not enough power to examine how modASPECTS performs among the various stroke risk factors that are associated with childhood AIS. Nonetheless, this study solidifies the association

between modASPECTS and outcome in a broader study cohort (not only limited to children with focal cerebral arteriopathy). Although modASPECTS has been shown to have excellent interrater reliability in a previous study, [9] we did not have consent to transfer images between institutions to determine the interrater reliability among the raters at these two centers. The modASPECTS and evaluation of the presence of hemorrhagic transformation were performed on the same MRI, so the rater was not blinded to either modASPECTS score or the presence or absence of hemorrhagic transformation which could have introduced bias in which hemorrhagic transformation was more likely to be identified in patients with higher modASPECTS. While the contemporaneous scoring could have introduced bias, the scoring and evaluation for hemorrhage were performed prior to this study's design, so the raters were not yet aware of the present study's objectives. Finally, a modASPECTS region is scored as positive if any portion has restricted diffusion, which can lead to higher (worse) scores in some subjects with milder clinical strokes. This could explain the modest correlations between modASPECTS and PedNIHSS and between modASPECTS and PSOM. In the future, a weighted modASPECTS in which regions with partial diffusion restriction are scored with a fraction of a point, for example a half point, should be investigated to determine whether the correlation between modASPECTS with PedNIHSS and PSOM can be improved.

ModASPECTS' correlation with and performance against perfusion measures is another area for future investigation. In an adult study, ischemic core volume assessed on automated CT perfusion was associated with functional outcome among those with successful reperfusion after endovascular therapy within 18 hours of stroke symptom onset, while ASPECTS did not predict outcome.[29] Prospective studies with imaging and clinical metrics performed at specific time intervals will aid in determining what role modASPECTS has in selecting children for acute therapies like endovascular therapy and intravenous tPA.

CONCLUSIONS

In summary, modASPECTS is associated with 12-month outcome in children with AIS as well as acute hemorrhagic transformation. The score also correlates with clinical stroke severity on PedNIHSS although other factors such as stroke location are likely to influence severity. However, the modest correlation between modASPECTS and PedNIHSS could indicate a potential mismatch between diffusion imaging and clinical symptoms/perfusion in some children. ModASPECTS should be investigated as a tool to identify children who would benefit from thrombectomy as low modASPECTS with high PedNIHSS could represent a child with a perfusion-diffusion mismatch. We also plan to validate the modASPECTS and its relationship to functional outcome in a broader international cohort with carefully collected data on time of stroke onset, time from stroke ictus to PedNIHSS and MRI, and with standardized outcomes at both 12-months post-stroke and long-term. Future studies are also needed to evaluate the utility of modASPECTS in children who undergo acute stroke therapies to determine whether certain ranges of scores identify children who may derive the most benefit from therapy or who might be at highest risk for symptomatic intracranial hemorrhages.

REFERENCES

1. Barber PA, Demchuk AM, Zhang J, Buchan AM. Validity and reliability of a quantitative computed tomography score in predicting outcome of hyperacute stroke before thrombolytic therapy. Lancet 2000;355:1670-1674.

2. Saver JL, Goyal M, Bonafe A, et al. Stent-retriever thrombectomy after intravenous t-PA vs. t-PA alone in stroke. N Engl J Med 2015;372:2285-2295.

3. Goyal M, Demchuk AM, Menon BK, et al. Randomized assessment of rapid endovascular treatment of ischemic stroke. N Engl J Med 2015;372:1019-1030.

4. Jovin TG, Chamorro A, Cobo E, et al. Thrombectomy within 8 hours after symptom onset in ischemic stroke. N Engl J Med 2015;372:2296-2306.

5. Powers WJ, Rabinstein AA, Ackerson T, et al. Guidelines for the early management of patients with acute ischemic stroke: 2019 update to the 2018 guidelines for the early management of acute ischemic stroke. Stroke 2019;50:e344-e418.

6. Bigi S, Dulcey A, Gralla J, et al. Feasibility, safety, and outcome of recanalization treatment in childhood stroke. Ann Neurol 2018;83:1125-1132.

7. Sporns PB, Strater R, Minnerup J, et al. Feasibility, safety, and outcome of endovascular recanalization in childhood stroke: the Save ChildS Study. JAMA Neurol 2020;77:25-34.

8. Wusthoff CJ, Kessler SK, Vossough A, et al. Risk of later seizure after perinatal arterial ischemic stroke: a prospective cohort study. Pediatrics 2011;127:e1550-1557.

9. Beslow LA, Vossough A, Dahmoush HM, et al. Modified pediatric ASPECTS correlates with infarct volume in childhood arterial ischemic stroke. Front Neurol 2012;3:122.

10. Mackay MT, Slavova N, Pastore-Wapp M, et al. Pediatric ASPECTS predicts outcomes following acute symptomatic neonatal arterial stroke. Neurology 2020;94:e1259-e1270.

11. Perez FA, Oesch G, Amlie-Lefond CM. MRI vessel wall enhancement and other imaging biomarkers in pediatric focal cerebral arteriopathy-inflammatory subtype. Stroke 2020;51:853-859.

12. Slavova N, Fullerton HJ, Hills NK, Breiding PS, Mackay MT, Steinlin M. Validation of the focal cerebral arteriopathy severity score (FCASS) in a Swiss cohort: Correlation with infarct volume and outcome. Eur J Paediatr Neurol 2020;28:58-63.

13. Ichord RN, Bastian R, Abraham L, et al. Interrater reliability of the pediatric National Institutes of Health stroke scale (PedNIHSS) in a multicenter study. Stroke 2011;42:613-617.

14. Beslow LA, Kasner SE, Smith SE, et al. Concurrent validity and reliability of retrospective scoring of the Pediatric National Institutes of Health Stroke Scale. Stroke 2012;43:341-345.

15. Bernard TJ, Beslow LA, Manco-Johnson MJ, et al. Inter-rater reliability of the CASCADE criteria: challenges in classifying arteriopathies. Stroke 2016;47:2443-2449.

16. deVeber GA, MacGregor D, Curtis R, Mayank S. Neurologic outcome in survivors of childhood arterial ischemic stroke and sinovenous thrombosis. J Child Neurol 2000;15:316-324.

17. Fisher RS, Acevedo C, Arzimanoglou A, et al. ILAE official report: a practical clinical definition of epilepsy. Epilepsia 2014;55:475-482.

18. Beslow LA, Smith SE, Vossough A, et al. Hemorrhagic transformation of childhood arterial ischemic stroke. Stroke 2011;42:941-946.

19. Andrade A, Bigi S, Laughlin S, et al. Association between prolonged seizures and malignant middle cerebral artery infarction in children with acute ischemic stroke. Pediatr Neurol 2016;64:44-51.

20. Demchuk AM, Hill MD, Barber PA, et al. Importance of early ischemic computed tomography changes using ASPECTS in NINDS rtPA Stroke Study. Stroke 2005;36:2110-2115.

21. Nagel S, Wang X, Carcel C, et al. Clinical utility of electronic Alberta Stroke Program Early Computed Tomography Score software in the ENCHANTED trial database. Stroke 2018;49:1407-1411.

22. Rafay MF, Pontigon AM, Chiang J, et al. Delay to diagnosis in acute pediatric arterial ischemic stroke. Stroke 2009;40:58-64.

23. Mallick AA, Ganesan V, Kirkham FJ, et al. Diagnostic delays in paediatric stroke. J Neurol Neurosurg Psychiatry 2015;86:917-921.

24. Liebeskind DS, Jahan R, Nogueira RG, Jovin TG, Lutsep HL, Saver JL. Serial Alberta Stroke Program Early CT Score from baseline to 24 hours in solitaire flow restoration with the intention for thrombectomy study: a novel surrogate end point for revascularization in acute stroke. Stroke 2014;45:723-727.

25. Goyal M, Menon BK, van Zwam WH, et al. Endovascular thrombectomy after large-vessel ischaemic stroke: a meta-analysis of individual patient data from five randomised trials. Lancet 2016;387:1723-1731.

26. Kaesmacher J, Chaloulos-Iakovidis P, Panos L, et al. Mechanical thrombectomy in ischemic stroke patients with Alberta Stroke Program Early Computed Tomography Score 0-5. Stroke 2019;50:880-888.

27. Roman LS, Menon BK, Blasco J, et al. Imaging features and safety and efficacy of endovascular stroke treatment: a meta-analysis of individual patient-level data. Lancet Neurol 2018;17:895-904.

28. Amlie-Lefond C, Shaw DWW, Cooper A, et al. Risk of intracranial hemorrhage following intravenous tPA (tissue-type plasminogen activator) for acute stroke is low in children. Stroke 2020;51:542-548.

29. Demeestere J, Scheldeman L, Cornelissen SA, et al. Alberta Stroke Program Early CT Score versus computed tomographic perfusion to predict functional outcome after successful reperfusion in acute ischemic stroke. Stroke 2018;49:2361-2367.

Appendix 1: Authors

Name	Location	Contribution

Lauren A. Beslow, MD, MSCE	Children's Hospital of Philadelphia, Philadelphia, PA	Designed and conceptualized study; data management; data acquisition; data analysis; data interpretation; figure preparation; drafted initial manuscript; revised manuscript for intellectual content
Arastoo Vossough, MD, PhD	Children's Hospital of Philadelphia, Philadelphia, PA	Data acquisition, data interpretation; figure preparation; revised manuscript for intellectual content
Rebecca N. Ichord, MD	Children's Hospital of Philadelphia, Philadelphia, PA	Designed and conceptualized study; data acquisition; data management; revised manuscript for intellectual content
Nedelina Slavova, MD	Bern University Hospital, Bern, Switzerland	Data acquisition; revised manuscript for intellectual content
Maggie L.Y. Yau, MBBS	Prince of Wales Hospital, Hong Kong, Hong Kong SAR	Data acquisition; revised manuscript for intellectual content
Jay Gajera, MD	The Alfred Hospital, Melbourne, Australia	Data acquisition; revised manuscript for intellectual content
Belinda	Royal Children's	Data acquisition; revised manuscript for intellectual

Stojanovski, BSc	Hospital, Melbourne, Australia	content
Malik M. Adil, MD	Johns Hopkins University, Baltimore, Maryland	Data analysis; data interpretation; figure preparation; revised manuscript for intellectual content
Jake Breimann, BA	Children's Hospital of Philadelphia, Philadelphia, PA	Data acquisition; data management; revised manuscript for intellectual content
Alexandra C. Kimmel, BA	Children's Hospital of Philadelphia, Philadelphia, PA	Data acquisition; data management; revised manuscript for intellectual content
Mark T. Mackay, MBBS, PhD	Royal Children's Hospital, Melbourne, Australia	Designed and conceptualized study; data acquisition; data interpretation; revised manuscript for intellectual content

Table 1. Stroke Subtypes and Location among 131 with Pediatric Stroke

Classification and Arterial Territory	**Number (%)**
CASCADE	
Small vessel arteriopathy	2 (1.5%)
Unilateral focal cerebral arteropathy	36 (27.5%)

Bilateral cerebral arteriopathy	13 (9.9%)
Aortic/cervical arteriopathy	6 (4.6%)
Cardioembolic	35 (26.7%)
Other	38 (29%)
Cryptogenic	28 (21.4%)
Thrombophilia	5 (3.8%)
Meningitis	3 (2.3%)
Tumor	2 (1.5%)
Multifactorial	1 (0.8%)
Location	
Middle cerebral artery	105 (80.2%)
Anterior cerebral artery	2 (1.5%)
Posterior cerebral artery	8 (6.1%)
Middle cerebral artery plus additional territory	16 (12.2%)

CASCADE, Childhood AIS Standardized Classification and Diagnostic Evaluation (CASCADE) criteria

Table 2. ModASPECTS, Hemorrhagic Transformation, Stroke Severity, and Functional Outcome

	Median (IQR) or Number (%)
MRI (n=131)	
modASPECTS (n=131)	4 (3-7)
Hemorrhagic transformation	27 (20.6%)

Days from stroke to MRI	1 (0-1)
0	59 (45.1%)
1	43 (32.8%)
≥2	29 (22.1%)
PedNIHSS (n=89 age ≥2 years)	6 (3-12)
Days from stroke ictus to PedNIHSS	0 (0-1)
0	52 (58.4%)
1	25 (28.1%)
≥2	12 (13.5%)
Retrospectively scored PedNIHSS	68 (76.4%)
Prospectively scored PedNIHSS	21 (23.6%)
Outcome (n=128)	
PSOM (n=122)	1 (0.5-2)
Death	6 (4.7%)
Follow-up time, months	12.2 (9.5-15.4)
Poor Outcome (PSOM≥1 or death)	80 (62.5%)
PSOM 0-1	74 (57.8%)
PSOM 1.5-3	38 (29.7%)
PSOM 3.5-6	9 (7%)
PSOM 6.5-10 or death	7 (5.5%)

ModASPECTS, modified pediatric Alberta Stroke Program CT score; n; number; MRI, magnetic resonance imaging; PedNIHSS, pediatric National Institutes of Health Stroke Scale; PSOM, pediatric stroke outcome measure

Figure Legends

Figure 1. Flow Diagram of Subject Inclusion

RCH, Royal Children's Hospital; CHOP, Children's Hospital of Philadelphia; AIS, arterial ischemic stroke; HCT, head computed tomography; DWI, diffusion-weighted imaging; MRI, magnetic resonance imaging; modASPECTS; modified pediatric Alberta Stroke Program CT score; PedNIHSS, pediatric National Institutes of Health Stroke Scale; PSOM, pediatric stroke outcome measure

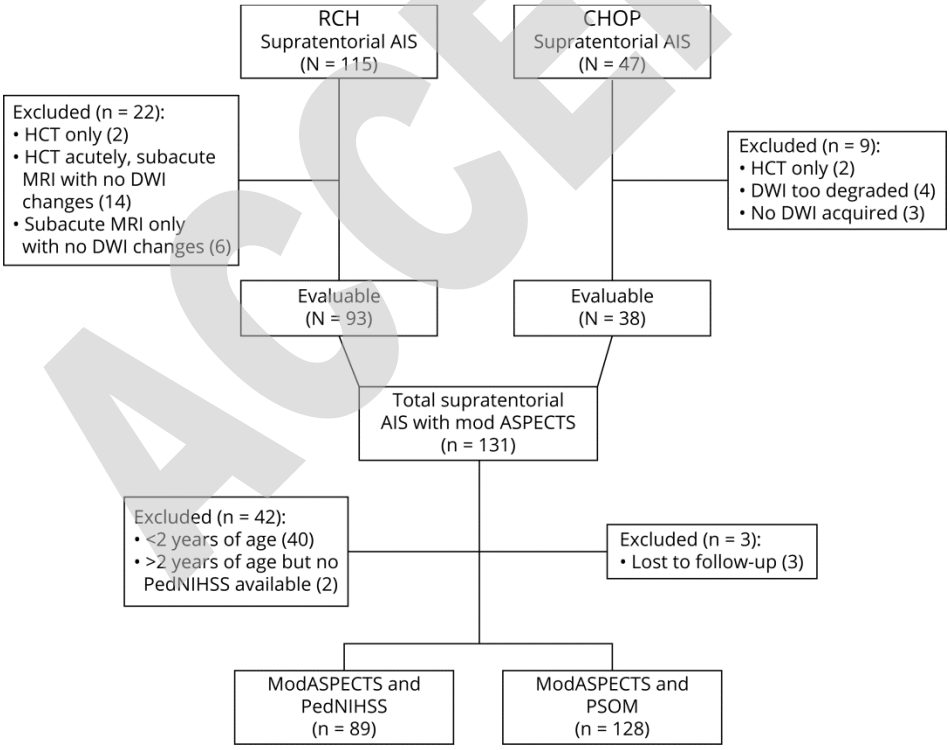


Figure 2. ModASPECTS scoring from two different children. (A-C) Patient with total modASPECTS of 10 (Left M1, M2, M4, M5, M6, IC, C, I, T). (D-F) Patient with total modASPECTS of 3 (Right M1, M4, I).

modASPECTS, modified pediatric Alberta Stroke Program CT score.

Red labels indicate modASPECTS scoring regions: A1-2, anterior cerebral artery regions; M1-6, middle cerebral artery regions; P1-2, posterior cerebral artery regions; I, insula region; C, caudate region; L, lentiform nucleus region; IC, internal capsule region; T, thalamus region

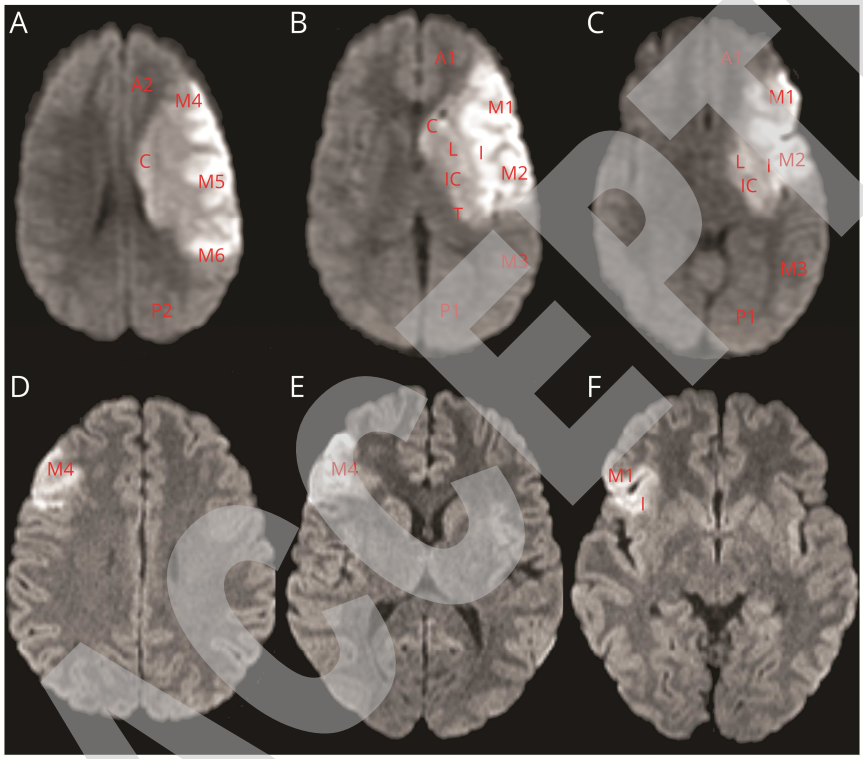
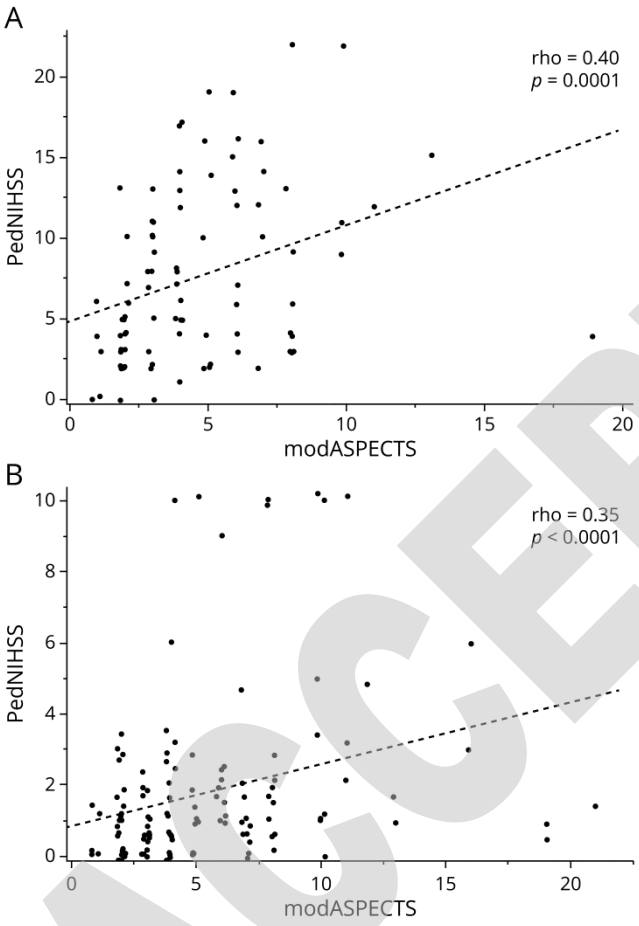


Figure 3. A) Scatterplot of modASPECTS and PedNIHSS scores in 89 children aged 2 years and older. B) Scatterplot of modASPECTS and PSOM scores in 128 children with 12-month follow-up.

modASPECTS; modified pediatric Alberta Stroke Program CT score; PedNIHSS, pediatric National Institutes of Health Stroke Scale; PSOM, pediatric stroke outcome measure



Association of Pediatric ASPECTS and NIH Stroke Scale, Hemorrhagic Transformation, and 12-Month Outcome in Children With Acute Ischemic Stroke

Lauren A. Beslow, Arastoo Vossough, Rebecca N. Ichord, et al.

Neurology published online August 13, 2021
DOI 10.1212/WNL.0000000000012558