

# Comorbidities Related to Clinical Outcomes in Patients With Acute Ischemic Stroke Undergoing Mechanical Thrombectomy: Review of Literature and Experience at a Single Comprehensive Stroke Center

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**Background:** Recent clinical trials have shown mechanical thrombectomy (MT) to have clinical benefit for patients with acute ischemic stroke. The purpose of this study was to identify comorbid conditions that correlate with functional nonindependence in patients with acute ischemic stroke who underwent MT at a single comprehensive stroke center.

**Methods:** Patients who had multiphase computed tomography angiography (MCTA) and subsequently underwent MT were included in this study. The modified Rankin Scale (mRS) scores at baseline (prestroke) and at 90 days were established by reviewing patients' histories and medical record documentation. Comorbid conditions were obtained from electronic medical records. Multivariate analysis was performed for body mass index, chronic hypertension, diabetes, hemoglobin A1c, peripheral artery disease, and hyperlipidemia to determine the impact of comorbidities on functional outcome. Age was analyzed using linear regression. Functional independence was defined as an mRS score of 0-2, and functional nonindependence was defined as an mRS score >2.

**Results:** During the study period, 721 patients underwent MCTA, and 134 patients were included for MT. Patients with chronic hypertension and peripheral artery disease showed a statistically significant association with functional nonindependence at 90 days ( $P=0.005$  and  $P=0.0125$ , respectively). Younger age at presentation was correlated with functional nonindependence using linear regression ( $P=0.0001$ ).

**Conclusion:** Hypertension, peripheral artery disease, and younger age at presentation are correlated with poor functional outcome in patients with acute ischemic stroke undergoing MT.

**Keywords:** Comorbidity, critical care outcomes, hypertension, peripheral arterial disease, stroke, thrombectomy

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## INTRODUCTION

Recent studies (2013-2018) have demonstrated the benefits of mechanical thrombectomy (MT) in patients with acute ischemic stroke as a result of large vessel occlusion.<sup>1-5</sup> Identifying which patients are most likely to benefit from MT remains at the forefront of stroke research.

Risk factors for stroke have been studied for decades and are commonly classified into those that are modifiable and those that are nonmodifiable.<sup>6</sup> Age, sex, race, ethnicity, and heredity are known nonmodifiable risk factors for stroke. Modifiable risk factors for ischemic stroke include hypertension, cardiac disease, diabetes mellitus, dyslipidemia, alcohol use, illicit drug use, obesity, lack of physical activity, and diet.<sup>6</sup>

Several studies have explored the impact of age, diabetes mellitus, smoking habits, atrial fibrillation, hyperten-

sion, hyperlipidemia, coronary artery disease, and peripheral artery disease on clinical outcomes in patients undergoing MT.<sup>1-5</sup> The randomized controlled DAWN trial compared the effect of MT 6-24 hours after the stroke in select patients vs medical therapy alone. The researchers found that age >80 years (given a prespecified infarct volume) and diabetes mellitus were associated with functional nonindependence at 90 days.<sup>2</sup>

A systematic review and metaanalysis performed by Lu et al assessed the effect of diabetes mellitus on the outcome of MT.<sup>5</sup> Data from 12,653 patients in 47 articles were evaluated and showed significantly lower odds of functional independence in patients with a history of diabetes mellitus in both the unadjusted metaanalysis (odds ratio [OR] 0.64; 95% confidence interval [CI] 0.54-0.75) and the multivariable analysis (OR 0.48; 95% CI 0.33-0.71).<sup>5</sup>

Le Bouc et al showed that MT was associated with improved functional outcome in older ( $\geq 50$  years) and more severe patients (based on National Institutes of Health Stroke Scale [NIHSS] scores) but not in younger and less severe patients.<sup>4</sup> Le Bouc et al created a stroke checkerboard score to incorporate age and stroke severity determined via the NIHSS. For their stroke checkerboard score, 1 point was given per decade  $\geq 50$  years of age and 2 points were given per 5 points on the NIHSS.<sup>4</sup> An analysis of 4,079 patients with acute ischemic stroke showed that stroke checkerboard scores  $< 8$  were predictive of good outcomes (modified Rankin Scale [mRS] score of 0-2) in patients not treated with MT, whereas stroke checkerboard scores  $> 12$  were predictive of poor outcomes (mRS score of 4-6).<sup>4</sup> MT was associated with good outcomes (mRS score of 0-2) in patients with stroke checkerboard scores  $> 12$  (common OR 1.70; 95% CI 1.13-2.56) and stroke checkerboard scores of 8-12 (OR 1.37; 95% CI 1.11-1.69) but not in patients with stroke checkerboard scores  $< 8$  (OR 0.72; 95% CI 0.56-0.93).<sup>4</sup> The common OR in this study refers to the increased chance of achieving a functionally independent outcome within certain sets of the stroke checkerboard scoring system.

Kurre et al studied 109 patients  $\geq 80$  years with recanalization procedures and examined smoking, atrial fibrillation, diabetes, hypertension, hyperlipidemia, coronary artery disease, and peripheral artery disease as potential variables determining post-MT functional independence.<sup>3</sup> The study found no disease states to be statistically significant predictors of favorable or unfavorable outcomes.<sup>3</sup>

The purpose of our study was to identify comorbid conditions that correlate with functional nonindependence in our population of patients with acute ischemic stroke who underwent MT. Our goal is to improve understanding of the variables that will aid in patient selection for intervention.

## METHODS

Approval from the institutional review board was obtained and compliance with the Health Insurance Portability and Accountability Act was maintained. The imaging database was queried for all multiphase computed tomography angiogram (MCTA) examinations at our comprehensive stroke center from August 1, 2016 through December 31, 2017.

All patients who had MCTA and underwent MT were included in this study. The patients' mRS scores at baseline (prestroke) and at 90 days were reviewed. The baseline mRS scores were established from the patients' histories (their functional status was immediately prior to the stroke) and assessed by the stroke team. However, because baseline values were not universally available and could not be validated, they were not included in the analysis. Age, body mass index (BMI), and diagnoses of chronic hypertension, diabetes, hemoglobin (Hb) A1c, peripheral artery disease, and hyperlipidemia were determined by querying the electronic medical record (EMR) database. Preexisting hypertension was determined from the EMR by searching for related International Statistical Classification of Disease codes.

We considered age, BMI, and HbA1c as continuous variables. Functional independence was defined as an mRS

**Table. Association of Age, Body Mass Index, and Comorbidities With Functional Nonindependence at 90 Days in Patients Undergoing Mechanical Thrombectomy**

Variable	P Value
Age	0.0001
Body mass index	0.3010
Chronic hypertension (n=112)	0.005
Diabetes (n=37)	0.9598
Hemoglobin A1c (n=134)	0.8492
Peripheral artery disease (n=14)	0.0125
Hyperlipidemia (n=56)	0.9459

Note: Age, body mass index, and hemoglobin A1c are considered continuous variables.

score of 0-2, and functional nonindependence was defined as an mRS score  $> 2$ . A multivariate analysis was performed using a nominal logistic fit to assess the impact of BMI, chronic hypertension, diabetes, HbA1c, peripheral artery disease, and hyperlipidemia on functional nonindependence after patients underwent MT. Age was analyzed using linear regression.

## RESULTS

During the study period, 721 patients underwent MCTA, 134 of whom underwent MT. The association of age, BMI, and comorbidities with functional nonindependence is shown in the Table.

In our MT cohort, the presence of chronic hypertension showed a statistically significant association with functional nonindependence at 90 days ( $P=0.005$ ). The presence of peripheral artery disease also showed a statistically significant association with functional nonindependence at 90 days ( $P=0.0125$ ). Younger age at presentation was correlated with functional nonindependence using linear regression ( $P=0.0001$ ). BMI, diabetes, HbA1c, and hyperlipidemia showed no statistically significant association.

## DISCUSSION

The comparative analysis of age, BMI, and comorbid conditions with outcomes in our population showed a statistically significant correlation to functional nonindependence in patients who presented with chronic hypertension, peripheral artery disease, and younger age at presentation. Our results agreed with those of Le Bouc et al that showed improved outcome with advanced age.<sup>4</sup> However, our results differed from the findings of the DAWN trial that showed age  $> 80$  years (given a prespecified infarct volume) was associated with worse functional outcomes.<sup>2</sup> One difference between our study and the Le Bouc et al and the DAWN studies is that we analyzed age as a continuous variable, whereas the Le Bouc et al and DAWN trials set thresholds for advanced age (50 years and 80 years, respectively).<sup>2,4</sup> We did not dichotomize age because of a general lack of evidence for a threshold effect and to prevent overfitting. Consequently, our results show a different age effect.

In our study, peripheral artery disease had a significant correlation with not achieving functional independence at

90 days. We suggest multiple possible explanations for this correlation. We theorize that the presence of diffuse atherosclerosis may make the vascular beds more prone to intraprocedural rupture or injury, potentially promoting rethrombosis and limiting recovery potential. Additionally, vascular disease may make the procedure more technically challenging and the removal of blood clots less successful. Finally, patients with vascular disease have less compliant blood vessels, potentially diminishing the ability of the vasculature to preserve flow to the brain during the ischemic period and, in turn, reducing the benefit of MT.

The only study we found assessing the impact of peripheral artery disease was the Kurre et al study that analyzed the outcomes of patients  $\geq 80$  years with chronic disease states.<sup>3</sup> The authors did not find a significant correlation between peripheral artery disease and the outcomes of MT, a result the authors attributed to the unrigorous characterization of the sample population, unreported comorbidities, and lack of prospective design. Furthermore, the authors explained that their study did not consider the severity of each pre-morbid condition.

Our data also show that hypertension is a variable likely to impact outcomes following MT. Goyal et al looked at the effect of hypertensive crisis during and after MT but did not examine hypertension as a comorbidity impacting long-term outcomes.<sup>7</sup> Our study adds evidence that hypertension is an outcome-determining variable not only when it occurs periprocedurally but also when it is a preexisting comorbidity.

Our finding that hypertension and peripheral artery disease are variables impacting the outcomes of MT is important considering the prevalence of these chronic conditions. According to Centers for Disease Control and Prevention data published in 2016, the overall prevalence of hypertension was 29.0%, and the prevalence increased with age: 18-39 years, 7.5%; 40-59 years, 33.2%; and  $\geq 60$  years, 63.1%.<sup>8</sup> Because of the high prevalence of hypertension, we suggest that prospective studies be conducted to validate our finding as we anticipate that the majority of patients who have a stroke and are evaluated for candidacy of MT will have hypertension.

Peripheral artery disease is present in approximately 8.5 million people in the United States including 12%-20% of individuals  $>60$  years.<sup>9</sup> Risk factors for peripheral artery disease include smoking, hyperlipidemia, hypertension, and diabetes.<sup>9</sup> While our study did not show correlations between hyperlipidemia and diabetes (we did not assess smoking) and MT outcomes, our study did show a correlation with peripheral artery disease.

Lu et al showed that patients with a prior history of diabetes mellitus had significantly lower odds of functional independence.<sup>5</sup> Conversely, Kurre et al did not find a statistically significant impact of diabetes on functional non-independence after MT.<sup>3</sup> Our study supports the finding of Kurre et al.

The other risk factors evaluated in our study—BMI, HbA1c, and hyperlipidemia—showed no statistically significant correlations. While this result may reflect an actual lack of correlation between these diagnoses and outcomes in this population, we suggest that the result could instead be attributable to low sample sizes for each of these diag-

noses, as well as underdocumentation in the EMR. Our study has additional limitations. First, the study is retrospective. Prospective studies with large sample sizes that rigorously ensure proper diagnoses of comorbid conditions and their severity are needed to confirm our results. Second, our study did not have a formal control as we did not compare our cohort to a non-MT group. Randomized controlled trials that compare treatment and nontreatment groups are needed to validate our results. Third, we obtained comorbidities from the EMR based on the documentation of diagnosis codes. Physicians and nurses manually enter these diagnoses at various times throughout patient care, possibly resulting in a great deal of variability in the accuracy of this documentation. Despite these concerns, our data add to the growing evidence related to existing comorbidities and the outcomes of patients with acute ischemic stroke who are undergoing MT.

## CONCLUSION

Hypertension, peripheral artery disease, and younger age at presentation are correlated with functional nonindependence at 90 days in patients with acute ischemic stroke undergoing MT. Our findings add to the growing fund of knowledge regarding patient comorbidities and outcomes for this proven beneficial therapy.

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