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# Incidence, predictors, and outcome of early seizures after mechanical thrombectomy

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ABSTRACT

*Objective:* Despite the wide utilization of mechanical thrombectomy (MT) for acute ischemic stroke treatment, little is known about the incidence of early post-thrombectomy seizures, its predictors, and association with long-term outcome.

*Methods:* Using a prospective registry of mechanical thrombectomy in ischemic stroke between January 2013 and July 2017, we identified patients who developed a seizure within 7 days (early seizure) of qualifying event. Backward stepwise regression analysis was used to assess independent predictors of seizure occurrence and the association between seizure and functional outcome (modified Rankin scale of 0–2 vs. ≥3).

*Results:* A total of 459 patients were included in the final analysis. Mean age was 67.5 (SD 15.1), and 49.9% of patients were female. Successful recanalization (TICI ≥ 2B) was achieved in 92.8% of patients. Eleven (2.4%) patients developed at least one seizure. Only an Alberta Stroke Program Early CT (ASPECT) score of < 6 was independently associated with the occurrence of early seizures [Odds ratio, 95% confidence interval: 8.188, (2.219–30.214); $P = .002$]. On multivariate analysis, early seizures were associated with 90-day mortality rate [OR,6.487; 95% confidence interval, (1.481–28.405); $P = .013$] and poor functional outcome (OR, 4.7; 95% confidence interval (1.08–20.83); $p = .039$).

*Conclusion:* In the studied cohort, 2.4% of ischemic stroke patients treated with MT developed at least one seizure within 7 days of stroke onset. A low ASPECT score was associated with the occurrence of early seizures. The occurrence of seizures was associated with 90-day mortality and poor functional outcome.

## 1. Introduction

Mechanical thrombectomy (MT) has become the standard of care of an acute ischemic stroke since the publication of five pivotal randomized trials which showed a remarkable benefit of mechanical thrombectomy over medical management in patients with large vessel occlusion (LVO) [1]. Well known complications of mechanical thrombectomy include intracerebral hemorrhage, emboli to new vascular territories, vessel dissection, vasospasm of the access vessel, and stent-related complications [2]. Seizure is a potential complication of thrombectomy after ischemic stroke through a reperfusion injury or intracerebral hemorrhage [3]. Prior to the thrombectomy era, evidence has emerged about the association between stroke and seizures. Post-stroke seizures are arbitrarily divided into early seizures when occurring within the first 1–2 weeks, and late seizures when they occur after 2 weeks of the stroke [5]. The reported post-stroke seizures incidence ranges from 2%–33% while that of late seizures spans from 3 to 67% [6]. Predictors of post-stroke seizures have been reported including cortical involvement [7,8], stroke severity [7,9], and treatment with intravenous tissue plasminogen activator [10] [11] [12]. There are suggestions that post-stroke seizures are associated with a midline shift and worse functional outcome after intracerebral hemorrhage [13,14]. With the projected utilization at a large scale of thrombectomy in the new guidelines [15], clinicians need to be informed about the risk of seizures, their predictors and association with functional outcome. In this study, we aimed to report the incidence of early seizures in patients treated with mechanical thrombectomy and to investigate the predictors of seizures and the correlation with 90-day functional outcome.

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## 2. Methods

### 2.1. Patient population

We used our prospectively maintained stroke database to identify patients who presented with an ischemic stroke due to large vessel occlusion and were treated with mechanical thrombectomy between January 2013 and July 2017. A detailed report regarding patient population was included in previous studies [16]. Patients with large vessel occlusion (LVO) were considered candidate for thrombectomy if the CT perfusion demonstrated mismatch between cerebral blood volume and cerebral blood flow/or mean transit time. Mechanical thrombectomy was performed using a Direct Aspiration, First Pass Technique (ADAPT) for all cases. Stent retriever was attempted if recanalization was not obtained using an aspiration catheter [17].

### 2.2. Early seizures

Retrospective chart review identified patients who developed early seizures post mechanical thrombectomy. Early seizures were defined as seizures that occurred within 7 days of the procedure (or until discharge or death, if sooner). Patients who had history of epilepsy were excluded. Both electrographic seizures and clinical seizures were included in this study. Clinical seizures were identified as reported seizures by the treating physician in patients' charts. In addition, all electroencephalography (EEG) reports were reviewed for evidence of electrographic or electroclinical seizures. At our institution, all EEGs are read by board certified electrophysiologists.

Seizures semiology, the time from MT to the first seizure onset, use of antiepileptic drugs (AEDs) and the EEG findings were recorded. Seizures were classified based on the operational ILEA classification [19].

### 2.3. Data collection

Collected variables included baseline characteristics, procedural variables, post procedural variables and seizures characteristics. Baseline characteristics included demographics, admission NIHSS, time from symptoms onset to groin, IV tPA administration and presence of medical comorbidities. Procedural variables included Thrombolysis in Cerebral Infarction (TICI) score. Successful revascularization was defined as TICI ≥ 2B which corresponds to ≥ 50% reperfusion of the affected vascular territory [21]. Hemorrhagic transformations were divided based on the European Cooperative Acute Stroke Study (ECASS) radiological criteria into hemorrhagic infarctions (HI) and parenchymal hemorrhages (pH) [22]. According to the ECASS criteria, HI represent petechial hemorrhage without space-occupying effect and PH is defined as blood clot(s) with space-occupying effect [23].

### 2.4. Primary outcomes

The dependent variables were seizure occurrence and 90-day functional outcome. Functional outcome was assessed using the 90-day modified Rankin Scale (mRS). The 90-day mRS was recorded during a clinic visit or through a telephone interview with an experienced nurse practitioners or stroke neurologists. A good outcome was defined as mRS = 0–2, and poor outcome was defined as mRS > 2. One of the authors (A.C.) is a neuro-radiologist with > 5 year-experience, and he reviewed admission CT scan for all patients and recorded Alberta Stroke Program Early CT (ASPECT) score. ASPECT < 6 was considered a "poor" ASPECT which is the cutoff commonly used in MT clinical trials [1,24]. Post-procedure MRIs (or CTs if MRIs were not available) were reviewed by blinded neurologists to determine if the stroke or the hemorrhagic transformation involved the cortical areas.

### 2.5. Covariates

Sex, race, medical comorbidities (diabetes, hypertension, atrial fibrillation, hyperlipidemia), admission national institute of health stroke scale (NIHSS), treatment modalities (intravenous recombinant tissue plasminogen activator, intra-arterial recombinant tissue plasminogen activator), hemorrhagic transformations, final TICI score (≥ 2B vs. < 2B), and ASPECT score (< 6 vs. ≥ 6).

### 2.6. Statistical analysis

All analyses were performed using SPSS V.24 (IBM Corporation, New York, USA). We have presented the results as counts, percentages, and mean. Differences between participants with seizures and those without seizures, and between participants with good and those with poor outcome were analyzed via Fisher exact test for qualitative variables and *t*-test for quantitative variables.

To assess the independent predictors of seizures, outcome and mortality, baseline characteristics associated with a $P < .10$ in univariate analyses were implemented into a backward-stepwise model with removal criteria of $P > .1$.

### 2.7. Standard protocol approvals, registrations, and patient consents

Authors confirm that the study is observational minimal risk study and no consent is required per the Medical University of South. Our study was approved by the institutional review board of the Medical University of South Carolina.

## 3. Results

### 3.1. Patients characteristics

A total of 459 patients underwent thrombectomy during the study period including 49.9% females and 60.3% whites. Mean age was 67.5 (SD 15.1) years. There was no significant difference in demographics, receipt of IV tPA, and comorbidities (diabetes mellitus, hypertension, Atrial fibrillation, and hyperlipidemia) between the seizures and no-seizures groups (Table 1). Similarly, variables related to thrombectomy procedure were comparable between the two groups including symptom-onset to groin time, procedure time, rate of successful recanalization and receipt of intra-arterial tPA (IA tPA). Patients with seizures had a higher rate of parenchymal hemorrhage and cortical hemorrhage, but the difference was not statistically significant. Patients in the seizures group were more likely to have low ASPECT score (ASEPCT < 6, 45.5% vs. 11.4%; $P < .001$), lower NIHSS on admission (mean NIHSS, 11.09 v. 15.88; $P = .036$) and were more likely to have a stroke in the right side of the brain (81.8% V. 47.3%, $P = .029$).

### 3.2. Early seizures predictors and outcome

A total of 11 (2.4%) patients had early seizures (within 7 days of acute stroke) during admission. Mean time from stroke symptoms onset to seizures onset time was 2.6 days (SD 1.6). Table 2 summarize the seizures description for each of the patients in the seizures group. In multivariate analysis adjusting for multiple confounders, only ASPECT score < 6 was independently associated with greater odds of having seizures (OR 8.188; 95% CI, 2.219–30.214; $P = .002$) (Table 3).

A total of 259 (55%) of patients had a poor outcome (90-day mRS > 2) including 7 (63.6%) in the seizures group and 252 (56.3%) in the non-seizure group, $P = .72$ (Table 4). On multivariate regression analysis, after controlling for extraneous factors, early seizures post thrombectomy was associated with a poor outcome (OR, 4.7; 95%CI (1.08–20.83); $p = .039$). An older age, worse admission NIHSS, unsuccessful recanalization (TICI < 2B), the presence of PH hemorrhagic transformation, female sex and worse baseline mRS also emerged as

**Table 1**
Characteristics of patients with and without seizures after mechanical thrombectomy for ischemic stroke.

| Variable | N[a] | No seizure (448) | Seizure (11) | *P*-value |
|---|---|---|---|---|
| Age (years) | 459 | 67.64 (14.5) | 62.55 (16.9) | 0.25 |
| Female | 459 | 225 (50.2) | 4 (36.4) | 0.36 |
| White | 459 | 269 (60) | 8 (72.7) | 0.39 |
| IV tPA | 459 | 176 (39.3) | 5 (45.5) | 0.67 |
| Admission NIHSS | 455 | 15.88 (7.4) | 11.09 (6.9) | 0.036 |
| ASPECT < 6 | 398 | 44 (11.4) | 5 (45.5) | < 0.001 |
| Thrombectomy procedural variables | | | | |
| Symptom-onset to groin[b] | 438 | 449 (640) | 341 (121) | 0.58 |
| Procedure time[b] | 442 | 27.1 (22) | 40.2 (38) | 0.310 |
| TICI ≥ 2B | 459 | 415 (92.6) | 11 (100) | 0.35 |
| IA tPA | 450 | 64 (14.6) | 2 (18.2) | 0.93 |
| Stroke location | | | | |
| In the posterior circulation | 459 | 57 (12.7) | 0 (0.0) | 0.20 |
| In the right side of the brain | 459 | 217 (47.3) | 9 (81.8) | 0.029 |
| Cortical involvement | 459 | 321 (71.7) | 9 (81.8) | 0.45 |
| Hemorrhagic transformation | | | | |
| Parenchymal hemorrhage | 456 | 48 (10.8) | 3 (27.3) | 0.087 |
| Cortical hemorrhage[c] | 459 | 37 (8.3) | 2 (18.2) | 0.244 |
| Comorbidities | | | | |
| DM | 459 | 129 (28.8) | 6 (54.5) | 0.064 |
| HTN | 459 | 333 (74.3) | 9 (81) | 0.57 |
| Atrial fibrillation | 459 | 141 (31.5) | 3 (27.3) | 0.76 |
| HLD | 459 | 195 (43.5) | 5 (45.5) | 0.89 |

Values are n (%) or mean (SD). Abbreviations: ASPECT, Alberta stroke program early CT score; DM, Diabetes; IA tPA, intraarterial tissue plasminogen activator; IV tPA, intravenous tissue plasminogen activator; HLD, hyperlipidemia; HTN, Hypertension; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; TICI, Thrombolysis in Cerebral Ischemia.

[a] Number of patients with available data for analysis.

[b] in minutes.

[c] cortical hemorrhage defined as intraparenchymal hemorrhage that involved the cortical surface.

independent predictors of a poor outcome (Table 5). Early seizures post thrombectomy was also found to be a significant predictor for 90-day mortality on multivariate analysis (OR, 6.4; 95% CI, (1.481–28.405); $P = .013$) as shown in Table 6.

## 4. Discussion

We found that about 2.4% of patients who underwent thrombectomy had at least one early seizure. Studies on early seizures among patients with an acute ischemic stroke prior to the era or mechanical thrombectomy, using a cut-off of one week for the definition of early seizures, have reported an incidence rate ranging from 3.2 to 4.1% [25–28].

Data on the seizure incidence after thrombectomy is scarce. In a study of 805 patients who received endovascular treatment between 1992 and 2010, 44/805 (5.5%) had seizures within 3 months after intervention with 3.2% occurring within 24 h of intervention [3]. The difference in the incidence of seizures between this study and our study has many potential explanations. First, the aforementioned study included patients who were treated with mechanical thrombectomy or only intra-arterial thrombolysis. Second, the type of retriever devices is different as MERCI, and other old devices were used as opposed to ADAPT in our study. Of note, the MERCI retriever is credited with a lower recanalization rate and a higher risk of hemorrhage in comparison to Solitaire stent retriever and aspiration devices [29,30].

In the current study, a low ASPECT score was associated with an early seizures post-MT. Our findings parallel those from an Australian cohort of 348 ischemic stroke patients treated with intravenous tissue plasminogen. The ASPECT score is a comprehensive evaluation of the extent of ischemia on non-contrast computerized tomography of the

**Table 2**
Seizures description for each of the patients in the seizure group.

| Patient # | Onset during post-stroke day | Semiology | Type of seizure | Captured on EEG | Number of seizures | Anti-epileptic drugs initiated |
|---|---|---|---|---|---|---|
| 1 | 2 | Behavioral arrest with left gaze deviation | Focal with impaired awareness | No | 2 | Levetiracetam |
| 2 | 4 | Right arm clonic movement with altered consciousness | Focal motor seizure | Yes | 1 | Levetiracetam |
| 3 | 4 | Behavioral arrest | complex partial | Yes | 1 | Levetiracetam |
| 4 | 1 | Left gaze deviation, left versive seizure with altered awareness | Focal motor with impaired awareness | Yes | 1 | Levetiracetam |
| 5 | 2 | Right gaze deviation, right arm tonic-clonic movement with altered awareness | Focal with impaired awareness | Yes | 2 | Levetiracetam |
| 6 | 6 | Generalized tonic-clonic seizure | Generalized | No | 1 | Levetiracetam |
| 7 | 2 | Behavioral arrest | Focal with impaired awareness | Yes | 3 | Lacosamide, Levetiracetam |
| 8 | 1 | Generalized tonic-clonic seizure | Generalized | No | 1 | None[a] |
| 9 | 1 | behavioral arrest | Focal with impaired awareness | Yes | 1 | Levetiracetam, depakote |
| 10 | 2 | Altered awareness and aphasia | Focal with impaired awareness | Yes | 1 | None[b] |
| 11 | 4 | Altered awareness | Focal with impaired awareness | Yes | 7 | Levetiracetam, Lacosamide, Topiramate |

Abbreviations: EEG, electroencephalography.

[a] Patient died shortly after seizure onset.

[b] Patient was transitioned to comfort care shortly after seizure onset.

**Table 3**
Multivariate backward stepwise regression analysis for predictors of early seizure post thrombectomy.

| Variable | OR (95% CI) | *P* value |
|---|---|---|
| Admission NIHSS | 0.902 (0.808–1.007) | 0.066 |
| ASPECT < 6 | 8.188 (2.219–30.214) | 0.002 |
| Right-sided stroke | 3.802 (0.745–19.608) | 0.108 |

ASPECT, Alberta stroke program early CT score; NIHSS, National Institute of Health stroke scale.

**Table 4**
Difference in 90-day outcome measures between two groups.

| Outcome measures | No seizure | Seizure | P-value |
|---|---|---|---|
| Poor outcome (mRS > 2) | 252 (56.3) | 7 (63.6) | 0.72 |
| Mortality (mRS 6) | 93 (20.8) | 4 (36.4) | 0.21 |

Values are n (%).
Abbreviations: mRS, modified Rankin Scale.

**Table 5**
Multivariate backward stepwise regression analysis for predictors of poor 90-day outcome post thrombectomy.

| Variable | OR (95% CI) | P value |
|---|---|---|
| Age | 1.042 (1.025–1.059) | < 0.001 |
| Seizure | 4.717 (1.08–20.833) | 0.039 |
| Admission NIHSS | 1.144 (1.103–1.186) | < 0.001 |
| TICI < 2b | 5.214 (1.799–15.115) | 0.002 |
| parenchymal hemorrhage | 2.488 (1.11–5.555) | 0.027 |
| Female | 1.629(1.019–2.597) | 0.041 |
| Location of occlusion (anterior vs. posterior) | 0.489(0.227–1.052) | 0.067 |
| Baseline mRS | 6.393(1.476–27.688) | 0.013 |

ASPECT, Alberta stroke program early CT score; mRS, modified Rankin scale; NIHSS, National Institute of Health stroke scale; TICI, Thrombolysis in Cerebral Ischemia.

**Table 6**
Multivariate backward stepwise regression analysis for predictors of 90-day mortality post thrombectomy.

| Variable | OR (95% CI) | P value |
|---|---|---|
| Age | 1.042(1.02–1.063) | < 0.001 |
| Baseline mRS | 0.278(0.118–0.653) | 0.003 |
| TICI ≥ 2b | 0.348(0.141–0.859) | 0.022 |
| Seizure | 6.487(1.481–28.405) | 0.013 |
| Admission NIHSS | 1.105(1.065–1.147) | < 0.001 |

mRS, modified Rankin scale; NIHSS, National Institute of Health stroke scale; TICI, Thrombolysis in Cerebral Ischemia.

head. A score of 6 or lower, implying the involvement of at least one cortical region, is more likely to predict the development of seizures. However, cortical involvement was not associated with increased risk of early seizures in our study. This is likely because most of the patients who underwent thrombectomy had cortical involvement.

We found that occurrence of early seizures was associated with a poor outcome at 90 days which correlates with the results of previous studies. In a population-based study [31], seizures were associated with a poor functional outcome among 489 ischemic stroke patients; however, no distinction was made between early and late seizures. Furthermore, acute stroke treatment modalities were not defined and mRS was assessed prior to "discharge" not at 90 days. These results were echoed at a larger scale in a large multicenter study of > 10,000 ischemic stroke patients from the registry of the Canadian Stroke network [32]. The authors concluded that seizures at stroke onset or during hospitalization was associated with a poor functional outcome on discharge. In the Canadian study, the type of seizures was not provided, and the rate of thrombectomy was not reported. Altogether, our results along with the aforementioned studies suggest that the occurrence of early seizures is associated with a short-term poor functional outcome in patients with ischemic stroke. Theoretical considerations and experimental evidence [33] indicate that seizures may result in diffusion weighted imaging changes, cause a midline shift, and therefore aggravate the neurological deficit and subsequently lead to worse functional outcomes.

Post-stroke seizures mechanisms are not entirely understood. Disruption of blood brain barrier, alteration of gene expression and hippocampal sclerosis secondary to hippocampal infarcts were suggested as potential causes [34]. In addition, reperfusion injury secondary to recanalization was proposed as a mechanism for an increased early seizures after tPA [11]. However, our study along with previous studies does not support that recanalization increases the risk of early seizures [34].

## 5. Limitations

Interpretation of our results should account for its limitations including its retrospective single-center design which has limited our analyses to only available data; however, this data was standardized and prospectively collected in a regularly updated stroke registry. In addition, EEG is used at our institution if clinically indicated to rule out seizures, therefore the incidence of electrographic seizures is likely underestimated in our study.

## 6. Conclusion

In this retrospective analysis, we found that nearly 2.4% of ischemic stroke patients treated with MT developed early seizures. Low ASPECT score independently predicted the risk of early seizures. The occurrence of seizures was associated with a poor 90-day functional outcome and higher 90-day mortality rate after MT.

## Authors contributions

Mohammad Anadani: Study concept and design, data interpretation, statistical analysis, and manuscript writing.

Alain Lekoubou: Study concept and design, data interpretation, and manuscript writing.

Eyad Almallouhi: Study concept and design, data collection, and critical revision of the manuscript for important intellectual content.

Ali Alawieh: Data collection.

Arindam Chatterjee: Data collection and critical revision of the manuscript for important intellectual content.

Jan Vargas: Data collection.

Alejandro M Spiotta: Study concept and design, critical revision of the manuscript for important intellectual content, and study supervision.

## Disclosures

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