JAMA Neurology | Original Investigation

Incidence and Natural History of Pediatric Large Vessel Occlusion Stroke
A Population Study

Kartik D. Bhatia, MBBS, PhD; Romain Briest, MBBS; Robert Goetti, MBBS; Richard Webster, MBBS; Christopher Troedson, MBBS; Russell C. Dale, MBBS, PhD; Prakash Muthusami, MD; Christina Miteff, MBBS; Ferdinand Miteff, MBBS; John Worthington, MBBS; Kylie Tastula, RN; Timothy Ang, MBBS; Ian Andrews, MBBS

IMPORTANCE The incidence and natural history of large vessel occlusion (LVO) stroke in children is largely unknown. These knowledge gaps limit the uptake of reperfusion therapies and reduce the efficiency of pediatric acute stroke pathways.

OBJECTIVE To determine the incidence and natural history of pediatric LVO stroke.

DESIGN, SETTING, AND PARTICIPANTS This retrospective population-based cohort study was conducted between January 2010 and December 2019, with a mean (SD) follow-up of 37.0 (28.8) months. Admissions from all pediatric hospitals in the state of New South Wales, Australia, with a final diagnosis of arterial ischemic stroke (AIS) in patients 1 month to younger than 17 years were included. A total of 85 of 251 identified cases were excluded based on selection criteria. Data were analyzed from July 2020 to June 2021.

EXPOSURES One-third of patients with LVO received mechanical thrombectomy with or without intravenous thrombolysis while the remainder were treated conservatively.

MAIN OUTCOMES AND MEASURES The primary outcome was the pediatric modified Rankin Scale (ped-mRS) score 3 months after stroke. Ordinal logistic regression was used to compare non-LVO, LVO without thrombectomy, and LVO with thrombectomy groups.

RESULTS Of 161 included patients, 56 (34.8%) were female, and the mean (SD) age was 6.1 (5.4) years. A total of 166 AIS admissions were studied, and clinical follow-up was available for 164 of 166 admissions. LVO was present in 39 admissions (23.5%). The incidence of LVO stroke was 0.24 per 100 000 patients per year (95% CI, 0.13-0.35). Patients with LVO who did not receive thrombectomy (n = 26) had poor neurological outcomes, with 19 (73.1%) experiencing moderate to severe disability or death (ped-mRS score of 3 to 6) at 3 months (6 of 12 patients receiving thrombectomy [50.0%]; 25 of 38 patients with LVO [65.8%]). Patients with LVO without thrombectomy had significantly worse clinical outcomes than patients with non-LVO at 3 months (odds ratio, 3.64; 95% CI, 1.68-7.87; P = .001). Most patients with LVO presented within time windows suitable for thrombectomy (27 of 39 [69.2%] within 6 hours; 35 of 39 [89.7%] within 24 hours).

CONCLUSIONS AND RELEVANCE In this population-based cohort study, the natural history of pediatric patients with LVO stroke treated conservatively was poor, with most experiencing lifelong disability or death. Nearly 90% of pediatric patients with LVO presented within time windows suitable for thrombectomy.

Supplemental content

Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Author: Kartik D. Bhatia, MBBS, PhD, Department of Medical Imaging, Children's Hospital at Westmead, Cnr Hainsworth Street and Hawkesbury Road, Westmead, NSW 2145, Australia (kartik.bhatia@health.nsw.gov.au).

JAMA Neurol. 2022;79(5):488-497. doi:10.1001/jamaneurol.2022.0323
Published online March 28, 2022.

Large vessel occlusion (LVO) causes approximately one-quarter of arterial ischemic stroke (AIS) presentations in adults[1] and has worse long-term outcomes than non-LVO stroke.[2] Five randomized clinical trials showed mechanical thrombectomy within 6 to 8 hours since last seen well improved outcome compared with standard medical therapy in those with anterior circulation LVO.[3-9] The time window of benefit was extended to 16 and then 24 hours by 2 additional trials in selected adult patients.[10,11]

Children and adolescents were not included in those trials, and to our knowledge, there are no randomized clinical trials for mechanical thrombectomy or any acute therapies for pediatric AIS. Evidence for thrombectomy in children is predominantly from studies that are retrospective and single arm and have small sample sizes.[12] A recent larger retrospective multicenter cohort study assessing outcomes following thrombectomy in 73 children reported favorable long-term outcomes, with a median modified Rankin Scale (mRS) score of 1.0.[13] Current guidelines for treatment of LVO stroke in children make only cautious recommendations on its use,[14,15] although recent literature suggests increasing uptake of thrombectomy.[12,13]

Absence of population data regarding the natural history of LVO stroke in children has hindered confident interpretation of the existing pediatric data. Randomizing pediatric patients to noninterventional treatment would be unethical given the benefit in adults (number needed to treat of 2.6).[8] In addition, such a trial would likely not be feasible, as observed in attempts to undertake a trial for intravenous (IV) thrombolysis in children.[16] Further limitations on the uptake of reperfusion therapies include absence of LVO stroke incidence data in children,[12] slow triage and imaging pathways,[17] and historic beliefs that children with LVO present too late for reperfusion and have better outcomes than adults when treated conservatively.[18,19] Addressing these evidence gaps may support resource allocation and facilitate formation of stronger, evidence-based guidelines for pediatric stroke.

In this study, we aim to address the following gaps in knowledge: (1) the annual incidence of pediatric LVO stroke; (2) the proportion of pediatric AIS cases caused by LVO; (3) the proportion of pediatric LVO cases that would fulfill adult selection criteria for mechanical thrombectomy (other than age); and (4) the long-term clinical outcomes of pediatric LVO stroke without thrombectomy.

Key Points

Question What is the incidence and natural history of arterial ischemic stroke due to large vessel occlusion in the pediatric population?

Findings In this cohort study that included 166 admissions for pediatric arterial ischemic stroke, 39 (23.5%) had a large vessel occlusion. The incidence of pediatric large vessel occlusion stroke was 0.24 per 100 000 children per year, and patients with large vessel occlusion who were treated conservatively had poor neurological outcomes, with 19 (73.1%) experiencing moderate to severe disability or death at 3 months.

Meaning In this study, the natural history of large vessel occlusion stroke in children was poor when treated conservatively, contrary to historic beliefs.

Methods

Study Design

Ethics approval was granted by the Sydney Children's Hospital Network Human Research Ethics Committee, including a waiver for consent. The design was a multicenter retrospective cohort study of all pediatric patients (1 month to younger than 17 years) with acute AIS across the state of New South Wales (NSW), Australia, covering the 10 years from January 1, 2010, to December 31, 2019. Four centers were included: all 3 pediatric hospitals in NSW and an adult comprehensive stroke center that provides thrombectomy to older adolescents. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.

Three centers had existing prospective databases for AIS, while the fourth center required creation of a retrospective database using diagnostic coding from which AIS cases were identified. Clinical and imaging records were then assessed for the inclusion and exclusion criteria to confirm the case. The presence of AIS was based on the final clinical diagnosis made by the treating pediatric neurologist.

Inclusion Criteria

Inclusion criteria were age 1 month to younger than 17 years on the date of initial assessment, admission, or follow-up at one of the 4 involved centers between January 2010 and December 2019, and *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision* (*ICD-10*) diagnostic codes of I63 (cerebral infarction), I65 (occlusion and stenosis of precerebral arteries, not resulting in cerebral infarction), or I66 (occlusion and stenosis of cerebral arteries, not resulting in cerebral infarction).

Exclusion Criteria

The following patient groups were excluded because they have markedly different etiologies, presentations, treatments, and outcomes: those with hemorrhagic stroke, neonatal stroke (younger than 29 days) (n = 35); those with cerebral venous sinus thrombosis (n = 9); those with group B *Streptococcal* meningitis–related stroke (n = 7); those with herniation syndromes from traumatic brain injury resulting in stroke (n = 8); and those with global hypoxic-ischemic injury (eg, cardiac arrest, drowning) (n = 26). Clinical and imaging records of patients identified with *ICD-10* diagnostic codes I65 and I66 were assessed for evidence of infarction; in the absence of infarction or reperfusion therapy, these patients were excluded. Patients 17 years and older were excluded because a substantial proportion were treated at adult hospitals.

Definition of LVO

For this study, LVO was defined as acute occlusion of the intracranial segments of the internal carotid artery (ICA), M1 (first) or M2 (second) segments of the middle cerebral artery, A1 or

A2 segments of the anterior cerebral artery (ACA), intracranial segment of the vertebral artery, basilar artery, and P1 or P2 segments of the posterior cerebral artery (PCA), as demonstrated on computed tomography angiography (CTA), magnetic resonance angiography (MRA), or digital subtraction angiography (DSA). Acute vs chronic occlusion was differentiated based on presence or absence of well-developed lenticulostriate or transdural collaterals.

This definition as it applies to the anterior circulation is derived from the first and largest positive randomized clinical trial for mechanical thrombectomy in AIS (Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands [MR CLEAN] trial: ICA, M1, M2, A1, A2),[3] supported by Class I (ICA, M1) and Class IIb (ACA, M2) recommendations for mechanical thrombectomy in adults from the American Heart Association (AHA).[3,9] For the posterior circulation, it is based on AHA Class IIb recommendations in adults.[9]

Epidemiological Data Collection

The population of persons younger than 17 years in NSW as estimated in June of each year from 2010 to 2019 by the Australian Bureau of Statistics was used to determine the state pediatric population.[20] The annual and mean incidence rates measured in cases per 100 000 persons younger than 17 per year were calculated for pediatric patients with AIS and LVO.

Outcome Measures and Analyses

The primary outcome was the functional clinical outcome 3 months after stroke onset measured using the pediatric mRS (ped-mRS) score. The primary analysis compared patients with LVO who did not undergo mechanical thrombectomy and/or IV thrombolysis with patients with non-LVO. Ped-mRS score was assessed retrospectively by a pediatric neurologist or pediatric interventional neuroradiologist based on prior assessments undertaken by a pediatric neurologist, neurosurgeon, or rehabilitation physician 2 to 4 months after AIS. Ped-mRS scores were able to be derived from the clinical records in 164 of 166 admissions (98.8%). The primary safety outcome was the rate of symptomatic intracranial hemorrhage.

Selection of patients with LVO to receive reperfusion therapy was not randomized or based on standardized selection criteria but rather was determined by the treating pediatric neurologist in the context of the clinical presentation and resource availability. The study period extended before and after mechanical thrombectomy became widely used in adults (2015 onwards), affecting patient selection. An a priori decision was thus made to make the primary analysis a comparison of the LVO without thrombectomy and non-LVO groups.

Secondary outcomes were final ped-mRS score available (including timing), stroke etiology, method of initial angiographic imaging (CTA, MRA, or DSA), timing of imaging (hours since last seen well), timing of clinical presentation (less than 6, 6 to 24, 24 to 48, or more than 48 hours since last seen well), IV thrombolysis status, mechanical thrombectomy status, and selection criteria fulfillment status (other than age) for the MR CLEAN trial,[3] DWI or CTP Assessment with Clinical Mismatch in the Triage of Wake-Up and Late Presenting Strokes Undergoing Neurointervention with Trevo (DAWN) trial,[11] and AHA Class I-IIb recommendations[9] for use of thrombectomy in adults. Note that the MR CLEAN trial[3] included only patients with anterior circulation stroke presenting within 6 hours since last seen well, and for the DAWN trial,[11] within 6 to 24 hours since last seen well. These criteria are detailed in eMethods 1 and 2 in the Supplement. Secondary analyses included comparison of ped-mRS scores between patients with LVO with and without thrombectomy, and dichotomous assessment of 3-month and final ped-mRS scores classified into favorable outcome (ped-mRS score of 0 to 2) or poor outcome (ped-mRS score of 3 to 6).

Imaging Analysis

All available CTA, MRA, and DSA studies for patients with AIS were analyzed independently by a pediatric interventional neuroradiologist (K.D.B.) for the presence of LVO. Imaging for all LVO cases was further independently assessed by 2 pediatric neuroradiologists at separate centers, blinded to the clinical presentation and outcome (R.G. and P.M.). Assessors recorded the presence, side, and location of the primary (most proximal) intracranial occlusion.

Statistical Analysis

The primary analysis was assessed by ordinal logistic regression using MiniTab version 19.2020.2.0 (MiniTab LLC) to determine the odds ratio (OR) and *P* value for a worse outcome on the ped-mRS score (ie, higher score on the scale from 0 to 6) comparing patients with non-LVO, LVO without thrombectomy, and LVO with thrombectomy. For secondary analyses, ped-mRS score data were compared using ordinal logistic regression, dichotomous variables using the χ^2 test, and continuous variables using the unpaired *t* test. Confounders contributing to selection for thrombectomy were analyzed using binary logistic regression. Complete-case analysis was used to account for missing data. All *P* values were 2-tailed, and significance was set at $P < .05$.

Results

From January 2010 to December 2019, 166 AIS admissions in 161 pediatric patients were identified in NSW. Of 161 included patients, 56 (34.8%) were female, and the mean (SD) age was 6.1 (5.4) years. A total of 166 AIS admissions were studied, and clinical follow-up was available for 164 of 166 admissions. Demographic characteristics, etiology, and timing of presentation are reported in **Table 1**.

LVO Status and Imaging

LVO was present in 39 of 166 admissions (23.5%). Initial angiographic imaging was available in 36 of 39 patients with LVO, with 100% agreement of occlusion location between blinded assessors. Follow-up imaging was available for the remaining 3 cases, all demonstrating territorial infarcts consistent with previous LVO. Imaging results are reported in **Table 2**.

A total of 13 patients (33.3%) underwent mechanical thrombectomy (10 underwent thrombectomy alone; 3 underwent

Table 1. Demographic Characteristics, Timing of Presentation, and Etiology

Characteristic	No. (%)			*P* value, non-LVO vs LVO
	AIS	Non-LVO	LVO	
Admissions	166 (100)	127 (76.5)	39 (23.5)	NA
Patients	161 (100)	122 (75.8)	39 (24.2)	NA
Age, y				
Mean (SD)	6.1 (5.4)	5.5 (5.2)	8.2 (5.5)	.007[a]
Median (IQR)	5.9 (1.0-11.5)	4.0 (0.95-10.0)	8.0 (3.0-13.0)	
Sex				
Female	56 (34.8)	40 (32.8)	16 (41.0)	
Male	105 (65.2)	82 (67.2)	23 (59.0)	
Intravenous thrombolysis, No.	4	1	3	.35[b]
Mechanical thrombectomy, No.	13	0	13	
Timing of clinical presentation since last seen well, h				
<6	71 (42.8)	44 (34.6)	27 (69.2)	
6-24	56 (33.7)	48 (37.8)	8 (20.5)	<.001[b]
24-48	13 (7.8)	11 (8.7)	2 (5.1)	
>48	26 (15.7)	24 (18.9)	2 (5.1)	
Total <24 h	127 (76.5)	92 (72.4)	35 (89.7)	
Fulfilled adult selection criteria for mechanical thrombectomy				
MR CLEAN trial[3]	NA	NA	20 (51.3)	
DAWN trial[11]	NA	NA	7 (17.9)	
Posterior circulation[9]	NA	NA	5 (12.8)	
Total	NA	NA	32 (82.1)	
Stroke etiology				
Cardioembolic	46 (27.7)	34 (26.8)	12 (30.8)	
Dissection	17 (10.2)	9 (7.1)	8 (20.5)	.02[b]
Focal cerebral arteriopathy	8 (4.8)	4 (3.1)	4 (10.3)	
Hypercoagulable	3 (1.8)	0	3 (7.7)	
Iatrogenic	23 (13.9)	20 (15.7)	3 (7.7)	
Idiopathic	32 (19.3)	26 (20.5)	6 (15.4)	
Moyamoya	9 (5.4)	9 (7.1)	0	
Other	12 (7.2)	11 (8.7)	1 (2.6)	
Paradoxical embolus	5 (3.0)	3 (2.4)	2 (5.1)	
Traumatic vasculopathy	4 (2.4)	4 (3.1)	0	
Vasculitis	7 (4.2)	7 (5.5)	0	

Abbreviations: AIS, arterial ischemic stroke; DAWN, DWI or CTP Assessment With Clinical Mismatch in the Triage of Wake-up and Late Presenting Strokes Undergoing Neurointervention With Trevo; LVO, large vessel occlusion; MR CLEAN, Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands; NA, not applicable.

[a] *t* Test.

[b] χ^2 Test.

thrombectomy and IV thrombolysis), and 26 patients (66.7%) did not (ie, conservative treatment). Patients with LVO were older than patients with non-LVO (mean [SD] age, 8.23 [5.45] years vs 5.48 [5.23] years; *P* = .007). Patients with LVO undergoing thrombectomy were older than conservatively treated patients (mean [SD; range] age, 12.41 [4.41; 4.0-16.9] years vs 6.23 [4.73; 0.4-14.5] years; *P* < .001).

Incidence of Pediatric AIS and LVO

Across the 10-year period, the mean (SD) annual incidence of pediatric (ie, younger than 17 years) AIS was 1.02 (0.18) cases per 100 000 persons per year (95% CI, 0.89-1.16). The mean (SD) annual incidence of acute pediatric LVO was 0.24 (0.15) cases per 100 000 persons per year (95% CI, 0.13-0.35). Annual estimated incidence data are reported in the eTable in the Supplement.

Primary Outcome

At 3 months following stroke, ped-mRS score was 3 to 6 in 19 of 26 patients with LVO without thrombectomy (73.1%), 6 of 12 with LVO with thrombectomy (50.0%), and 52 of 126 with non-LVO (41.2%) (**Table 3**). A total of 24 of 26 cases involved the anterior circulation, of which 18 patients (75%) had a poor outcome at 3 months. Patients with LVO without thrombectomy had significantly worse outcomes than patients with non-LVO on the ped-mRS 3 months after stroke using ordinal logistic regression analysis (OR, 3.64; 95% CI, 1.68-7.87; *P* = .001) (Table 3).

Secondary Outcomes

Patients with LVO without thrombectomy also had significantly worse outcomes than patients with non-LVO on final available ped-mRS assessment (mean [SD] time from stroke,

Table 2. Angiographic Imaging Modality, Timing, and Occlusion Location

Characteristic	No. (%)			*P* value, non-LVO vs LVO
	AIS	Non-LVO	LVO	
Admissions, No.	166	127	39	NA
Initial imaging modality				
CTA	38 (22.9)	15 (11.8)	23 (59.0)	<.001[a]
MRA	128 (77.1)	112 (88.2)	16 (41.0)	
Time to angiographic imaging since last seen well, h[b]				
Mean (SD)	39.1 (52.8)	46.7 (57.7)	14.4 (15.8)	<.001[c]
Median (IQR)	20.0 (8.0-48.0)	22.0 (11.0-63.0)	7.5 (4.0-21.0)	
Occlusion location				
Intracranial ICA	NA	NA	14 (35.9)	NA
MCA				
M1 segment	NA	NA	12 (30.8)	NA
M2 segment	NA	NA	7 (17.9)	NA
ACA				
A1 segment	NA	NA	0	NA
A2 segment	NA		1 (2.6)	NA
Anterior circulation, total	NA	NA	34 (87.2)	NA
Intracranial vertebral artery	NA	NA	1 (2.6)	NA
Basilar artery	NA	NA	3 (7.7)	NA
PCA				
P1 segment	NA	NA	1 (2.6)	NA
P2 segment	NA	NA	0	NA
Posterior circulation - total	NA	NA	5 (12.8)	NA

Abbreviations: ACA, anterior cerebral artery; AIS, arterial ischemic stroke; CTA, computed tomography angiography; DSA, digital subtraction angiography; ICA, internal carotid artery; LVO, large vessel occlusion; MCA, middle cerebral artery; MRA, magnetic resonance angiography; NA, not applicable; PCA, posterior cerebral artery.

[a] χ^2 Test.

[b] Time in hours since last seen well until first diagnostic angiographic imaging was performed (CTA, MRA, or DSA).

[c] *t* Test.

37.0 [28.8] months; OR, 3.23; 95% CI, 1.50-6.95; *P* = .003) (**Table 4**). Dichotomous analysis results comparing ped-mRS scores of 0 to 2 vs 3 to 6 between groups were also significantly worse for patients with LVO without thrombectomy than for patients with non-LVO at 3 months (χ^2_2 = 8.803; *P* = .01) and final assessment (χ^2_2 = 7.695; *P* = .02).

Patients with LVO without thrombectomy had significantly worse outcomes than those treated with thrombectomy at (3 months: OR, 3.75; 95% CI, 1.05-13.45; *P* = .04; final assessment: OR, 6.07; 95% CI, 1.55-23.73; *P* = .01). These worse outcomes were more pronounced in the anterior circulation subgroup (**Table 5**).

Safety Outcomes

Among 13 patients undergoing thrombectomy, there were no occurrences of symptomatic intracranial hemorrhage. One patient had a retroperitoneal hemorrhage from the access site (treated with a covered stent) (Table 5). Two patients with dissection and 1 with focal cerebral arteriopathy were treated with thrombectomy, with no procedural complications.

Timing of Presentation and Eligibility for Thrombectomy

Patients with LVO presented more quickly than patients with non-LVO (Table 1). Most with LVO (27 of 39 [69.2%]) presented to the hospital within 6 hours since last seen well and 35 of 39 (90%) presented within 24 hours. Selection criteria other than age for the MR CLEAN trial[3] were fulfilled in 20 of 39 patients (51.3%) and the DAWN trial[11] in an additional 7 patients (17.9%). If posterior circulation occlusions are included (AHA Class IIb recommendations[9]), then 32 of 39 patients (82.1%) were potentially eligible. Binary logistic regression analysis of potential confounders (age, sex, timing of imaging, year, site of occlusion) only identified age (OR, 1.31; 95% CI, 1.06-1.61; *P* = .01) as a significant predictor that patients with LVO underwent thrombectomy.

Discussion

The Natural History of Pediatric LVO Stroke

In our study, outcomes for pediatric LVO stroke treated conservatively were poor. Moderate to severe disability or death (ped-mRS score of 3 to 6) was present in 19 of 26 (73.1%) at 3 months (75% of anterior circulation LVO cases). The HERMES collaboration,[8] which pooled data from 5 randomized trials on thrombectomy for anterior circulation LVO in adults, found 73.5% of control patients had a poor outcome (mRS score of 3 to 6) at 3 months—remarkably similar to the rate we identified in children (75%). In their interventional group, 54.0% had a poor outcome, and the OR of a favorable outcome following thrombectomy was 2.35.[8] These results indicate children with LVO stroke treated conservatively have similarly poor outcomes to adults with LVO and worse outcomes than adult patients undergoing thrombectomy.

With only 5 posterior circulation strokes due to LVO, we have insufficient data to comment on this cohort. A recent literature review of pediatric basilar artery occlusion, however, reported poor long-term neurological outcomes in patients

Table 3. Clinical Outcomes at 3 Months After Stroke (Primary Outcome)

Outcomes	No. (%)					OR (95% CI)	*P* value
	AIS	Non-LVO	LVO				
			All	No thrombectomy	Thrombectomy		
ped-mRS score at 3 mo, No.							
0	21	19	2	0	2	NA	NA
1	30	26	4	1	3	NA	NA
2	36	29	7	6	1	NA	NA
3	39	29	10	7	3	NA	NA
4	25	14	11	9	2	NA	NA
5	3	1	2	2	0	NA	NA
6	10	8	2	1	1	NA	NA
Total	164	126	38	26	12	NA	NA
Data missing	2	1	1	0	1	NA	NA
Anterior circulation	NA	NA	33	24	9	NA	NA
Ordinal logistic regression analysis: OR of a worse functional outcome at 3 mo							
LVO with no thrombectomy vs non-LVO[a]	NA	NA	NA	NA	NA	3.64 (1.68-7.87)	.001
LVO with thrombectomy vs non-LVO[a]	NA	NA	NA	NA	NA	1.13 (0.30-3.22)	.82
LVO with no thrombectomy vs LVO with thrombectomy[b]	NA	NA	NA	NA	NA	3.75 (1.05-13.45)	.04
LVO with no thrombectomy (anterior circulation) vs LVO with thrombectomy (anterior circulation)[b]	NA	NA	NA	NA	NA	7.14 (1.59-23.10)	.01
Dichotomous analysis[c]							
ped-mRS score	NA	NA	NA	NA	NA		
0-2	87 (53.0)	74 (58.7)	13 (34.2)	7 (26.9)	6 (50.0)	χ^2_2, 8.803	.01
3-6	77 (47.0)	52 (41.2)	25 (65.8)	19 (73.1)	6 (50.0)		
0-2 (anterior circulation)	NA	NA	11 (33.3)	6 (25.0)	5 (55.6)	NA	NA
3-6 (anterior circulation)	NA	NA	22 (66.7)	18 (75.0)	4 (44.4)		

Abbreviations: AIS, arterial ischemic stroke; LVO, large vessel occlusion; NA, not applicable; OR, odds ratio; ped-mRS, pediatric modified Rankin Scale.

[a] Primary analysis performed with ordinal logistic regression comparing ped-mRS score at 3 months after stroke between 3 groups: non-LVO, LVO with no thrombectomy, and LVO with thrombectomy. Non-LVO was the reference group. OR of a worse functional outcome (higher score on the ped-mRS scale from 0 to 6) compared with the non-LVO group was determined.

[b] Secondary analysis performed with ordinal logistic regression comparing ped-mRS score at final available assessment after stroke between patients with LVO with thrombectomy and patients with LVO with no thrombectomy. LVO with no thrombectomy was the reference group. OR of a worse functional outcome (higher score on the ped-mRS scale from 0 to 6) comparing LVO with no thrombectomy with the LVO with thrombectomy group was determined. Subgroup analysis was performed using the same method but including only individuals with anterior circulation (34 of 39 patients with LVO and 9 of 13 with thrombectomy and data available; 24 without thrombectomy).

[c] Secondary dichotomous analysis performed using Pearson χ^2 test for favorable (ped-mRS score of 0 to 2) vs poor (ped-mRS score of 3 to 6) clinical outcomes 3 months after stroke between 3 groups: non-LVO, LVO with no thrombectomy, and LVO with thrombectomy groups.

treated conservatively (n = 111), with moderate to severe disability or death in 58%.[21]

Our natural history cohort consists of patients not treated with thrombectomy or IV thrombolysis. This group may have had a worse baseline prognosis, and their outcomes may be affected by selection bias. However, 73% of patients with LVO without thrombectomy fulfilled adult selection criteria for thrombectomy, patients were included from before (2010 to 2014) and after (2015 to 2019) the publication of positive adult trials, and uptake of thrombectomy in children was variable until recently.

Previous studies assessing outcomes from pediatric AIS did not analyze patients by LVO status.[15,22,23] Pooling of patients with LVO among all stroke cases allowed for a potential underestimate of LVO stroke severity. Pediatric patients with LVO (Table 1) have differing stroke etiology to patients with non-LVO, with higher proportions of cardioembolic, dissection, and focal cerebral arteriopathy cases. However, demonstration of worse outcomes for adult patients with LVO[1,2] was a major impetus for the thrombectomy trials.[3,8] Demonstration of worse outcomes in children with LVO is important to distinguish an identifiable subgroup with poor outcomes when treated conservatively.

Evidence for Mechanical Thrombectomy in Children

In our study, patients with LVO treated conservatively had significantly worse functional outcomes than patients undergoing thrombectomy (final assessment: OR, 6.07; 95% CI, 1.55-23.73; *P* = .01). However, the sample size is small, and these patients were older than those in the conservatively treated group. Therefore, these results should be interpreted with caution.

A retrospective single-arm cohort study of pediatric patients who underwent thrombectomy (n = 73) demonstrated favorable neurological outcomes, with 87% having an mRS score of 0 to 2 at 6 months.[13] Symptomatic intracranial hem-

Table 4. Clinical Outcomes at Final Available Assessment After Stroke (Secondary Outcome)

Outcome	No. (%)					OR (95% CI)	*P* value
	AIS	Non-LVO	LVO				
			All	No thrombectomy	Thrombectomy		
ped-mRS Score at final available assessment, No.							
0	33	29	4	0	4	NA	NA
1	32	29	3	1	2	NA	NA
2	43	31	12	10	2	NA	NA
3	31	18	13	10	3	NA	NA
4	4	2	2	2	0	NA	NA
5	1	1	0	0	0	NA	NA
6	20	16	4	3	1	NA	NA
Total	164	126	38	26	12	NA	NA
Data missing	2	1	1	0	1	NA	NA
Anterior circulation	NA	NA	33	24	9	NA	NA
Timing of final available ped-mRS score poststroke, mo							
Mean (SD)	37.0 (28.8)	34.7 (26.7)	44.6 (34.1)	53.0 (37.0)	26.4 (16.6)	NA	NA
Median (IQR)	35.0 (12.0-48.0)	30.0 (12.0-48.0)	36.0 (16.75-60.0)	41.0 (24.0-94.5)	27.0 (10.5-42.75)	NA	NA
Ordinal logistic regression analysis: OR of a worse functional outcome at final assessment							
LVO with no thrombectomy vs non-LVO[a]	NA	NA	NA	NA	NA	3.23 (1.50-6.95)	.003
LVO with thrombectomy vs non-LVO[a]	NA	NA	NA	NA	NA	0.80 (0.28-2.29)	.68
LVO with no thrombectomy vs LVO with thrombectomy[b]	NA	NA	NA	NA	NA	6.07 (1.55-23,73)	.01
LVO with no thrombectomy (anterior circulation) vs LVO with thrombectomy (anterior circulation)[b]	NA	NA	NA	NA	NA	8.60 (1.78-41.53)	.007
Dichotomous analysis[c]							
ped-mRS score	NA	NA	NA	NA	NA		
0-2	108 (65.9)	89 (70.6)	19 (50.0)	11 (42.3)	8 (66.7)	$\chi^2_2 = 7.695$	.02
3-6	56 (34.1)	37 (29.4)	19 (50.0)	15 (57.7)	4 (33.3)		
0-2 (anterior circulation)	NA	NA	16 (48.5)	10 (41.7)	6 (66.7)		
3-6 (anterior circulation)	NA	NA	17 (51.5)	14 (58.3)	3 (33.3)		

Abbreviations: AIS, arterial ischemic stroke; LVO, large vessel occlusion; NA, not applicable; OR, odds ratio; ped-mRS, pediatric modified Rankin Scale.

[a] Primary analysis performed with ordinal logistic regression comparing ped-mRS score at final available assessment after stroke between 3 groups: non-LVO, LVO with no thrombectomy, and LVO with thrombectomy. Non-LVO was the reference group. OR of a worse functional outcome (higher score on the ped-mRS scale from 0 to 6) compared with the non-LVO group was determined.

[b] Secondary analysis performed with ordinal logistic regression comparing ped-mRS score at final available assessment after stroke between LVO with thrombectomy and LVO with no thrombectomy. LVO with no thrombectomy was the reference group. OR of a worse functional outcome (higher score on the ped-mRS scale from 0 to 6) comparing LVO with no thrombectomy with the LVO with thrombectomy group was determined. Subgroup analysis was performed using the same method but including only anterior circulation cases (34 of 39 patients with LVO and 9 of 13 with thrombectomy and data available; 24 without thrombectomy).

[c] Secondary dichotomous analysis performed using Pearson χ^2 test for favorable (ped-mRS score of 0 to 2) vs poor (ped-mRS score of 3 to 6) clinical outcomes at final available assessment after stroke between 3 groups: non-LVO, LVO with no thrombectomy, and LVO with thrombectomy groups.

orrhage occurred in 1 patient.[13] A meta-analysis of pediatric patients undergoing thrombectomy (n = 113) demonstrated favorable long-term outcomes in 90.6%.[12] These results were superior to adult trials (mRS score of 0 to 2 in 46% at 3 months[8]) and are likely affected by selection bias.[13] However, they indicate mechanical thrombectomy in children is feasible and effective.[12,13] In our study, 50% of patients undergoing thrombectomy had a ped-mRS score of 0 to 2 at 3 months and 67% at final assessment.

Our results can now provide a natural history reference group for this population. Given the poor natural history and feasibility of thrombectomy in children, the risk-benefit balance for intervention is likely altered, and pediatric guidelines should be updated. Prospective multinational registries should be encouraged and funded.

Timing of Clinical Presentation in Pediatric LVO Stroke

In our cohort, 69% of children with LVO presented within 6 hours since last seen well, and 90% presented within 24 hours. Four of 5 children with LVO (82.1%) fulfilled adult selection criteria for consideration of thrombectomy other than age.[3,9,11] These high rates of early presentation likely reflect the sever-

Table 5. Clinical Presentation and Outcomes in Patients With Large Vessel Occlusion (LVO)

Outcome	LVO, No. (%)		*P* value
	No thrombectomy	Thrombectomy	
Patients, No.	26	13	
Age, mean (SD; range), y	6.23 (4.73; 0.4-14.5)	12.41 (4.41; 4.0-16.9)	<.001[a]
Sex			
Female	13 (50.0)	3 (23.1)	.11[b]
Male	13 (50.0)	10 (76.9)	
Clinical presentation			
Timing of clinical presentation since last seen well, h			
<6	17 (65.4)	10 (76.9)	NA
6-24	5 (19.2)	3 (23.1)	NA
24-48	2 (7.7)	0	NA
>48	2 (7.7)	0	NA
Total <24 h	22 (84.6)	13 (100)	NA
Fulfilled adult selection criteria for mechanical thrombectomy			
MR CLEAN trial[3]	12 (46.2)	8 (61.5)	NA
DAWN trial[11]	5 (19.2)	2 (15.4)	NA
Posterior circulation[9]	2 (7.7)	3 (23.1)	NA
Total	19 (73.1)	13 (100)	NA
Stroke etiology			
Cardioembolic	8 (30.8)	4 (30.8)	NA
Dissection	6 (23.1)	2 (15.4)	NA
Focal cerebral arteriopathy	3 (11.5)	1 (7.7)	NA
Hypercoagulable	2 (7.7)	1 (7.7)	NA
Iatrogenic	3 (11.5)	0	NA
Idiopathic	4 (15.4)	2 (15.4)	NA
Other	0	1 (7.7)	NA
Paradoxical embolus	0	2 (15.4)	NA
IV thrombolysis	0	3 (23.1)	NA
Clinical outcome			
ped-mRS Score at 3 mo poststroke, No.			
0	0	2	NA
1	1	3	NA
2	6	1	NA
3	7	3	NA
4	9	2	NA
5	2	0	NA
6	1	1	NA
Total	26	12	.04[c]
Data missing, No.	0	1	NA
Anterior circulation, No.	24	9	NA
0-2	7 (26.9)	6 (50.0)	NA
3-6	19 (73.1)	6 (50.0)	NA
Timing of final available ped-mRS score poststroke, mo			
Mean (SD)	53.0 (37.0)	26.4 (16.6)	NA
Median (IQR)	41.0 (24.0-94.5)	27.0 (10.5-42.75)	NA
Safety outcomes			
Symptomatic ICH[d]	4 (15.4)	0	.03[e]
Access site complications	NA	1 (7.7)[f]	NA

Abbreviations: ICH, intracranial hemorrhage; LVO, large vessel occlusion; NA, not applicable; ped-mRS, pediatric modified Rankin Scale.

[a] *t* Test.

[b] χ^2 Test.

[c] Ordinal regression analysis: odds ratio, 3.75; 95% CI, 1.05-13.45. Ordinal logistic regression analysis performed comparing ped-mRS score at 3 months poststroke between LVO with no thrombectomy and LVO with thrombectomy groups to determine the odds ratio of a worse functional outcome for the conservatively treated group on the ped-mRS scale (ie, higher score on the scale from 0 to 6).

[d] Symptomatic ICH defined as radiologically confirmed acute intracranial hemorrhage associated with acute worsening in neurological state, specifically an increase in the Pediatric National Institutes of Health Stroke Scale score of 4 or more.

[e] Two-proportions test.

[f] Single case of retroperitoneal hemorrhage arising from the femoral access site, treated with a covered stent.

ity of the neurological syndrome in LVO. The focus of pediatric stroke pathways should therefore be on reducing triage and imaging times with appropriate anesthetic support.[15,18]

While we have used adult stroke criteria for reference, time-based limits from adult practice may be too restrictive for children. Children have strong pial collaterals, providing greater

compensation in acute ischemic stroke.[24,25] Low Pediatric National Institutes of Health Stroke Scale score or presentation more than 24 hours since last seen well should not be absolute contraindications for thrombectomy in children. Rather, imaging assessment of perfusion or infarct volume may be valuable.[23,24,26]

Epidemiology of Pediatric LVO Stroke

LVO was present in nearly one-quarter of pediatric AIS admissions (23.5%)—similar to the rate in adults (18% to 24%).[1,27,28] Even if ACA and PCA occlusions are excluded, the rate of LVO in our study was 22.3% (37 of 166). Our estimate of pediatric AIS incidence (1.02 cases per 100 000 persons per year) is concordant with that of the Canadian Pediatric Ischemic Stroke Registry when neonatal strokes are excluded (1.2).[22] Our cohort was predominantly male (65.2%), and this sex imbalance is well established for pediatric AIS.[15,22,29] In the state of NSW, with a pediatric population of approximately 1.7 million persons[20] and a mean annual LVO incidence of 0.24 cases per 100 000 persons per year (95% CI, 0.13-0.35), we could anticipate 2 to 6 pediatric LVO cases per year. This data allows for greater planning of pediatric stroke services.

Limitations

There are several limitations of this study. Patients from border communities may have been transferred to interstate centers. However, we expect a similar number of transfers into our state. Pediatric patients with no deficit may have been treated in community hospitals. We deviated from our original protocol by excluding patients aged 17 years after determining that a substantial proportion were treated in adult hospitals. We excluded neonatal stroke because of differing presentation, etiology, and treatment.[15]

The absence of randomization or standardized selection criteria for thrombectomy is a major limitation owing to selection bias. Comparison of patients with LVO treated with thrombectomy with conservatively treated patients is also weakened by the small sample size and age difference. Patients with AIS are more likely to have underlying long-term health conditions that may also affect long-term outcomes.[15,22,28]

Our study used retrospective assessment of ped-mRS scores, which is more prone to bias. Reviewers of the ped-mRS score were not blinded to thrombectomy status. The mRS score was originally adapted for children by Bigi et al[30] but has not been validated in prospective pediatric stroke studies. Dichotomous classification of outcome into favorable (ped-mRS score of 0 to 2) and poor (ped-mRS score of 3 to 6) is not validated in children, and thus, the primary analysis was undertaken using ordinal logistic regression.

Conclusions

In this population-based cohort study, LVO was present in nearly one-quarter of pediatric patients with AIS, and most fulfilled adult selection criteria for mechanical thrombectomy. Pediatric patients with LVO treated conservatively had poor long-term outcomes that were significantly worse than those with non-LVO and those treated with thrombectomy. Future pediatric stroke guidelines may take account of this poor natural history.

ARTICLE INFORMATION

Accepted for Publication: January 28, 2022.

Published Online: March 28, 2022. doi:10.1001/jamaneurol.2022.0323

Author Affiliations: Department of Medical Imaging, Children's Hospital at Westmead, Westmead, Australia (Bhatia, Goetti); Children's Hospital at Westmead Clinical School, Faculty of Medicine and Health, University of Sydney, Westmead, Australia (Bhatia, Webster, Troedson, Dale); Faculty of Medicine, Macquarie University, Sydney, Australia (Bhatia); Department of Neurology, Sydney Children's Hospital, Randwick, Sydney, Australia (Briest, Andrews); T.Y. Nelson Department of Neurology and Neurosurgery, Children's Hospital at Westmead, Westmead, Australia (Webster, Troedson, Dale); Division of Image-Guided Therapy, Department of Radiology, Hospital for Sick Children, Toronto, Ontario, Canada (Muthusami); Department of Neurology, John Hunter Children's Hospital, New Lambton Heights, Australia (C. Miteff); Department of Neurology, John Hunter Hospital, New Lambton Heights, Australia (F. Miteff); Department of Neurology, Royal Prince Alfred Hospital, Camperdown, Australia (Worthington, Tastula, Ang); School of Women's and Children's Health, Faculty of Medicine, University of New South Wales, Randwick, Australia (Andrews).

Author Contributions: Messrs Bhatia and Andrews had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Bhatia, Muthusami, Worthington, Andrews.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Bhatia, Goetti, Ang.
Critical revision of the manuscript for important intellectual content: Bhatia, Briest, Webster, Troedson, Dale, Muthusami, C. Miteff, F. Miteff, Worthington, Tastula, Andrews.
Statistical analysis: Bhatia, Briest.
Administrative, technical, or material support: Bhatia, Briest, Goetti, Webster, Dale, C. Miteff, Tastula, Andrews.
Study supervision: Ang, Andrews.

Conflict of Interest Disclosures: None reported.

REFERENCES

1. Dozois A, Hampton L, Kingston CW, et al. PLUMBER study (Prevalence of Large Vessel Occlusion Strokes in Mecklenburg County Emergency Response). *Stroke*. 2017;48(12):3397-3399. doi:10.1161/STROKEAHA.117.018925

2. Smith WS, Lev MH, English JD, et al. Significance of large vessel intracranial occlusion causing acute ischemic stroke and TIA. *Stroke*. 2009;40(12):3834-3840. doi:10.1161/STROKEAHA.109.561787

3. Berkhemer OA, Fransen PS, Beumer D, et al; MR CLEAN Investigators. A randomized trial of intraarterial treatment for acute ischemic stroke. *N Engl J Med*. 2015;372(1):11-20. doi:10.1056/NEJMoa1411587

4. Saver JL, Goyal M, Bonafe A, et al; SWIFT PRIME Investigators. Stent-retriever thrombectomy after intravenous t-PA vs. t-PA alone in stroke. *N Engl J Med*. 2015;372(24):2285-2295. doi:10.1056/NEJMoa1415061

5. Jovin TG, Chamorro A, Cobo E, et al; REVASCAT Trial Investigators. Thrombectomy within 8 hours after symptom onset in ischemic stroke. *N Engl J Med*. 2015;372(24):2296-2306. doi:10.1056/NEJMoa1503780

6. Goyal M, Demchuk AM, Menon BK, et al; ESCAPE Trial Investigators. Randomized assessment of rapid endovascular treatment of ischemic stroke. *N Engl J Med*. 2015;372(11):1019-1030. doi:10.1056/NEJMoa1414905

7. Campbell BC, Mitchell PJ, Kleinig TJ, et al; EXTEND-IA Investigators. Endovascular therapy for ischemic stroke with perfusion-imaging selection. *N Engl J Med*. 2015;372(11):1009-1018. doi:10.1056/NEJMoa1414792

8. Goyal M, Menon BK, van Zwam WH, et al; HERMES collaborators. Endovascular thrombectomy after large-vessel ischaemic stroke: a meta-analysis of individual patient data from five randomised trials. *Lancet*. 2016;387(10029):1723-1731. doi:10.1016/S0140-6736(16)00163-X

9. 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: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2019;50(12):e344-e418. doi:10.1161/STR.0000000000000211

10. Albers GW, Lansberg MG, Kemp S, et al. A multicenter randomized controlled trial of endovascular therapy following imaging evaluation for ischemic stroke (DEFUSE 3). *Int J Stroke*. 2017;12(8):896-905. doi:10.1177/1747493017701147

11. Nogueira RG, Jadhav AP, Haussen DC, et al; DAWN Trial Investigators. Thrombectomy 6 to 24 hours after stroke with a mismatch between deficit and infarct. *N Engl J Med*. 2018;378(1):11-21. doi:10.1056/NEJMoa1706442

12. Bhatia K, Kortman H, Blair C, et al. Mechanical thrombectomy in pediatric stroke: systematic review, individual patient data meta-analysis, and case series. *J Neurosurg Pediatr*. 2019;24(5):1-14. doi:10.3171/2019.5.PEDS19126

13. Sporns PB, Sträter R, Minnerup J, et al. Feasibility, safety, and outcome of endovascular recanalization in childhood stroke: the Save Childs study. *JAMA Neurol*. 2020;77(1):25-34. doi:10.1001/jamaneurol.2019.3403

14. Medley TL, Miteff C, Andrews I, et al. Australian Clinical Consensus Guideline: the diagnosis and acute management of childhood stroke. *Int J Stroke*. 2019;14(1):94-106. doi:10.1177/1747493018799958

15. Ferriero DM, Fullerton HJ, Bernard TJ, et al; American Heart Association Stroke Council and Council on Cardiovascular and Stroke Nursing. Management of stroke in neonates and children: a scientific statement from the American Heart Association/American Stroke Association. *Stroke*. 2019;50(3):e51-e96. doi:10.1161/STR.0000000000000183

16. Rivkin MJ, deVeber G, Ichord RN, et al. Thrombolysis in pediatric stroke study. *Stroke*. 2015;46(3):880-885. doi:10.1161/STROKEAHA.114.008210

17. Harrar DB, Salussolia CL, Kapur K, et al. A stroke alert protocol decreases the time to diagnosis of brain attack symptoms in a pediatric emergency department. *J Pediatr*. 2020;216:136-141.e6. doi:10.1016/j.jpeds.2019.09.027

18. deVeber GA. Delays in the timely diagnosis of stroke in children. *Nat Rev Neurol*. 2010;6(2):64-66. doi:10.1038/nrneurol.2009.228

19. Lagman-Bartolome AM, Pontigon AM, Moharir M, et al. Basilar artery strokes in children: good outcomes with conservative medical treatment. *Dev Med Child Neurol*. 2013;55(5):434-439. doi:10.1111/dmcn.12092

20. Australia Bureau of Statistics. National, state, and territory population. Accessed September 1, 2021. https://www.abs.gov.au/statistics/people/population/national-state-and-territory-population/latest-release#data-downloads-data-cubes

21. Macdonald-Laurs E, Wenderoth J, Cardamone M, Sampaio H, Andrews PI. Endovascular clot retrieval for acute ischaemic stroke due to basilar artery occlusion in childhood. *Dev Med Child Neurol*. 2020;62(10):1221-1223. doi:10.1111/dmcn.14449

22. deVeber GA, Kirton A, Booth FA, et al. Epidemiology and outcomes of arterial ischemic stroke in children: the Canadian Pediatric Ischemic Stroke Registry. *Pediatr Neurol*. 2017;69:58-70. doi:10.1016/j.pediatrneurol.2017.01.016

23. Steinlin M, Pfister I, Pavlovic J, et al; Swiss Societies of Paediatric Neurology and Neonatology. The first three years of the Swiss Neuropaediatric Stroke Registry (SNPSR): a population-based study of incidence, symptoms and risk factors. *Neuropediatrics*. 2005;36(2):90-97. doi:10.1055/s-2005-837658

24. Khalaf A, Iv M, Fullerton H, Wintermark M. Pediatric stroke imaging. *Pediatr Neurol*. 2018;86:5-18. doi:10.1016/j.pediatrneurol.2018.05.008

25. Wintermark M, Lepori D, Cotting J, et al. Brain perfusion in children: evolution with age assessed by quantitative perfusion computed tomography. *Pediatrics*. 2004;113(6):1642-1652. doi:10.1542/peds.113.6.1642

26. Grigoriadis S, Gomori JM, Grigoriadis N, Cohen JE. Clinically successful late recanalization of basilar artery occlusion in childhood: what are the odds? case report and review of the literature. *J Neurol Sci*. 2007;260(1-2):256-260. doi:10.1016/j.jns.2007.03.028

27. Waqas M, Mokin M, Primiani CT, et al. Large vessel occlusion in acute ischemic stroke patients: a dual-center estimate based on a broad definition of occlusion site. *J Stroke Cerebrovasc Dis*. 2020;29(2):104504. doi:10.1016/j.jstrokecerebrovasdis.2019.104504

28. Rennert RC, Wali AR, Steinberg JA, et al. Epidemiology, natural history, and clinical presentation of large vessel ischemic stroke. *Neurosurgery*. 2019;85(suppl 1):S4-S8. doi:10.1093/neuros/nyz042

29. Golomb MR, Fullerton HJ, Nowak-Gottl U, Deveber G; International Pediatric Stroke Study Group. Male predominance in childhood ischemic stroke: findings from the International Pediatric Stroke Study. *Stroke*. 2009;40(1):52-57. doi:10.1161/STROKEAHA.108.521203

30. Bigi S, Fischer U, Wehrli E, et al. Acute ischemic stroke in children versus young adults. *Ann Neurol*. 2011;70(2):245-254. doi:10.1002/ana.22427