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Prognostic significance of age within the adolescent and young adult acute ischemic stroke population after mechanical thrombectomy: insights from STAR

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OBJECTIVE Although younger adults have been shown to have better functional outcomes after mechanical thrombectomy (MT) for acute ischemic stroke (AIS), the significance of this relationship in the adolescent and young adult (AYA) population is not well defined given its undefined rarity. Correspondingly, the goal of this study was to determine the prognostic significance of age in this specific demographic following MT for large-vessel occlusions.

METHODS A prospectively maintained international multi-institutional database, STAR (Stroke Thrombectomy and Aneurysm Registry), was reviewed for all patients aged 12–18 (adolescent) and 19–25 (young adult) years. Parameters were compared using chi-square and t-test analyses, and associations were interrogated using regression analyses.

RESULTS Of 7192 patients in the registry, 41 (0.6%) satisfied all criteria, with a mean age of 19.7 ± 3.3 years. The majority were male (59%) and young adults (61%) versus adolescents (39%). The median prestroke modified Rankin Scale

ABBREVIATIONS ADAPT = A Direct Aspiration First Pass Technique; AIS = acute ischemic stroke; AYA = adolescent and young adult; LVO = large-vessel occlusion; mRS = modified Rankin Scale; MT = mechanical thrombectomy; STAR = Stroke Thrombectomy and Aneurysm Registry; TICI = Thrombolysis in Cerebral Infarction.

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(mRS) score was 0 (range 0–2). Strokes were most common in the anterior circulation (88%), with the middle cerebral artery being the most common vessel (59%). The mean onset-to–groin puncture and groin puncture–to-reperfusion times were 327 ± 229 and 52 ± 42 minutes, respectively. The mean number of passes was 2.2 ± 1.2, with 61% of the cohort achieving successful reperfusion. There were only 3 (7%) cases of reocclusion. The median mRS score at 90 days was 2 (range 0–6). Between the adolescent and young adult subgroups, the median mRS score at last follow-up was statistically lower in the adolescent subgroup (1 vs 2, $p = 0.03$), and older age was significantly associated with a higher mRS at 90 days (coefficient 0.33, $p < 0.01$).

CONCLUSIONS Although rare, MT for AIS in the AYA demographic is both safe and effective. Even within this relatively young demographic, age remains significantly associated with improved functional outcomes. The implication of age-dependent stroke outcomes after MT within the AYA demographic needs greater validation to develop effective age-specific protocols for long-term care across both pediatric and adult centers.

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KEYWORDS mechanical thrombectomy; stroke; pediatric; young adult; adolescent; outcome; vascular disorders

Large-vessel occlusions (LVOs) are estimated to occur in 0.2 to 2.0 per 100,000 children per year, with moderate disability and death seen in the majority of cases treated conservatively.[1–4] Although mechanical thrombectomy (MT) has proven to be a very effective treatment for acute ischemic stroke (AIS) secondary to LVOs in adults,[5,6] MT for LVOs in the pediatric and adolescent and young adult (AYA) populations is not as well understood.

In a 2015 American Heart Association/American Stroke Association guideline on MT, the authors stated that endovascular MT may be reasonable for some patients with acute AIS patients who are younger than 18 years, using adult parameters, while acknowledging that the benefits and risks are not established in this age group.[7] Since then, a small number of case reports and series have been published, advocating for MT efficacy in this setting.[8–10] However, what remains to be seen is if aggregate primary data can reveal any prognosticative trends in this rare age group. Correspondingly, the aims of this study were twofold: 1) to determine the efficacy of MT to manage AIS secondary to LVO in AYA patients using a large primary data set, and 2) to determine any prognostic associations with improved long-term outcomes in this demographic.

Methods

Database

This study was a retrospective review of requested data from the Stroke Thrombectomy and Aneurysm Registry (STAR) database, a prospectively maintained database of 10 stroke centers across the United States and Europe. Local institutional review board approval was received from each participating institution, and informed consent for data admission and abstraction was waived.

Selection Criteria

Patients reviewed were those being treated for AIS secondary to LVO with approved second-generation MT devices from June 2013 through June 2020. Patients were screened against set selection criteria. Inclusion criteria were 1) adolescent (12–18 years) and young adult (19–25 years) patients 2) with complete presentation, management, and clinical/functional outcome data available. An exclusion criterion was absent functional outcome data at the 90-day follow-up.

Outcomes

Presentation data included demographic and socioeconomic parameters. Management data included stroke characteristics and technical specifics from presentation to thrombectomy. Clinical outcomes included the Thrombolysis in Cerebral Infarction (TICI) scale, a scale used to evaluate intracranial reperfusion after MT.[11] Briefly, TICI categories span from no reperfusion (grade 0) to complete reperfusion (grade 3). The "partial reperfusion" category (grade 2) is defined by the presence of contrast past the obstruction but with rates of entry and washout slower than normal and is divided into subcategories 2a and 2b.[12] Successful reperfusion was defined as TICI grade 2b or greater. Functional outcomes included the modified Rankin Scale (mRS) score, a scale that measures the degree of disability or dependence in the daily activities of people.[13] Briefly, the scale has 7 categories from 0 to 6, with a score of 0 being asymptomatic; 1, symptomatic without any disability; 2, symptomatic with slight disability; 3, moderate disability but able to walk; 4, moderately severe disability and unable to walk; 5, severe disability and bedridden; and 6, dead. A good functional outcome was defined as an mRS score ≤ 2.

Statistical Analysis

Continuous data were analyzed using the Student t-test, and categorical data were analyzed using the chi-square test. Then, ordered logistic regression analyses were performed to identify possible predictors of functional outcome at 90 days according to the mRS score, with regression coefficient being the primary summary statistic accompanied by 95% confidence interval. Univariable analysis was conducted to identify candidate predictors ($p < 0.10$). If more than one candidate predictor was found, these variables would then be incorporated into backward stepwise multivariable analysis to determine those independently significant associations. All analyses were conducted using Stata version 14.1 (StataCorp); statistical tests were two-sided, and significance was defined using the uncorrected alpha threshold of 0.05.

Results

Demographics

Of 7192 registered patients in the STAR registry, 41 (0.6%) patients satisfied all selection criteria with a mean age of 19.7 ± 3 years (Table 1). There were 16 (39%) adolescent and 25 (61%) young adult patients, with 24 (59%) males and 17 (41%) females. The mean ages in the adolescent and young adult groups were 16.6 ± 2 years and 21.6 ± 2 years, respectively ($p < 0.01$) (Fig. 1). The most common race was White (76%), with minimal presence of other comorbidities. The comorbidities reported included diabetes, hypertension, atrial fibrillation, and congestive heart failure, reported in 1 (6%) patient each. The median mRS score prior to presentation was 0 (range 0–2) (Fig. 2). There were no differences between adolescent and young adult patients with respect to these parameters.

Management

The majority of strokes localized to the anterior circulation (88%), with the middle cerebral artery (59%) and internal carotid artery (27%) being the most common locations for the LVO (Table 1). The mean time from onset to groin puncture was 327 ± 229 minutes, and tPA was used intravenously in 18 (44%) cases. There was an approximately even proportion of first technique used between A Direct Aspiration First Pass Technique (ADAPT; 34%), stent retriever (37%), and Solumbra technique (29%). The mean number of total attempts to clot evacuation was 2.2 ± 1.2, at a mean time from groin puncture to reperfusion of 52 ± 42 minutes. There were no differences between adolescent and young adult patients with respect to these parameters.

Outcomes

There were no fatal events at initial presentation in the cohort (Table 1). According to the TICI scale, reperfusion by grade 2b or above was achieved in 61% of cases, with the majority of cases achieving a grade 3 outcome (51%); grade 2a (34%) and grade 2b (10%) were also common (Fig. 3). Intra-arterial tPA was used in 6 (15%) cases, and reocclusion occurred in 3 (7%) cases. There were no cases of hemorrhagic conversion. At 90 days after intervention, the median mRS score was 2 (range 0–6), with 73% of cases achieving an mRS score ≤ 2 (Fig. 2). Between adolescent and young adult patients, the median final mRS score at 90 days was significantly lower in the adolescent group versus young adult group with 1 (range 0–4) versus 2 (range 0–6) ($p = 0.03$).

Associations

Regression analysis of the median final mRS score at 90 days was performed to identify candidate associations with better functional outcome (Table 2). Age was the only factor that was statistically significant among all parameters interrogated, and, as such, no multivariate analysis was needed. Older age was significantly associated with higher final mRS score at 3 months (coefficient 0.33, 95% CI 0.12–0.55, $p < 0.01$).

Discussion

The AYA demographic is an emerging one where clinical outcomes blur the line between pediatric and adult spheres. Given that AIS secondary to LVO is primarily associated with older age, there has yet to be any distinction made between adolescents and young adults treated by MT following AIS. Furthermore, the incidence of stroke in the AYA population is rare, and thus the utility and prognostication of MT for AIS in this age group continues to emerge. Our study not only demonstrates that MT is a safe and effective intervention modality within this setting, but also affirms the more generalized concept that age prognosticates outcome even within this younger demographic. Based on this, there is a need for the development of specialized transition programs from pediatric to adult care to ensure that longer-term functional outcomes are maximally optimized in this population.

To date, the evidence regarding the utility of MT in pediatric and AYA stroke patients is limited. In terms of primary data, even most recent recounts of MT for pediatric patients after stroke, including adolescents, have been limited to case reports with rates of long-term good functional outcomes ranging from 57% to 100%.[8–10,14–18] Literature reviews[8,9] of published metadata have reported long-term good functional outcomes ranging from 80% to 91%. Therefore, our reported good outcome (mRS score ≤ 2) rate of 73% appears to correlate to much of what is published by smaller experiences, and the higher metadata rates may reflect more inflated estimates secondary to the propensity of publication and selection biases in the metadata over multiple decades.[2] Our mean onset-to–groin puncture time of approximately 6 hours reflects the general trend in the literature of a longer mean time for pediatric patients (6–12 hours)[19,20] than for adults (4–6 hours).[21] Although the rationale behind this difference may simply be a matter of experience and familiarity with older patients by adult specialists, this trend also alludes to the possibility that MT should be considered for AYA patients presenting with stroke in a working window longer than that for adult patients. Future studies are needed to validate this possibility.

Within the pediatric and AYA literature, there has been no documentation of possible prognostic associations with outcome, which is likely attributable to a lack of robust, homogeneous data for analysis. Our finding that age as a continuous variable prognosticates outcome in the setting of AYA stroke is the first posited association involving the pediatric and AYA demographic. This association appears to agree with extrapolating trends reported in the adult literature, in which age analyses were primarily categorized as variables biased toward the elderly. The HERMES (Highly Effective Reperfusion Evaluated in Multiple Endovascular Stroke Trials) collaboration, which pooled patient-level data from five adult MT stroke trials, found that age older than 80 years was associated with worse outcomes than age younger than 80 years.[6] This was confirmed in the analysis of the ETIS (Endovascular Treatment in Ischemic Stroke) Registry.[22] Stratified against slightly younger age thresholds, the STRATIS (Systematic Evaluation of Patients Treated With Neurothrombectomy Devices for Acute Ischemic Stroke) Registry found that

TABLE 1. Demographic, management, and outcomes of all AYA patients

Parameter	Overall	Adolescent	Young Adult	p Value
No. of patients	41	16 (39)	25 (61)	
Mean age, yrs	19.7 ± 3	16.6 ± 2	21.6 ± 2	
Sex				0.68
Male	24 (59)	10 (62)	14 (56)	
Female	17 (41)	6 (38)	11 (44)	
Race				0.64
White	31 (76)	12 (75)	19 (76)	
Black	4 (10)	2 (12)	2 (8)	
Hispanic	4 (10)	2 (12)	2 (8)	
Other	2 (5)	0	2 (8)	
Comorbidities				
Diabetes	1 (2)	1 (6)	0	0.21
Hypertension	1 (2)	0	1 (4)	0.42
Atrial fibrillation	1 (2)	1 (6)	0	0.21
Congestive heart failure	1 (2)	1 (6)	0	0.21
Median prestrike mRS score (range)	0 (0–2)	0 (0–2)	0 (0–1)	0.45
Management				
Location, circulation				0.35
Anterior	36 (88)	15 (94)	21 (84)	
Posterior	5 (12)	1 (6)	4 (16)	
Location, vessel				0.26
MCA	24 (59)	11 (69)	13 (52)	
ICA	11 (27)	4 (25)	7 (28)	
Basilar	4 (10)	0	4 (16)	
ACA	1 (2)	0	1 (4)	
PCA	1 (2)	1 (6)	0	
IV tPA	18 (44)	7 (44)	11 (44)	0.99
Mean onset-to–groin puncture time, mins	327 ± 229	243 ± 139	382 ± 263	0.10
1st attempt technique				0.53
ADAPT	14 (34)	4 (25)	10 (40)	
Stent retriever	15 (37)	6 (38)	9 (36)	
Solumbra	12 (29)	6 (38)	6 (24)	
Balloon-guided catheter	5 (12)	3 (19)	2 (8)	0.31
Intra-arterial tPA	6 (15)	4 (25)	2 (8)	0.13
Mean no. of total attempts	2.2 ± 1.2	2.1 ± 1.3	2.3 ± 1.1	0.61
Mean groin puncture–to-reperfusion time, mins	52 ± 42	51 ± 44	53 ± 42	0.91
Outcome				
TICI scale grade				0.18
0	1 (2)	0	1 (4)	
1	1 (2)	0	1 (4)	
2A	14 (34)	9 (56)	5 (20)	
2B	4 (10)	1 (6)	3 (12)	
3	21 (51)	6 (38)	15 (60)	
Reocclusion	3 (7)	0	3 (12)	0.15
Median 90-day mRS score (range)	2 (0–6)	1 (0–4)	2 (0–6)	**0.03**

ACA = anterior cerebral artery; ICA = internal carotid artery; IV = intravenous; MCA = middle cerebral artery; PCA = posterior cerebral artery; tPA = tissue plasminogen activator.
Values represent the number of patients (%) unless stated otherwise. Categorical data are presented as total with total percentage in parentheses, and continuous data are presented as mean ± SD unless stated otherwise. Boldface type indicates statistical significance.

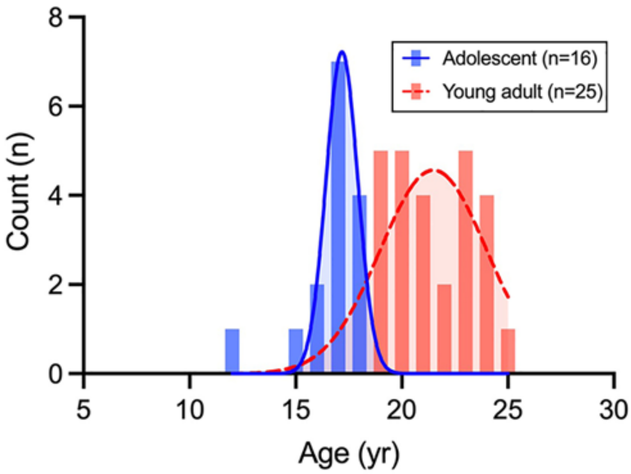

FIG. 1. Age distribution of all patients, including adolescent (12–18 years) and young adult (18–25 years) subgroups. Figure is available in color online only.

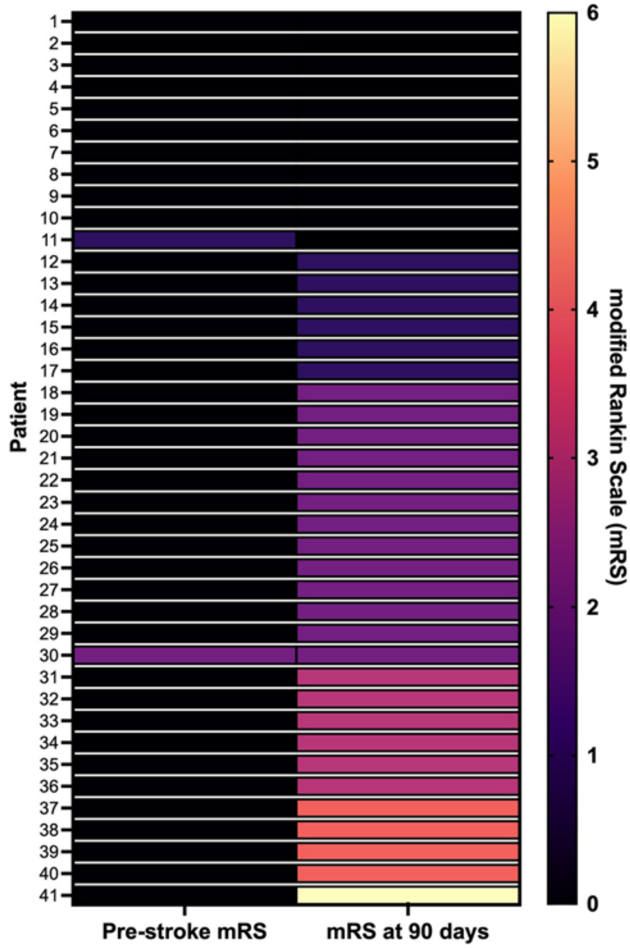

FIG. 2. Individual mRS scores of patients prior to stroke presentation and at 90 days after MT. Figure is available in color online only.

patients younger than 65 years with large core infarction have better rates of functional independence and lower rates of mortality compared with patients older than 75 years.[23]

One possible reason for better functional outcomes in younger patients after MT for AIS is that a younger brain is biologically more adaptable to recovery based on multiple animal studies. Increased neuroplasticity in the younger brain has been associated in many conditions with improved recovery from neurological insults.[24] It has been proposed that this is because mechanisms underlying functional reorganization in aged animals are distinctly different from those in young animals.[25] It has been demonstrated that stroke causes functional impairment in the hippocampus, and recovery of behavioral and synaptic function is more robust in the young brain than in the aged brain.[26] While this theory intuitively argues that younger brains may recover more efficiently after stroke than aged brains, leading to better functional outcomes, it does not convincingly account for the trend in poorer outcomes in young adult stroke patients versus adolescent stroke patients given their closeness in actual ages. Ultimately, larger cohorts of AYA patients are needed to discern this difference, both clinically and biologically.

The translational consequences of our findings may reach beyond prognostication. In the hematology and oncology specialty, the AYA demographic not only has led to the emergence of specialized AYA clinic and interventions aimed at addressing the psychosocial elements specific to the AYA demographic[27,28] but also was designed to ensure a smooth transition of adolescent care from pediatric centers to young adult care in adult centers.[29] This concept of bridging pediatric to adult care following stroke does not currently exist. Given that adolescents may achieve better functional outcomes, persistent and thorough post-MT follow-up care early and later after AIS into young adulthood may enhance and maximize their outcomes further (e.g., more aggressive physical therapy in adolescents to encourage functional recovery and more aggressive occupational therapy in young adults to encourage functional adaptation).

There are limitations to this study. First, the size of the cohort, while the largest aggregate of primary data to date, is small. A larger cohort size will augment statistical power to infer more subtle associations of outcome, in addition to older age, that may not have been elucidated in this study. These potential associations include time to groin puncture and the proportion of patients with posterior AIS, which is known to influence outcomes in the adult population,[30] but these factors did not reach statistical significance in our study. Longer-term follow-up will also enable us to determine if previously evaluated parameters develop functional significance in the long term, as well as demonstrate the durability of the MT benefit in this setting.

The retrospective analysis component of our study means that it is not possible to ascertain effectiveness of MT intervention based on time from symptom onset as these data are not available, and, as such, we defer any inference to this based on our results. Furthermore, we can-

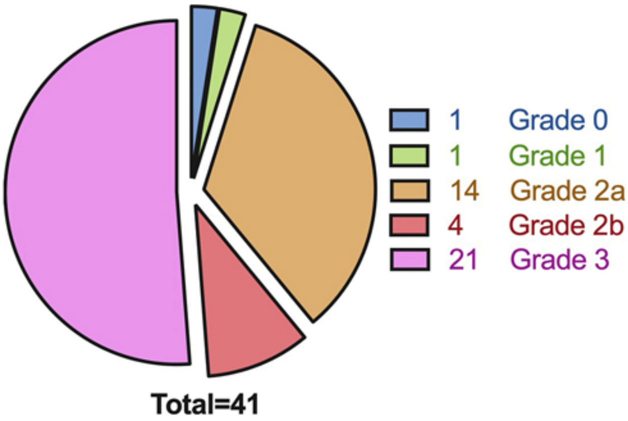

FIG. 3. Count distribution of TICI scale grades among all patients after MT. Figure is available in color online only.

TABLE 2. Results of univariate regression analysis for final mRS at 90 days after intervention

Parameter	Coefficient (95% CI)	p Value
Age	0.33 (0.12 to 0.55)	**<0.01**
Male sex	0.71 (−0.41 to 1.84)	0.22
White race	−0.71 (−1.95 to 0.52)	0.26
Comorbidity	0.38 (−1.49 to 2.24)	0.69
Prestroke mRS score	−0.24 (−1.72 to 1.24)	0.75
Anterior circulation location	−0.60 (−1.31 to 0.12)	0.10
IV tPA	−0.23 (−1.35 to 0.87)	0.67
Time to groin puncture	0.00 (−0.002 to 0.003)	0.56
ADAPT technique	0.18 (−0.94 to 1.29)	0.76
Balloon-guided catheter	0.42 (−1.26 to 2.11)	0.63
Intra-arterial tPA	−0.52 (−2.04 to 1.00)	0.50
Total attempts	0.18 (−0.29 to 0.65)	0.46
Time to reperfusion	0.00 (−0.02 to 0.01)	0.78
TICI scale	0.20 (−0.30 to 0.70)	0.43
Reocclusion	0.81 (−1.03 to 2.65)	0.38

Boldface type indicates statistical significance.

not rule out selection bias of stroke presentations based on etiology. Although the majority of pediatric stroke causes are poorly understood,[31] individual institutional experiences have suggested that cardiac comorbidities, with which a minority of our cohort presented, are a common risk factor in the AYA demographic.[32] Arteriopathies, which can contribute to AIS,[33] are also known to occur in this demographic, but they were not explicitly documented in the registry, indicating that future studies should incorporate these parameters into their workup to enhance clinical homogeneity.

Next, there is also heterogeneity in the management of adolescent stroke between centers, as well as MT technique, and this may partially limit the generalization of our results.[2] STAR was not able to retrospectively confirm homogeneity among the stroke response protocols between institutions, leaving it not possible to compare response team experience and treatment by pediatric versus adult specialists. These parameters, and more, are needed to better understand how best to triage and manage AIS in the AYA demographic from an organizational perspective. Nevertheless, our data remain primary in nature, which offers greater confidence in their statistical heterogeneity compared with analyses involving secondary data. Finally, quality-of-life metrics were not included in this study, and prospective collection of these data in future studies will guide the specialization of AYA stroke care from general adult stroke care.

Conclusions

The management of stroke in the AYA demographic with MT is poorly understood given its rarity in this age group. Our study is the largest to date involving primary data and demonstrates the safety and efficacy of this intervention modality. Furthermore, it highlights age as a prognostic factor for long-term functional outcome between adolescents versus young adults despite the narrow age range. These findings lay the first blueprint to develop specialized AYA stroke care to better tailor post-MT care and therapy based on age for these patients.

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Disclosures

Dr. Rai: consultant for Stryker Neurovascular, Cerenovus, and MicroVention. Dr. Yoshimura: speakers bureau for Bristol-Meyers Squibb, Stryker, Medtronic, Johnson & Johnson, Kaneka Medics, and Daiichi Sankyo. Dr. Polifka: consultant for DePuy Synthes and Stryker. Dr. Mascitelli: consultant for Stryker. Dr. Levitt: direct stock ownership in Hyperion Surgical, Proprio, Synchron, and Cerebrotech; consultant for Medtronic, Aeaean Advisers, and Metis Innovative; support of non–study-related clinical or research effort overseen by the author from Medtronic and Stryker; and financial interest in Fluid Biomed. Dr. Yavagal: consultant for Medtronic, Cerenovus, Poseydon, and Rapid Medical.

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Conception and design: Lu, Starke. Acquisition of data: Lu, Luther, Maier, Al Kasab, Jabbour, Kim, Wolfe, Rai, Psychogios, Samaniego, Arthur, Yoshimura, Grossberg, Alawieh, Fragata, Polifka, Mascitelli, Osbun, Park, Levitt, Dumont, Cuellar, Williamson, Romano, Crosa, Gory, Mokin, Moss, Limaye, Kan, Yavagal, Spiotta, Starke. Analysis and interpretation of data: Lu, Luther, Elarjani, Starke. Drafting the article: Lu, Luther, Silva, Abdelsalam, Starke. Critically revising the article: Lu, Luther, Silva, Elarjani, Abdelsalam, Spiotta, Starke. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Lu. Statistical analysis: Lu. Administrative/technical/material support: Lu. Study supervision: Spiotta, Starke.

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