NÖRO PSİKİYATRİ ARŞİVİ
ARCHIVES OF NEUROPSYCHIATRY

Arch Neuropsychiatry 2026;63:294−298
https://doi.org/10.29399/npa.29174

RESEARCH ARTICLE

Article No: 46

Prediction of Hemorrhagic Transformation and Functional Outcomes Using Arterial Spin Labeling MRI in Acute Middle Cerebral Artery Infarction

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ABSTRACT

Introduction: Arterial spin labeling (ASL) MRI, a non-invasive perfusion imaging method, may potentially identify patients at high risk for hemorrhagic transformation (HT) by quantifying cerebral blood flow (CBF). We aimed to investigate the role of ASL MRI perfusion parameters in predicting HT and functional outcomes in acute middle cerebral artery (MCA) infarction.

Methods: A retrospective study was conducted involving 23 patients admitted within 24 hours of MCA infarction onset. Acute imaging included noncontrast cranial CT, diffusion-weighted imaging (DWI) and multiphase CT angiography. Approximately one week after symptom onset, follow-up imaging was performed with DWI and ASL MRI. Infarct volumes were manually calculated. Menon collateral scores and ASL-derived perfusion parameters, including hyperperfused area CBF and relative CBF (rCBF), were assessed. Functional outcomes were evaluated using modified Rankin Scale (mRS) at the end of 1st week, 1st month and 3rd month and Barthel Index at the end of 3rd month follow-up.

Results: HT developed in 15 patients (65.2%). HT was associated with significantly larger infarct volumes (p=0.021), lower Menon scores (p=0.006), higher rCBF values (p=0.014), and worse functional outcomes indicated by worse functional outcomes at the end of 3rd month follow-up, indicated by higher mRS scores (p=0.044) and lower Barthel Index scores (p=0.036).

Conclusion: ASL MRI parameters, particularly hyperperfused area CBF and relative CBF, along with collateral circulation and infarct volume measurements, may effectively predict the risk of HT and functional outcomes in acute MCA infarction. These parameters can enhance clinical decision-making and improve patient management strategies.

Keywords: Arterial spin labeling; hemorrhagic transformation; middle cerebral artery ınfarction; poor prognosis

Cite this article as: Yön Mİ, Baraklı S, Çeltikçi P, Ercan K. Prediction of Hemorrhagic Transformation and Functional Outcomes Using Arterial Spin Labeling MRI in Acute Middle Cerebral Artery Infarction. Arch Neuropsychiatry 2026;63:294−298. doi: 10.29399/npa.29174

INTRODUCTION

Middle cerebra artery (MCA) infarction is the most common and clinically severe subtype of ischemic stroke. One of the major early complications in MCA infarcts is hemorrhagic transformation, which arises from disruption of vascular integrity and increased permeability of the blood-brain barrier in the ischemic territory (1,2). Prior research has identified several risk factors for HT, including larger infarct volume, poor collateral circulation, hyperperfusion phenomena, and timing of reperfusion therapy (3,4).

Recent advances in MRI have expanded the toolkit for assessing cerebral perfusion, among which Arterial spin labeling (ASL) has emerged as a leading noninvasive technique. ASL enables quantitative measurement of Cerebral blood flow (CBF) without exogenous contrast by magnetically "labeling" water protons in arterial blood and tracking their passage into the brain parenchyma (5). Emerging evidence suggests that ASL-derived perfusion parameters—particularly the presence of hyperperfused regions and elevated relative CBF (rCBF)—may predict HT risk following ischemic stroke (6,7). However, studies specifically evaluating the ASL–HT relationship in MCA infarction remain scarce, and further validation is needed.

The aim of this study is to evaluate, in patients with acute MCA infarction, the predictive value of clinical comorbidities, radiological characteristics of the infarct, and ASL-derived perfusion metrics for HT development and functional outcome. In doing so, we seek to determine whether ASL imaging can serve as a reliable early indicator of HT in the acute setting and thus enhance clinical decision-making.

METHODS

This retrospective study was conducted based on imaging data obtained from patients who presented to the Emergency Department of Ankara

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Received: 12.06.2025, **Accepted:** 27.06.2025, **Available Online Date:** 30.10.2025

Bilkent City Hospital between February 2020 and December 2020 with a preliminary diagnosis of acute ischemic stroke and were admitted to either the Neurology Ward or the Neurology Intensive Care Unit within the first 24 hours of symptom onset. The study protocol was approved by the Ethics Committee of the Institute of Health Sciences at Ankara Yıldırım Beyazıt University. Due to the retrospective nature of the study, written informed consent forms from previous hospital records were reviewed for each included patient, and no additional consent was required.

The inclusion criteria were as follows: presentation within 24 hours of symptom onset; absence of intracranial hemorrhage on non-contrast cranial CT; availability of both technically adequate diffusion-weighted MRI (DWI) and multiphase CT angiography (mpCTA) sequences obtained during the same admission; age ≥18 years; and availability of complete follow-up imaging data approximately one week later, enabling the evaluation of HT. Exclusion criteria included prior neurosurgical intervention within the first 24 hours; evidence of intracranial hemorrhage on initial imaging; significant motion artifacts on DWI or ASL sequences that hindered interpretation; advanced renal failure (serum creatinine > 2 mg/dL) precluding contrast administration; and technically suboptimal imaging quality. Based on these criteria, retrospective review identified 23 eligible patients: 15 who developed HT and 8 who did not.

All patients underwent a non-contrast cranial CT scan (slice thickness: 0.625 mm) within the first 24 hours following symptom onset. In the absence of hemorrhage, mpCTA was performed before any recanalization procedure. The mpCTA protocol involved the injection of 35 mL of iohexol (350 mg I/mL) at a rate of 4 mL/s via an antecubital vein. The first phase was acquired as a dynamic series (slice thickness: 0.625 mm) from the aortic arch to the vertex within four seconds. The second phase was obtained eight seconds later, with imaging from the skull base to the vertex. The third phase consisted of two-second dynamic series initiated at eight-second intervals. These three phases allowed evaluation of internal carotid artery and M1–M2 segment occlusions.

On average, 6.92 ± 0.58 days after symptom onset, follow-up imaging was performed using 3 Tesla MRI scanners (GE Discovery MR750), including non-contrast CT, DWI, and ASL sequences. The DWI protocol used b-values of 0 and 1000 s/mm², 5 mm slice thickness, and 1 mm interslice gap; ADC maps were generated automatically. ASL images were acquired using a 3D pseudocontinuous (pCASL) technique, with a labeling duration of 1500 ms and post-label delay of 1525 ms. Slice thickness was 4 mm, with an in-plane resolution of 3.5 × 3.5 mm², and 30 label-control image pairs were collected. Head motion was minimized during image acquisition.

Infarct volume was calculated manually on DWI using a free-hand region of interest (ROI) technique. Infarct areas were delineated on each slice, converted to cm² based on voxel dimensions, and multiplied by the slice thickness (6 mm: 5 mm slice + 1 mm gap) to obtain per-slice volume. Summing all slices yielded the baseline infarct volume. The same method was applied to follow-up DWI performed after approximately one week to determine the change in infarct volume.

On ASL-derived CBF maps, ROIs were manually drawn to correspond with infarct regions identified on DWI, and the mean CBF value (mL/100g/min) was calculated. A contralateral ROI was placed on the anatomically symmetric region to derive a control CBF value, which was used to compute the relative CBF (rCBF) as a ratio of infarct-side to contralateral perfusion. The volume of hyperperfusion areas was also measured using manual ROI drawing and reported in cm³.

Highlights

- **CBF in hyperperfused infarct regions significantly predicts HT risk.**
- **Elevated relative CBF on ASL MRI significantly predicts HT risk.**
- **Low Menon collateral scores are strongly associated with HT development.**
- **Larger diffusion MRI infarct volumes markedly increase HT risk.**

Collateral circulation was assessed using the 6-point Menon scoring system based on mpCTA findings (8). This system evaluates the extent and delay of pial arterial filling in the anterior cerebral artery–MCA and posterior cerebral artery–MCA territories on the unaffected hemisphere relative to the ischemic side. A total collateral score between 8–10 was classified as good, 6–7 as moderate, and 0–5 as poor. Hemorrhagic transformation was defined on follow-up non-contrast CT imaging at approximately one week post-event according to the Heidelberg criteria (9).

Demographic characteristics and clinical histories were retrieved from archived medical records. The time of symptom onset or last known well, initial National Institutes of Health Stroke Scale (NIHSS) score, vital signs, and time of neuroimaging were recorded. Functional outcomes were assessed using the modified Rankin Scale (mRS) at 1 and 3 months, and the Barthel Index at 3 months. mRS scores were categorized as favorable (0–2) or unfavorable (3–6). Barthel scores were interpreted as follows: 0–20 (total dependence), 21–61 (severe dependence), 62–90 (moderate dependence), 91–99 (mild dependence), 100 (independent), and deceased (exitus).

Statistical Analyses

All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) for Windows, version 25.0 (IBM Corp., Armonk, NY, USA). The distribution of continuous variables was assessed using the Kolmogorov–Smirnov test. Variables with a normal distribution were expressed as mean ± standard deviation (SD), while those not normally distributed or measured on an ordinal scale were presented as median and range (minimum–maximum). Categorical variables were summarized as absolute frequencies (n) and percentages (%).

For group comparisons, independent samples t-test was used for normally distributed continuous variables between two groups, whereas the Mann–Whitney U test was applied for non-normally distributed or ordinal variables. For categorical data, Fisher's exact test was employed when expected cell frequencies were less than five; otherwise, the chi-square test was used. A two-tailed p-value of less than 0.05 was considered statistically significant for all analyses.

RESULTS

A total of 23 patients presenting with acute MCA syndrome were included in the study. Based on follow-up imaging, patients were categorized into two groups: those who developed HT (n=15) and those who did not (n=8).

Gender distribution was similar between groups, with 62.5% females (n = 5) and 37.5% males (n = 3) in the non-HT group and 53.3% females (n = 8) and 46.7% males (n = 7) in the HT group (p = 1.000). Mean age was 73.37 ± 8.55 years in the non-HT group and 76.64 ± 8.70 years in the HT group, with no significant difference between them (p = 0.423).

Evaluation of comorbidities revealed a history of prior stroke in 25% (n = 2) of non-HT patients and 13.3% (n = 2) in the HT group; diabetes mellitus in 25% (n = 2) and 20% (n = 3), respectively; hypertension in 75% (n = 6) and 73.3% (n = 11); hyperlipidemia in 25% (n = 2) and 40% (n = 6); coronary artery disease in 25% (n = 2) and 6.7% (n = 1); and atrial fibrillation in 0% (n = 0) vs 13.3% (n = 2), respectively.

Use of antithrombotic therapy prior to stroke was 100% in the non-HT group (n = 5 on antiplatelets, n = 3 on anticoagulants) and 60% in the HT group (n = 4 on antiplatelets, n = 5 on anticoagulants). Regarding lifestyle factors, 75% of non-HT patients (n = 6) reported no smoking or alcohol use, while 25% (n = 2) reported both. In contrast, 60% of HT patients (n = 9) reported no use, 33.3% (n = 5) reported smoking only, and 6.7% (n = 1) reported both smoking and alcohol use. Atrial fibrillation on admission ECG was absent in the non-HT group and present in one patient (6.7%) in the HT group. Due to the small number of cases in each subgroup, statistical comparisons for comorbidities and medication history were not performed.

Mean baseline NIHSS scores were 13.75 ± 4.37 (range: 8–19) in the non-HT group and 15.13 ± 3.91 (range: 9–21) in the HT group, with no significant difference (p = 0.446). Mean admission mean arterial pressure (MAP) was 142.00 ± 12.68 mmHg and 146.27 ± 15.34 mmHg, respectively (p = 0.553). Reperfusion therapy was administered to 25% (n = 2) of the non-HT group and 40% (n = 6) of the HT group; however, statistical analysis was not conducted due to the small sample size.

At one-week follow-up, NIHSS scores were 8.25 ± 3.68 (range: 4–14) in the non-HT group and 10.33 ± 4.12 (range: 5–19) in the HT group, without a significant difference (p = 0.210).

Initial infarct volume on diffusion MRI was significantly smaller in the non-HT group (35.25 ± 8.12 cm³) compared to the HT group (47.60 ± 10.35 cm³; p = 0.021). Similarly, follow-up infarct volume at one week remained significantly lower in the non-HT group (32.10 ± 7.68 cm³) versus the HT group (43.80 ± 9.25 cm³; p = 0.046). However, the absolute difference in infarct volume between baseline and follow-up was not significantly different (non-HT: 3.15 ± 1.35 cm³; HT: 3.80 ± 1.50 cm³; p=0.209).

The average day of ASL imaging was 6.89 ± 0.70 in the non-HT group and 6.93 ± 0.53 in the HT group (p = 0.896). Hyperperfused lesion volume did not differ significantly between groups (non-HT: 12.45 ± 4.22 cm³; HT: 12.65 ± 5.10 cm³; p = 0.943). However, mean CBF values in the hyperperfused regions were significantly higher in the non-HT group (62.10 ± 8.15 mL/100 g/min) compared to the HT group (55.25 ± 7.98 mL/100 g/min; p = 0.010).

Ipsilateral MCA region CBF was 38.75 ± 5.30 mL/100 g/min in the non-HT group and 36.90 ± 6.12 mL/100 g/min in the HT group, showing no significant difference (p = 0.366). Contralateral CBF values were similarly comparable (42.50 ± 6.05 vs 41.90 ± 5.85 mL/100 g/min; p = 0.929). The relative CBF (rCBF) was significantly higher in the HT group (0.985 ± 0.062) compared to the non-HT group (0.912 ± 0.055; p = 0.014).

Multiphase CTA-based Menon collateral scores were significantly lower in the HT group (5.33 ± 2.05) compared to the non-HT group (7.25 ± 1.60; p = 0.006), indicating impaired collateral circulation among patients who developed HT.

Table 1. Clinical and Radiological Parameters in Patients With and Without Hemorrhagic Transformation

	HT Present (n=15) Mean ± SD	**HT Absent (n=8) Mean ± SD**	**p-value**
Admission NIHSS	15.13 ± 3.91	13.75 ± 4.37	0.446
NIHSS at the end of 1st Week	10.33 ± 4.12	8.25 ± 3.68	0.210
Menon Collateral Score	5.33 ± 2.05	7.25 ± 1.60	**0.006**
Admission DWI Infarct Volume (cm³)	47.60 ± 10.35	35.25 ± 8.12	**0.021**
DWI Infarct Volume at the end of 1st Week (cm³)	43.80 ± 9.25	32.10 ± 7.68	**0.046**
ASL Hyperperfused Region Volume at the end of 1st Week (cm³)	12.65 ± 5.10	12.45 ± 4.22	0.943
ASL Hyperperfused Region CBF at the end of 1st Week (ml/100 g/min)	55.25 ± 7.98	62.10 ± 8.15	**0.010**
ASL Ipsilateral MCA Territory CBF at the end of 1st Week (ml/100 g/min)	36.90 ± 6.12	38.75 ± 5.30	0.366
ASL Relative CBF (rCBF) at the end of 1st Week	0.985 ± 0.062	0.912 ± 0.055	**0.014**
mRS at the end of 1st Week	3.07 ± 0.80	2.25 ± 0.71	**0.040**
mRS at the end of 1st Month	2.33 ± 0.87	1.50 ± 0.76	**0.028**
mRS at the end of 3rd Month	2.07 ± 0.88	1.38 ± 0.52	**0.044**
Barthel Index at the end of 3rd Month	75.33 ± 10.61	90.00 ± 8.66	**0.036**

ASL: Arterial Spin Labeling; CBF: Cerebral Blood Flow; DWI: Diffusion Weighted Image; HT: Hemorrhagic Transformation; mRS: Modified Rankin Scale; NIHSS: National Institutes of Health Stroke Scale

Functional outcomes were significantly worse in the HT group at all time points. One-week mRS scores were 2.25 ± 0.71 in the non-HT group versus 3.07 ± 0.80 in the HT group (p = 0.040). One-month mRS scores were 1.50 ± 0.76 and 2.33 ± 0.87, respectively (p = 0.028), and three-month mRS scores were 1.38 ± 0.52 versus 2.07 ± 0.88 (p = 0.044). The three-month Barthel Index was also significantly lower in the HT group (75.33 ± 10.61) than in the non-HT group (90.00 ± 8.66; p = 0.036). (Clinical and radiological findings are summarized in detail in Table 1.)

DISCUSSION

In this study, we investigated factors associated with the development of HT in patients followed for acute MCA infarction. Our analysis revealed that both acute and follow-up infarct volumes were significantly larger in patients who developed HT compared to those who did not. These findings align with existing literature suggesting that larger infarct volumes are associated with increased necrotic tissue burden, which in turn elevates vascular permeability and the risk of HT (10,11). Large infarcts often result from occlusions in the main MCA trunk or major branches, and the risk of hemorrhage becomes more pronounced following reperfusion therapy due to the fragility of necrotic tissue. Thus, infarct volume appears to be an important early predictor of HT.

In terms of cerebral perfusion, ASL-derived CBF values showed that both the mean CBF within hyperperfused regions and the relative CBF (rCBF; ipsilateral-to-contralateral ratio) were significantly higher in the HT group. This phenomenon is consistent with the concept of "luxury perfusion," wherein ischemic brain tissue loses its ability to autoregulate following reperfusion (12). When autoregulatory mechanisms fail, excessive perfusion may occur in necrotic or penumbral regions, increasing intravascular pressure and permeability. This process compromises the integrity of the blood–brain barrier, ultimately heightening the risk of HT (13). Therefore, the presence of hyperperfusion and elevated rCBF values on ASL imaging may serve as useful indicators for predicting HT following reperfusion therapy.

Collateral circulation, as assessed by the Menon score on multiphase CTA, was significantly lower in the HT group. This finding corroborates prior studies indicating that poor collateral flow contributes to infarct expansion and increases the likelihood of HT due to insufficient cerebral perfusion (8,14). Particularly in cases with inadequate collateral reserves, failure to salvage the ischemic penumbra may result in more extensive tissue necrosis and increased disruption of the blood–brain barrier, thereby amplifying the risk of hemorrhagic conversion (15). Consequently, the Menon score may hold clinical relevance as a predictive marker of HT during the acute phase of stroke.

With regard to functional outcomes, patients who developed HT had significantly worse scores on both the mRS and the Barthel Index. These results are consistent with earlier reports showing that HT adversely impacts functional recovery (16). By exacerbating neurological injury, HT leads to increased dependence in daily activities and greater overall functional impairment. Thus, the detrimental impact of HT on clinical outcomes underscores its importance in post-stroke rehabilitation planning and long-term prognosis.

Several limitations of this study should be acknowledged. First, its retrospective design limits the ability to establish causal relationships. The relatively small sample size may have reduced statistical power, particularly for subgroup comparisons. Furthermore, functional outcomes such as mRS and Barthel Index scores were partially based on subjective assessments, which may introduce reporting bias. Lastly, as the follow-up period was limited to the early post-stroke phase (three months), long-term outcomes could not be evaluated.

In conclusion, our findings support the clinical utility of infarct volume, ASL-derived perfusion parameters, and the Menon collateral score as predictors of HT in acute MCA infarction. These variables may aid in the early identification of patients at higher risk for hemorrhagic conversion and may also help anticipate functional outcomes. Future prospective studies with larger cohorts are needed to validate these findings and to explore the potential role of ASL imaging in routine stroke management.

Ethics Committee Approval: The research protocol was approved by the Ethics Committee of the Institute of Health Sciences, Ankara Yıldırım Beyazıt University (date: April 17, 2025; approval number: 04/1238).

Peer-review: Externally peer-reviewed.

Author Contributions: Concept- MİY, SB, KE; Design- MİY, SB, KE; Supervision- KE, MİY; Resource- SB, MİY; Materials- SB, MİY; Data Collection and/or Processing- PÇ, MİY; Analysis and/or Interpretation- MİY, PÇ; Literature Search- SB, MİY; Writing- MİY, SB; Critical Reviews- SB, PÇ.

Conflict of Interest: The authors declared that there is no conflict of interest.

Financial Disclosure: None.

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