Trends and Outcomes of Primary, Rescue, and Adjunct Middle Meningeal Artery Embolization for Chronic Subdural Hematomas

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■ BACKGROUND: **Middle meningeal artery embolization (MMAE) is an effective minimally invasive treatment for chronic subdural hematomas (cSDHs). The authors investigated outcomes of primary, adjunct, and rescue MMAE and primary surgery for the treatment of cSDH using a large-scale national database.**

■ METHODS: **A retrospective study of all patients who underwent MMAE and/or surgery to treat cSDH was performed using the TriNetX Analytics Network. Primary MMAE was compared with adjunct and rescue MMAE and primary surgery. Primary outcomes included headache, facial weakness, mortality, and treatment failure, within 6 months.**

■ RESULTS: **A total of 4274 patients with cSDH met the inclusion criteria. Of these, 209 (4.9%) were treated with primary MMAE, 4050 (94.8%) were treated with primary surgery, 15 (0.35%) were treated using MMAE as an adjunct therapy, and 18 (0.42%) were treated using MMAE as a rescue following a failed surgical intervention. There were no significant differences in headache, facial weakness, and mortality between the groups. Patients who underwent primary MMAE had a significantly higher Charlson comorbidity index ($P < 0.0001$) than those who underwent primary surgery. The need for surgical rescue was not significantly different between primary MMAE, adjunct MMAE, and rescue MMAE ($P > 0.05$). Additionally, patients with primary surgery had significantly higher treatment failure than those with primary MMAE (odds ratio = 2.11, 95% confidence interval = 1.11–4.01, $P = 0.020$).**

■ CONCLUSIONS: **This analysis suggests no significant difference in the need for surgical rescue, complication, or mortality between primary MMAE, adjunct MMAE, and rescue MMAE. Additionally, primary MMAE is associated with a significantly lower need for surgical rescue than primary surgery.**

INTRODUCTION

Chronic subdural hematoma (cSDH) is an increasingly common neurosurgical pathology with an estimated incidence of 10 cases per 100,000 persons in the United States.[1] cSDH is hypothesized to develop due to a prior traumatic acute subdural hemorrhage or subdural hygroma that forms at the dural border cell layer between the dura and arachnoid layer. Chronic inflammation with subsequent hyperfibrinolysis and release of angiogenic factors can lead to neovascularization and neomembrane formation.[2,3] Surgical evacuations of the cSDH are the standard of surgical management for symptomatic patients. Unfortunately, in elderly patients who undergo treatment with surgical intervention, the 1-year mortality rate is up to 32%.[4] Surgical intervention is additionally complicated by high recurrence and reoperation rates of up to 30%,[1] making

Key words
- Adjunct MMA embolization
- Chronic subdural hematoma
- cSDH
- Middle meningeal artery
- MMA embolization of cSDH
- Refractory subdural hematoma
- Rescue MMA embolization

Abbreviations and Acronyms
CCI: Charlson comorbidity index
CI: Confidence interval
cSDH: Chronic subdural hematoma
HCO: Healthcare organization
ICD-10: International Classification of Diseases 10th revision
MMAE: Middle meningeal artery embolization
OR: Odds Ratio

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*Citation: World Neurosurg. (2022) 164:e568-e573.
https://doi.org/10.1016/j.wneu.2022.05.011*

Journal homepage: www.journals.elsevier.com/world-neurosurgery

Available online: www.sciencedirect.com

this approach particularly challenging in elderly patients with various cardiovascular comorbidities and coagulopathies.

Middle meningeal artery embolization (MMAE) has recently increased in popularity as an alternative treatment modality. It is intended to devascularize the dural supply of neomembranes, thereby treating the potential underlying cause of cSDH. MMAE is currently utilized as a standalone treatment and adjunct to surgical evacuation.[5-7] Only a few studies have compared MMAE with conventional therapy/surgery, which is limited in the number of cases with MMAE (<40 patients).[8,9] Additionally, there are no reports in the literature trending the outcomes of primary MMAE (i.e., MMAE as the initial treatment), adjunct MMAE (i.e., MMAE along with surgical evacuation), and rescue MMAE (MMAE after failed surgery).

This study describes the trends and outcomes of primary, adjunct, and rescue MMAE utilizing a large cohort of patients with cSDH from a national registry who underwent surgical evacuation or endovascular embolization.

METHODS

Study Design

The TriNetX Analytics Network (TriNetX, Cambridge, Massachusetts, USA), a global federated network comprised of deidentified electronic health records from 55 health care organizations (HCOs) and 63.3 million patients, was utilized for these analyses. HCOs in the United States provide the data within TriNetX. The data available for querying include demographics, diagnoses, procedures, medications, and laboratory measurements. To comply with legal frameworks and ethical guidelines against patient and site reidentification, the identity of HCOs and contribution to each data set are undisclosed. In addition, the TriNetX platform provides deidentified patient data with various date shifting schemes implemented by individual HCOs (e.g., ±7 days).

Figure 1 shows the study inclusion and exclusion criteria. Our TriNetX query contained cases until January 15, 2021, to allow a 6-month follow-up. The inclusion criteria consisted of a confirmed diagnosis of nontraumatic cSDH (International Classification of Diseases 10th revision [ICD-10] code I62.03) and nontraumatic subdural hemorrhage (ICD-10 code I62.00) in patients who had either undergone embolization (Current Procedural Terminology: 61624 and 61626) or surgical procedures for evacuation of hematoma (Current Procedural Terminology: 61312 and 61314) within 1 month of the cSDH diagnosis. The exclusion criteria were patient age <18 years and diagnosis of cerebral arteriovenous malformation (ICD-10 code Q28.2), malignant neoplasm of the brain (ICD-10 code C71), malignant neoplasm of the head, face, and neck (ICD-10 code C76.0), epistaxis (ICD-10 code R04.0), and cerebral aneurysm/acquired cerebral

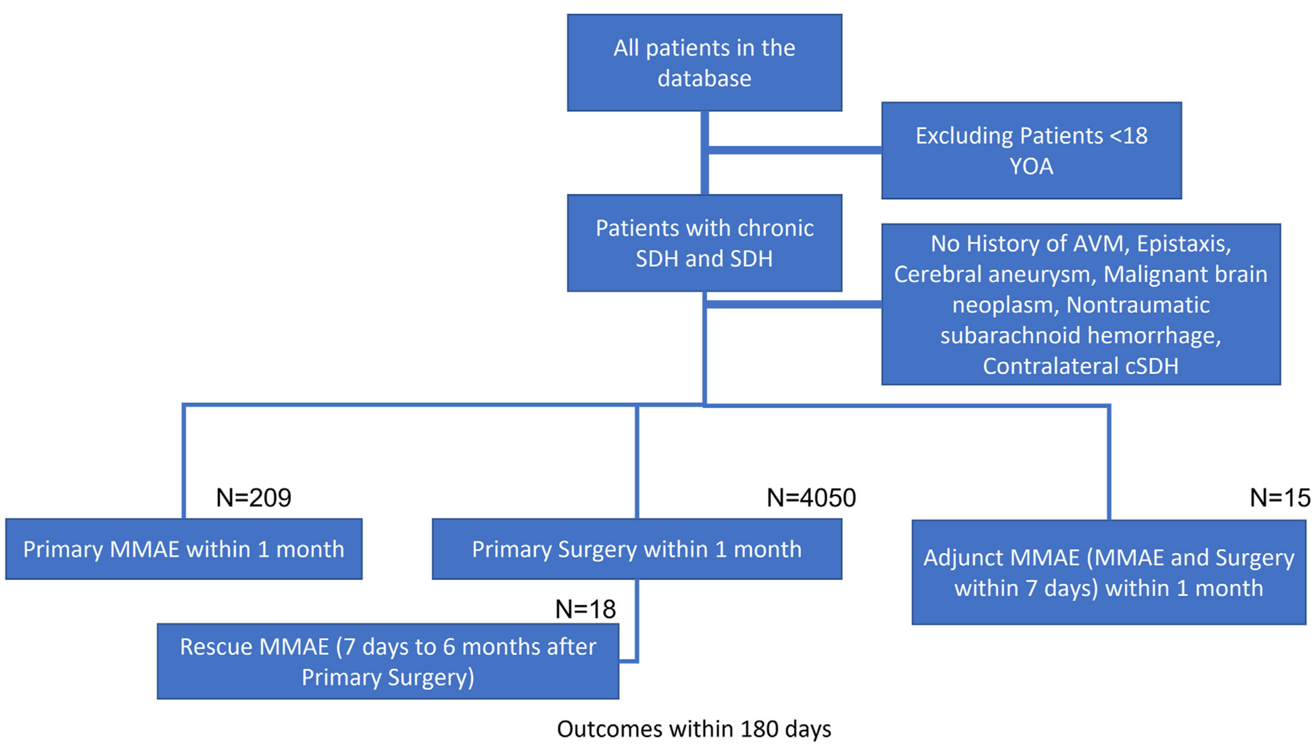

Figure 1. Flowchart demonstrating the inclusion and exclusion criteria for the study. YOA, years of age; SDH, subdural hematoma; AVM, arteriovenous malformation; MMAE, middle meningeal artery embolization.

arteriovenous fistula (ICD-10 code I67.1) to ensure that the embolization was not for a different indication. Additionally, patients who received a primary MMAE and a subsequent MMAE within 3 days (same code utilized twice) were assumed to have received treatment for contralateral cSDH and, thus, removed from the study ($n = 5$).

A cohort of 4274 patients from 31 HCOs met the inclusion and exclusion criteria for outcome analysis. The patients were divided into 4 cohorts based on the treatment modality: primary MMAE, primary surgery, MMAE as an adjunct to surgery, and MMAE as rescue following a failed surgical intervention. Primary MMAE patients received embolization within 1 month of cSDH diagnosis. Primary surgery patients had a surgical procedure for hematoma evacuation within 1 month of cSDH diagnosis. Adjunct therapy patients received both embolization and surgical evacuation procedures within 7 days of each other and 1 month of cSDH diagnosis. Finally, rescue MMAE patients received a surgical evacuation within 1 month of cSDH diagnosis, followed by MMAE beyond 7 days to 6 months. This treatment cohort is a subset of the primary surgery group. However, the outcomes are evaluated 6 months after the rescue MMAE procedure.

Outcome Analysis

Primary clinical outcomes were defined as the proportion of patients who had the outcome of interest within 6 months of cSDH treatment. Outcomes studied included mortality, Kaplan-Meier survival analysis, length of hospitalization (patients with an encounter length of 0 days/outpatients were excluded), MMAE recurrence needing surgery, surgical recurrence requiring further surgery, facial weakness, and headaches.

Statistical Analysis

Cohort statistics were collected for each outcome of interest. The cohort statistics include patients in the cohort, patients with the outcome, and the risk of the outcome within a 180-day/6-month time window. We evaluated the odds ratio with conditional maximum likelihood estimation (Fisher) and confidence interval (CI) using Fisher's exact method in R 4.1.0 with the "epitools" package.[10] Kaplan-Meier survival curve analysis was performed on the mortality outcome of patients over 180 days using GraphPad Prism 9.1.0 (GraphPad Software, San Diego, California, USA). The log-rank hazard ratio and Mantel-Cox log-rank test were used to evaluate the survival curves between the treatment cohorts.

The Charlson comorbidity index (CCI), a measure of 10-year mortality risk based on patient comorbidities, was used to characterize every group's overall state of health before treatment. The CCI was calculated based on the individual patient's medical history up to the day of the procedure using a modified comorbidity v0.5.3.9000 package in R.[11,12] The patients' age was not factored into the calculation in the original package but was added to our calculations.[11,13] The Kruskal-Wallis test and Dunn multiple comparison tests were used for evaluating the statistical significance of the differences in procedure, race, sex, ethnicity, length of the encounter, and CCI between treatment groups. The comparative and descriptive statistics were performed using GraphPad Prism 9.1.0.

Data for this study are not publicly available because of a data-use agreement. For requests to access the study data, please contact the corresponding author.

RESULTS

This section describes the outcomes of primary, adjunct, and rescue MMAE utilizing a large cohort of patients with cSDH from a national registry who underwent surgical evacuation or endovascular embolization.

Baseline Patient Characteristics

A total of 4274 cSDH patients were treated and included for analysis. Of those 4274 patients, 4050 (94.8%) patients were treated with primary surgery, 209 (4.9%) patients were treated with primary MMAE, 15 (0.03%) patients had adjunct therapy (i.e., surgery and embolization within 7 days), and 18 patients from the primary surgery cohort had rescue MMAE. The mean age for primary MMAE, primary surgery, adjunct MMAE, and rescue MMAE was 72 ± 12, 62 ± 18, 68 ± 17, and 70 ± 14, respectively. Patients who underwent primary MMAE were significantly older, 72 (95% CI = 70—74) versus 62 (95% CI = 62—63) years, and the CCI was found to be substantially higher, 7.02 (95% CI = 6.44—7.60) versus 4.87 (95% CI = 4.74—5.00), by the Dunn multiple comparisons test than those in primary surgery ($P < 0.0001$). Additionally, patients who underwent primary MMAE had significantly higher use of anticoagulant medication than those who underwent primary surgery (76.6%, 95% CI: 70.4—81.8 vs. 48.1%, 95% CI: 46.6—49.7). There was no difference in antiplatelet or anticoagulant medication between primary MMAE, adjunct MMAE, and rescue MMAE (**Table 1**).

Outcome

Clinical outcomes within a 6-month follow-up showed a significantly lower length of hospital stay for primary MMAE than for primary surgery, 7.74 (95% CI: 6.04—9.44) versus 30.20 (26.38—34.02), ($P < 0.0001$). The Kaplan-Meier survival analysis in **Figure 2** shows no significant differences between the cohorts. In particular, the 6-month survival ratio was estimated to be 1.2% higher from primary MMAE versus primary surgery, but this difference was not statistically significant ($P = 0.35$). Additionally, there were no significant differences in the occurrence of headaches or facial weakness between the cohorts (all $P > 0.05$). The need for subsequent surgery (i.e., surgical rescue) was similar across primary MMAE, adjunct MMAE, and rescue MMAE. Primary MMAE was found to have significantly lower treatment failure or need for surgical rescue than primary surgery (odds ratio [OR] = 0.47; 95% CI [0.25—0.90], $P = 0.02$) (**Figure 3**).

DISCUSSION

cSDH primarily affects elderly patients and has a poor prognosis. It is estimated that the incidence of cSDH will be over 17 cases per 100,000 persons in 2030 due to the aging population,[14] increased alcohol consumption,[15-17] and the use of anticoagulants to mitigate cardiovascular risk factors (obesity, diabetes).[18] The incidence rate is especially high in the U.S. veteran population and is estimated to reach 121 cases per 100,000 persons in 2030. To date, there are 2 multicenter[5,7] and multiple single-site

Table 1. Comparison of Baseline Characteristics Between the Treated Cohorts

Baseline Data	Primary Surgery	Primary MMAE	Adjunct MMAE	Rescue MMAE
Age	62.4 (95% CI: 61.8—63.0)	72.0 (95% CI: 70.3—73.7)	67.9 (95% CI: 58.6—77.2)	69.8 (95% CI: 62.9—76.8)
Gender				
Male	2787 (68.8%)	156 (74.6%)	10 (66.7%)	13 (72.2%)
Female	1263 (31.2%)	53 (25.4%)	5 (33.3%)	5 (27.8%)
Ethnicity				
Not Hispanic or Latino	2573 (63.5%)	160 (76.6%)	10 (66.7%)	10 (55.6%)
Hispanic or Latino	301 (7.4%)	16 (7.7%)	1 (6.7%)	2 (11.1%)
Unknown	1176 (29.0%)	33 (15.8%)	4 (26.7%)	6 (33.3%)
Race				
White	2747 (67.8%)	148 (70.8%)	12 (80.0%)	14 (77.8%)
Unknown	660 (16.3%)	23 (11.0%)	1 (6.7%)	2 (11.1%)
Asian	68 (1.7%)	7 (3.3%)	0 (0.0%)	0 (0.0%)
African American	554 (13.7%)	29 (13.9%)	2 (13.3%)	2 (11.1%)
Pacific Islander	8 (0.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
American Indian	13 (0.3%)	2 (1.0%)	0 (0.0%)	0 (0.0%)
Charlson comorbidity index	4.9 (95% CI: 4.7—5.0)	7.0 (95% CI: 6.4—7.6)	6.3 (95% CI: 3.6—9.1)	7.2 (95% CI: 5.5—8.9)
Antiplatelet	856 (21.1%, 95% CI: 19.9—22.4)	55 (26.3%, 95% CI: 20.8—32.7)	4 (26.7%, 95% CI: 10.9—52.0)	0 (0%, 95% CI: 0—17.6)
Anticoagulant	1950 (48.1%, 95% CI: 46.6—49.7)	160 (76.6%, 95% CI: 70.4—81.8)	9 (60.0%, 95% CI: 35.7—80.2)	0 (0%, 95% CI: 0—17.6)

MMAE, middle meningeal artery embolization; CI, confidence interval.

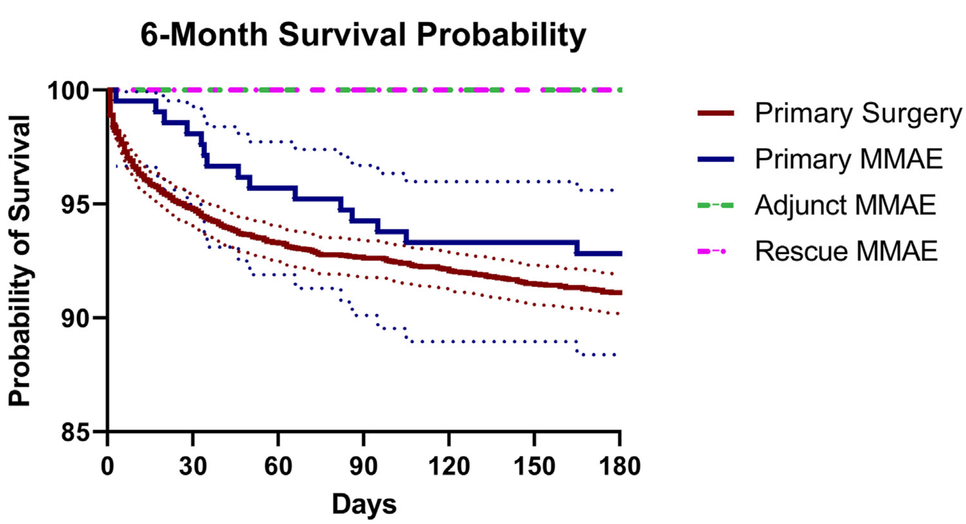

Figure 2. Kaplan-Meier curves for primary middle meningeal artery embolization (MMAE), primary surgery, adjunct MMAE, and rescue MMAE. The difference in survival probability at the end of the time window is 1.25% for the primary MMAE versus primary surgery with $P = 0.35$ using a log-rank (Mangel-Cox) test.

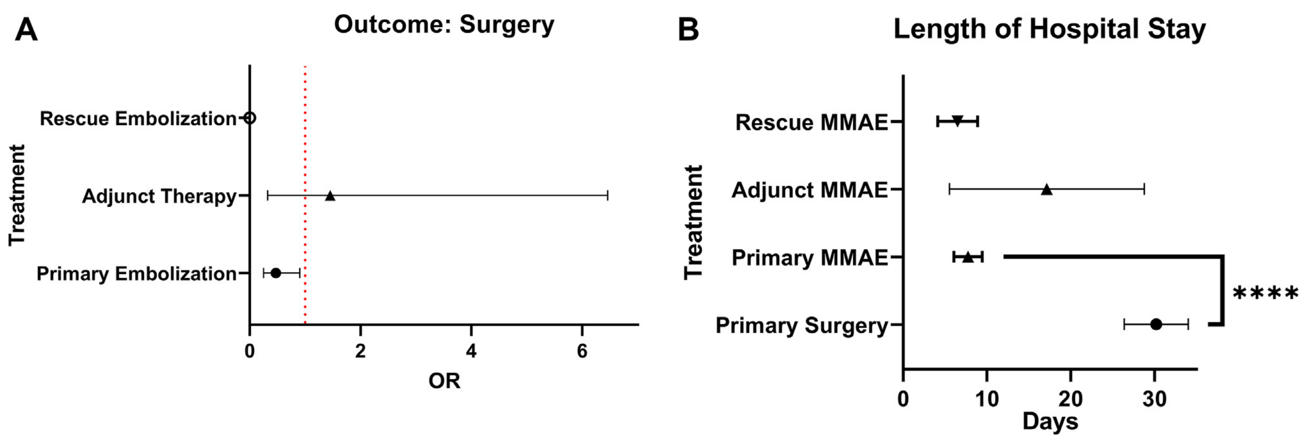

Figure 3. Outcome comparison between the treated cohorts. (**A**) Treatment failure or need for surgical rescue within 6 months compared to primary surgery. Only primary middle meningeal artery embolization (MMAE) had a significantly lower need for surgical rescue than primary surgery (odds ratio = 0.47; 95% confidence interval (0.25–0.90), $P = 0.02$). Additionally (not shown in the figure), there was no significant difference between the primary MMAE, adjunct MMAE, or rescue MMAE ($P > 0.05$). (**B**) Length of hospital stay in each cohort.

studies[19-22] that investigated the MMAE clinical outcomes and showed MMAE as an effective and safe treatment for patients with cSDH either as standalone or adjunctive therapy. The present retrospective cohort study represents the largest cohort of MMAE (n = 224) and the first effort to compare primary MMAE with adjunct MMAE and rescue MMAE for cSDH treatment.

The major finding of this study is that the treatment failure rates were similar across primary MMAE, adjunct MMAE, and rescue MMAE. Additionally, the primary MMAE cohort, despite the significantly older age and higher comorbidity index, is associated with significantly lower treatment failure (lower recurrence) and lower length of hospital stay than the primary surgery cohort. Additionally, there were no significant differences in headaches, facial weakness, and mortality between the cohorts within 6 months postoperatively. The accomplished low complication rate and significantly lower treatment failure place primary MMAE potentially superior to primary surgery. The studies by Marulanda et al.[9] and Catapano et al.[8] that compared MMAE versus conventional therapy did not distinguish whether the MMAE was attempted as a primary treatment, adjunct, or rescue, which may have altered outcomes in these groups. Additionally, the number of patients who underwent MMAE (n = 25 and n = 35) was limited in these studies. Concurrently with the studies by Catapano et al.[8] and Srinivasan et al.,[6] which found a lower recurrence rate in the MMAE cohort than in conventional treatment (OR = 12, 95% CI = 1.5–90; P = 0.02 and 2.1% vs. 27.7%; P < 0.01), our study found 4.8% absolute risk difference in favor of primary MMAE (OR = 2.11, 95% CI = 1.11–4.01; P = 0.02) compared to primary surgery. Furthermore, Shotar et al.[23] reported significantly lower treatment failure in adjunct MMAE than in surgery alone (OR = 0.28, 95% CI = 0.07–0.86, P = 0.02).

The present study provides additional evidence that MMAE can be as effective as if not potentially a more effective standalone therapy in treating cSDH. The mean age of patients undergoing primary MMAE was significantly higher, with a substantially higher comorbidity index. Yet, the mortality was unchanged with lower treatment failure than primary surgery. Thus, primary MMAE can be a more attractive treatment option in this patient population in which general anesthesia can pose significant cardiovascular and pulmonary complications.[24] However, it is essential to note that in most institutions, most patients who have larger compressive hematomas (i.e., the higher initial diameter of cSDH at presentation) and likely associated neurological deficits will undergo surgical intervention, which limits the utilization of embolization in these particular cases.

The significant limitations of this study are its retrospective nature, lack of the radiographic data for evaluating baseline hematoma characteristics and thickness of the hematoma before and after the procedure, and functional scores, such as the National Institutes of Health Stroke Scale and modified Rankin Scale that are not currently available on the platform to be used for estimating the gross functional state of the patients before and after the procedures. Additionally, patients with cSDH who undergo observation only without any intervention are not captured in the study. Our study is limited in its ability to compare outcomes because of the lack of variables mentioned above but describes the current state of MMAE versus other interventions.

CONCLUSION

The present study is the first multi-institutional cohort study using an up-to-date database of patient medical records that represents the trends and outcomes of primary MMAE, primary surgery, adjunct MMAE, and rescue MMAE, with the most significant number of patients in the MMAE cohort reported thus far in the literature. There was no significant difference in headache, facial weakness, and mortality between the cohorts. However, patients in the primary surgery cohort had a significantly higher need for surgical rescue than those in the primary MMAE cohort, all within a 6-month follow-up.

CRediT AUTHORSHIP CONTRIBUTION STATEMENT

Anna M. Nia: Conceptualization, Methodology, Validation, Formal analysis, Investigation, Data curation, Writing – original draft, Visualization, Writing – review & editing. **Visish M. Srinivasan:** Conceptualization, Validation, Writing – review & editing. **Farhan Siddiq:** Conceptualization, Validation, Writing – review & editing. **Ajith Thomas:** Conceptualization, Validation, Writing – review & editing. **Jan-Karl Burkhardt:** Conceptualization, Validation, Writing – review & editing. **Rishi R. Lall:** Writing – review & editing. **Peter Kan:** Conceptualization, Validation, Writing – review & editing, Supervision.

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Conflict of interest statement: The data access was supported by NIH grant TR001439 and Clinical and Translational Science Award (UL1).

Received 23 January 2022; accepted 4 May 2022

Citation: World Neurosurg. (2022) 164:e568-e573.
https://doi.org/10.1016/j.wneu.2022.05.011

Journal homepage: ***www.journals.elsevier.com/world-neurosurgery***

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1878-8750/$ - see front matter