# **Original Article**

# Is It Possible to Predict the Outcome of Endovascular Thrombectomy for Hyperdense Middle Cerebral Artery Sign at the Time of First Admission?

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## INTRODUCTION

The hyperdense middle cerebral artery sign (HMCAS), detected in the first non-contrast computed tomography (NCCT) at the time of admission, is a well-defined phenomenon in acute ischemic stroke patients.<sup>[1-5]</sup> In acute ischemic stroke, the HMCAS sensitivity has been reported as 27–54% and its specificity was close to 100%.<sup>[6]</sup> It has been reported that sensitivity will increase by reducing the time from the symptom onset to NCCT imaging, and by taking better quality and thinner cross sections.<sup>[7]</sup> Hemoglobin level, cross-sectional thickness of CT, and

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**Background:** The hyperdense middle cerebral artery sign (HMCAS) on admission non-contrast computed tomography (NCCT) is a well-characterized phenomenon in acute ischemic stroke. Aim: The purpose of this study is to determine the impact of HMCAS on the outcome of patients who underwent endovascular thrombectomy. Materials and Methods: A retrospective analysis of a prospectively collective database included 136 consecutive patients with anterior circulation acute ischemic stroke who underwent endovascular thrombectomy. We collected the demographics, and clinical and brain imaging as well as functional and imaging outcomes data at baseline. Patients were divided into two groups with hyperdense artery sign and those without the sign. The difference between the two groups in terms of mortality and prognosis was analyzed. Results: There were 136 patients, 50.7% of them were women. The mean age was 59.1 years. The subgroup with HMCAS present consisted of 93 patients. There were no differences in demographics and clinical characteristics between the two groups; however, tobacco use is more common in patients with HMCAS. No significant difference was observed in clinical outcomes and mortality between the two groups at 3 months. Patients with HMCAS had statistically more new territory emboli during the procedure (9.7%) compared to patients without HMCAS. Conclusion: We showed that the presence of HMCAS in initial CT was not helpful in predicting good clinical outcomes in patients undergoing endovascular therapy patients. However, the presence of HMCAS is related to more new territory embolism during the procedure. Different endovascular strategies may be applied to these patients.

**Keywords:** Endovascular thrombectomy, hyperdense middle cerebral artery sign, new territory emboli

the experience of the physician significantly affect sensitivity.<sup>[6]</sup>

Studies have shown that HMCAS can predict clinical outcome in patients who underwent intravenous thrombolytic treatment.<sup>[6,8]</sup> More severe neurological deficits and worse clinical outcomes have been reported

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in studies comparing groups of patients with and without HMCAS.<sup>[5,9]</sup> However, our knowledge about whether HMCAS can be used to predict the outcome of endovascular thrombectomy is limited.<sup>[3]</sup>

Our aim is to determine the predictive power of the hyperdense artery sign in CT imaging in patients undergoing endovascular thrombectomy in predicting functional outcome and possible complications due to thrombectomy.

## **MATERIALS AND METHODS**

## **Patient selection**

The local ethics committee of the XXX University approved the study. A retrospective analysis was performed on 166 consecutive patients with acute ischemic stroke who underwent endovascular thrombectomy between January 2012 and May 2017.

All patients included in the study received a CT, then underwent CT angiography (CTA). All anterior circulation stroke patients with proximal vessel occlusion (e.g., internal carotid artery and middle cerebral artery) were included in the first 6 h after the onset of symptoms. The patients with posterior circulation occlusion and isolated anterior cerebral artery occlusion were excluded from the study. One hundred thirty-six patients in whom mechanical thrombectomy were performed, enrolled in the study. Two interventional neurologists independently reviewed the clinical and radiological outcomes.

#### **Clinical assessment**

Age, sex, medical history, stroke risk factors and baseline National Institutes of Health Stroke Scale (NIHSS), endovascular treatment time, and modified Rankin Scales (mRS) at 90 days were collected from the database. Classification of the stroke subtypes was determined using the Trial of Org 10172 in acute stroke treatment trial criteria after completing a diagnostic workup.<sup>[10]</sup>

The severity of the stroke was measured at baseline and 24 h after the symptom onset using the National Institute of Health Stroke Scale (NIHSS). Dramatic neurological improvement was defined as an NIHSS score improvement of 8 points during the 24-h follow-up. Neurological and functional outcomes in the third month were assessed by the mRS and 0–2 was considered a favorable outcome. The poor outcome in the third month was defined as an mRS score  $\geq 3$ .

#### **Radiological assessment**

The axial CT was done in a multi-section scanner (SOMATOM Perspective; Siemens Healthcare) using 130 kV and 280 mas with a 2.5 mm section

thickness. Continuous axial sections were obtained from the base of the skull to the apex, parallel to the orbitomeatal line. After NCCT, CTA was obtained by a helix scanning technique using the same scanner. Following the single bolus i.v. contrast injection of 70–90 ml nonionic contrast at 5ml/s with a delay of 20–25 seconds after the start of contrast injection, acquisitions were achieved. The imaging was automatically started by the appearance of contrast material in the aorta. The CTA was reconfigured at 0.625 mm intervals to 1.25 mm thick. At least 24 h after the symptom began, a follow-up NCCT was performed.

In the NCTT, clot location and thrombus length were recorded. Early ischemic changes were detected by baseline NCCT using the Alberta stroke program early CT *score* (ASPECT).<sup>[7]</sup>

All patients were examined using CT imaging 24 h after the thrombectomy.

#### **Treatment procedure**

Intravenous thrombolysis (IVT) was given to the patients who presented with a proximal artery occlusion and no contraindication to thrombolytic therapy during the first 4.5 h after the onset of the symptom (with tissue plasminogen activator (tPA, alteplase), 0.9 mg/kg).

Patients who had a symptom time of 4.5–6 h and had contraindications to thrombolytic therapy were taken directly to the angiography unit for endovascular treatment.

All of the procedures were performed under conscious sedation. In case of internal carotid artery occlusion, the 8 or 9 French balloon guide catheter or 6 f Neuron Max long sheath was inserted distal of the internal carotid artery or common carotid artery. An endovascular technique such as Thrombectomy with Stent Retrievers, aspiration with large-bore aspiration catheters, or a combination of aspiration and thrombectomy (ARTS or Solumbra technique) was performed.<sup>[11,12]</sup>

The thrombolysis in cerebral infarction (TICI) score was used to evaluate cerebral perfusion after thrombectomy by a digital cerebral angiogram.<sup>[13]</sup> The TICI 2a score is defined as partial reperfusion of  $\leq$ 50% of the vascular territory of the occluded artery, and TICI 2b score is defined as partial reperfusion of >50% of the occluded artery. The TICI 3 score is complete perfusion of the occluded artery ischemic territory. Successful recanalization was defined as TICI2b-3.

The presence of new territory emboli, distal emboli, rupture, and dissection related to endovascular acute stroke treatment was recorded. New territory emboli are defined as an angiographic occlusion of the previously unaffected artery during mechanical thrombectomy. Patients were divided into two groups: those with and without the hyperdense artery sign. The cut-off value of the hyperdense artery length was considered 8 mm in the NCCT. Patients above and below this value were analyzed in two groups. The difference between the two groups was analyzed in terms of mortality and prognosis.

#### Statistical analysis

All analyses were performed using Statistical Package for Social Sciences 11.0 (SPSS Inc., Chicago, IL, USA), and P < 0.05 was defined as statistically significant. Patients' demographics, clinical predictors, and imaging feature outcomes were summarized using descriptive statistics. Categorical variables were compared using Fisher's exact or  $\chi^2$  test. Continuous variables were compared using the Mann–Whitney test for independent samples. Statistical test results were considered significant at P < 0.05. Multivariate regression analysis was performed to evaluate possible correlations of HMCAS with the functional outcome (mRS at 3 months), stroke severity (NIHSS), age, atrial fibrillation, use of balloon catheter, first pass thrombectomy, and location of occlusion (Middle cerebral artery (MCA) and internal cerebral artery (ICA)). The odds ratio (OR) and its 95% confidence interval (CI) were calculated for the variables found to be significantly associated with the endpoint in the multivariate model test.

#### RESULTS

During the study period, 136 consecutive patients [69 females (50.7%) and 67 males (49.3%)] with acute large vessel occlusions underwent endovascular treatment. Mean age ( $\pm$  SD) was 59.1  $\pm$  11.3 years (range

	Variables	Patient with	<b>Patients without</b>	р	OR
	variables	HMCAS n=93	HMCAS n=43		
Patient demographics	Age, y (mean, SD)	60±10.7	56±12.4	0.106‡	-
	Female	50 (53.8%)	19 (44.2%)	0.358†	-
	Male	43 (46.2%)	24 (55.8%)	0.358†	-
Cause of stroke	Atherothrombosis	13 (14.6%)	11 (27.5%)	$0.206^{+}$	-
	Cardioembolic	56 (62.9%)	23 (57.5%)		-
	Other causes	3 (23%)	0 (0%)		-
	Cryptogenic	14 (15.7%)	6 (14%)		-
	Coagulopathy	1 (1.1%)	2 (4.7%)		-
Vascular risk factors	Hypertension	56 (60.2%)	26 (60.1%)	$1.000^{+}$	-
	Diabetes mellitus	23 (24.7%)	10 (23.3%)	1.000 <sup>†</sup>	-
	Atrial fibrillation	45 (48.4%)	18 (41.9%)	$0.600^{\dagger}$	-
	Dyslipidemia	40 (43%)	28 (65.1%)	0.027 <sup>†</sup>	-
	Tobacco smoking	39 (41.9%)	30 (68.8%)	0.003 <sup>†</sup>	0.313
	Alcohol use	7 (7.5%)	3 (7%)	0.909†	-
	Coronary artery disease	26 (28%)	19 (44.2%)	0.094†	-
Admission clinical and	Baseline NIHSS Median Interquartile				-
adiological data	range				
	Median	20	21	0.423*	-
	Interquartile range	6-25	10-25		
	NIHSS >10	92 (98.9%)	40 (93%)	0.093†	-
	Plasma glucose (mean±SD), mmol/l	$151\pm63.73$	$140\pm53.50$	0.364‡	_
	Platelet	252.98±71.46	247.70±2.18	0.734‡	-
	Triglycerides	124.54±4.21	144.17±70.33	0.200*	-
	HDL	44.48±3.66	48.22±15.00	0.252‡	-
	LDL	110.70±30.27	118.53±30.98	0.262‡	-
	Carotid occlusion	39 (41,9%)	14 (32.6%)	0.393†	-
	Tandem occlusion	23 (24.7%)	9 (20.9%)	$0.788^{\dagger}$	-
	T occlusion	16 (17.2%)	4 (9.3%)	0.342 <sup>†</sup>	-
	Baseline ASPECT	8.18±1.45	8.51±1.36	0.067*	-
	ASPECT >7	78 (65.5%)	41 (34.5%)	0.109†	-
	Right-sided stroke	46 (69.7%)	20 (30.3%)	0.446 <sup>†</sup>	-
	Left-sided stroke	47 (67.1%)	23 (32.9%)	0.749 <sup>†</sup>	-
	rt-PA treatment	47 (50,5%)	18 (42,9%)	0.460 <sup>†</sup>	-

\*Mann-Whitney U-test. †Chi-square test. ‡Student t-test, HDL: High-density lipoprotein, LDL: Low-density lipoprotein

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	Patient with	Patients without	р
	HMCAS n=93	HMCAS n=43	-
Stroke symptom onset to recanalization time, min (mean±SD)	250±106.55	236±80.80	0.500‡
Onset to groin puncture, min (mean±SD)	194.58±80.42	201±81	0.659‡
CT to DSA time, min (mean±SD)	77.82±48.88	60.60±33.75	0.045‡
Use of balloon catheter	44 (49.4%)	17 (39.5%)	$0.285^{\dagger}$
First pass thrombectomy	46 (58.2%)	21 (60%)	$1.000^{+}$
Number of passes	2	2	0.860*
Median Interquartile range	1-5	1-7	
Technique			
Aspiration system	5 (11.6%)	10 (10.8%)	
Stent retriever	26 (60.5%)	49 (52.7%)	0.654 <sup>†</sup>
Combined technique	12 (27.9%)	33 (35.5%)	
Successful recanalization (TICI 2b, 3)	77 (82.8%)	35 (81.4%)	$0.842^{\dagger}$
Distal embolism	2 (5.1%)	14 (16.5%)	$0.144^{\dagger}$
New territory emboli during procedure	9 (9.7%)	0 (0%)	0.035†
Futile recanalization	30 (40.5%)	11 (31.4%)	0.481 <sup>†</sup>
m RS at 3 month	2.88±2.24	2.58±2.10	0.552*
Modified Rankin scale 0-2	24 (33.8%)	47 (66.2%)	$0.608^{\dagger}$
Dramatical neurologic improvement	45 (48.4%)	21 (48.8%)	0.960†
Median NIHSS score at 24 h Median	12	11	0.530
Interquartile range	0-22	1-25	
Mortality	21 (22.8%)	8 (18.6%)	$0.740^{\dagger}$
Symptomatic ICH	7 (7.5%)	1 (2.3%)	0.435†

\*Mann-Whitney U-test. <sup>†</sup>Chi-square test. <sup>‡</sup>Student *t*-test

Table 3: The effect of the length of hyperdense MCA segment on mortality and clinical outcome						
	HMCAS under HMCAS above		Р			
	8 mm <i>n</i> =20	8 mm <i>n</i> =73				
Mortality	3 (13.6%)	19 (86,4%)	$0.384^{\dagger}$			
Favorable outcome	10 (20.8%)	38 (79.2%)	$0.871^{\dagger}$			
Unfavorable outcome	10 (22.2%)	35 (77.8%)	$0.871^{\dagger}$			
mRS at 3 months	$2.80\pm2.11$	$2.90\pm2.29$	0.887*			

\*Mann-Whitney U-test. <sup>†</sup>Chi-square test. <sup>‡</sup>Student *t*-test

18–82). The HMCAS subgroup consisted of 93 patients (68.4%), of which 50 (53.8%) were female, and 43 (46.2%) were male. Mean age ( $\pm$  SD) was 60  $\pm$  10.7 years (range 26–82). The non-HMCAS subgroup consisted of 43 patients (19 (44.2%) females, 24 (55.8%) males). Mean age ( $\pm$  SD) was 56  $\pm$  12.4 years (range 18–75 years).

Details on demographics, clinical variables, radiological findings, stroke etiology, and treatment are presented in Table 1. The median NIHSS and ASPECT score did not differ in patients with HMCAS and without HMCAS [Table 1].

IVT was performed in 50.5% of patients with HMCAS and 42.9% of non-HMCAS patients. There was no difference in IVT between the two groups.

The time from stroke symptom onset to recanalization, symptom onset to time of non-contrast CT, onset to

groin puncture, and puncture to recanalization time did not differ between the subgroups [Table 2].

No significant difference was found between both groups in terms of the endovascular treatment technique (P = 0.654). The recanalization rate at TICI2b-3 did not differ between the subgroups (82.8 vs. 81.4%, P = 0.842).

The use of balloon guiding catheter was similar between both groups (49 vs. 39.5%, P = 0.285). There were no differences between the groups in terms of the rate of first pass thrombectomy, distal embolism, number of passes, and dramatic neurological recovery rates [Table 2]. Symptomatic hemorrhage and mortality rates were similar. There was no significant difference between the two groups in the favorable and unfavorable outcomes, compared to mRS scores after 30 days [Table 2].

Patients without HMCAS had no new territory emboli. However, 9.7% of the patients with HMCAS had new territory emboli. This difference was considered statistically significant (P = 0.035).

Hyperdense artery length was measured as  $18.91 \pm 11.12$  (4.32–69) mm in HMCAS patients. In 21.5% of patients with a hyperdense artery sign, the lesion was below 8mm and 78.5% was above 8 mm. There was no difference between mortality, favorable and unfavorable results [Table 3]. In the multiple logistic

regression analysis, any parameter affecting the result did not result in significant results.

## DISCUSSION

Our study showed that the hyperdense artery sign in patients with acute middle cerebral artery occlusion had no effect in predicting the success of endovascular treatment. There was no difference between groups with and without HMCAS in terms of successful recanalization rates. Symptomatic hemorrhage, mortality, and good clinical outcome rates at 90 days were similar between both groups.

One of the earliest indicators of acute ischemic stroke is the hyperdense artery sign seen in non-contrast CT and representing arterial occlusion.<sup>[14,15]</sup> The hyperdense artery sign is an early radiological finding indicating intraluminal thrombus.[16,17] Furthermore, NCCT is an important examination that not only shows ischemic changes in the brain parenchyma, but also the location of clots in intracranial arteries.<sup>[18]</sup> When CT and magnetic resonanse (MR) angiography cannot be performed technically, the presence of hyperdense artery sign in NCCT is a very effective sign in predicting proximal vessel occlusion and planning revascularization therapy during the acute period. Studies on acute ischemic stroke patients, particularly those treated with thrombolytic therapy, have shown that the presence of the hyperdense artery sign is associated with severe neurological deficits, increased brain damage, and worse clinical outcomes.<sup>[5,6,14]</sup> One study showed that intra-arterial thrombolytic treatment in patients with HMCAS was associated with better prognosis and lower mortality rates than IVT.<sup>[19]</sup> However, there are a limited number of studies comparing clinical and radiological characteristics, recanalization rates, neurological outcomes, and endovascular treatment responses between groups of patients with and without a hyperdense artery sign in acute ischemic stroke patients who underwent endovascular therapy.

Of the 136 patients included in our study, 68.4% had HMCAS. In the literature, the reported rate of incidence of HMCAS was 5–41%.<sup>[20,21]</sup> In our study, this rate was higher than the previous studies since our study included only acute stroke patients with large vessel occlusion. The lack of hyperdense sign in 31.6% of our patients with proximal vessel can be explained by the structure of the thrombus.<sup>[22]</sup> Histopathological studies can provide information about the composition of the thrombus. HMCAS have been shown to be more visible in erythrocyte-rich clots than fibrin-dominant clots.<sup>[23,24]</sup> Moreover, in a recent systematic review and meta-analysis on CT imaging and histological features

of clots in acute stroke patients, the HMCAS group has been shown to have erythrocyte-rich clots, according to the pathological examination of the MCA clots. In contrast, non-HMCAS patients are likely to have fibrin/ platelet dominant clots.<sup>[24,25]</sup> Studies have shown that early reperfusion of ischemic brain tissue is the strongest predictor of neurological recovery.<sup>[17]</sup> In our study, there was no statistical difference between temporal parameters, prognosis and mortality rates between the groups. It was found that the presence of HMCAS did not adversely affect endovascular treatment outcome.

In the MR CLEAN study, the risk of new territory emboli after endovascular treatment was reported at 8.6%.<sup>[26]</sup> In parallel to the MR CLEAN study, the risk of new territory emboli was 6.6% in all patients.[27] Interestingly, no new territory embolism was observed in the non-HMCAS patient group, whereas all patients with new territory embolism were seen in the HMCAS group.<sup>[28]</sup> In our study, only three of the nine patients with new territory emboli patients underwent thrombectomy alone by providing proximal protection with a balloon guiding catheter. In the detailed analysis, three of the nine patients with new territory emboli received the first-line aspiration technique without proximal protection. In addition, three of the nine patients with new territory emboli underwent thrombectomy with a stent-retriever alone without a balloon guiding catheter. No patient experienced new territory emboli during endovascular treatment under combined aspiration and thrombectomy regardless of balloon guiding catheter use.

The hyperdense MCA sign on a CT scan is associated with erythrocyte-rich clots and treatment techniques should be decided carefully in patients with HMCAS to prevent fragmentation and embolization of the clot. In PROTECT <sup>PLUS</sup>, after the stent-retriever deployment, large-bore aspiration catheter was advanced under continuous aspiration. Afterward, the aspiration catheter and stent-retriever were withdrawn as a unit under proximal protection with a balloon guiding catheter.<sup>[29,30]</sup> This technique is almost similar to Stent retriever Assisted Vacuum-locked Extraction (SAVE) technique in which a balloon guiding catheter was not used.<sup>[31]</sup>

In PROTECT <sup>PLUS</sup> technique, no new territory emboli were observed. Hence, in the presence of HMCAS, stent retrievers in combination with large-bore aspiration catheters under proximal protection with balloon guiding catheters may provide safer endovascular technique to prevent new territory emboli.<sup>[32]</sup>

#### **Study limitations**

Our study has several limitations. The retrospective nature of the study and small number of patients are among the limitations of the study. Data were extracted from a prospective database. Demographic data, risk factors, and clinical data were evaluated prospectively, but radiological data were retrospectively examined. We did not perform a histological analysis of the thrombus and this may be considered as another limitation of the study.

## CONCLUSION

In our study, we demonstrated that the HMCAS in CT at the time of admission is not useful in predicting favorable outcome in patients receiving endovascular treatment, but the presence of HMCAS can be a predictor of new territory emboli. Several endovascular techniques using a stent-retriever and a large-bore aspiration catheter under balloon protection may be useful to prevent new territory emboli in patients with HMCAS on CT.

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## **Conflicts of interest**

There are no conflicts of interest.

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