

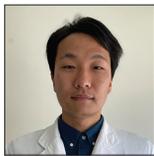
Original Article

## The claw sign predicts first-pass effect in mechanical thrombectomy for cerebral large vessel occlusion in the anterior circulation

Yuki Yamamoto<sup>1</sup>, Nobuaki Yamamoto<sup>1</sup>, Yasuhisa Kanematsu<sup>2</sup>, Izumi Yamaguchi<sup>2</sup>, Manabu Ishihara<sup>2</sup>, Takeshi Miyamoto<sup>2</sup>, Shu Sogabe<sup>2</sup>, Kenji Shimada<sup>2</sup>, Yasushi Takagi<sup>2</sup>, Yuishin Izumi<sup>1</sup>

Departments of <sup>1</sup>Clinical Neuroscience, <sup>2</sup>Neurosurgery, Tokushima University, Tokushima, Japan.

E-mail: \*Yuki Yamamoto - yuki.yamamoto412@gmail.com; Nobuaki Yamamoto - nobuyamamoto521129@gmail.com; Yasuhisa Kanematsu - yasuhisa\_kanematsu@yahoo.co.jp; Izumi Yamaguchi - blond007peace@hotmail.com; Manabu Ishihara - ishihara.manabu.2@tokushima-u.ac.jp; Takeshi Miyamoto - takeshi\_edit@yahoo.co.jp; Shu Sogabe - c200001043@yahoo.co.jp; Kenji Shimada - s\_kenji1032@yahoo.co.jp; Yasushi Takagi - ytakagi@tokushima-u.ac.jp; Yuishin Izumi - yizumi@tokushima-u.ac.jp



**\*Corresponding author:**

Yuki Yamamoto,  
Department of Clinical  
Neuroscience, Tokushima  
University, Tokushima, Japan.

yuki.yamamoto412@gmail.com

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### ABSTRACT

**Background:** Mechanical thrombectomy (MT) is an effective treatment for acute cerebral large vessel occlusion (LVO). Complete recanalization of vessels in a single procedure is defined as the first-pass effect (FPE) and is associated with good prognosis. In this study, angiographic clot protruding sign termed the “claw sign,” was examined as candidate preoperative imaging factor for predicting the FPE.

**Methods:** We retrospectively analyzed data from 91 consecutive patients treated for acute LVO in the anterior circulation by MT between January 2014 and December 2019. The claw sign was defined as a thrombus that protruded proximally by more than half of the diameter of the parent artery. Radiological findings such as claw sign, clinical and etiological features, and outcomes were compared between groups with and without successful FPE. Multivariate analysis was conducted to evaluate perioperative factors associated with FPE.

**Results:** FPE was achieved in 26 of 91 (28.6%) patients and the claw sign was observed in 34 of 91 (37.4%) patients. The claw sign was significantly more frequent in the successful FPE group than in the failed FPE group (53.8% vs. 30.8%;  $P = 0.040$ ). After the multivariate analysis, the claw sign was the only pretreatment parameter that could predict FPE (odds ratio, 2.67; 95% confidence interval, 1.01–7.06;  $P = 0.047$ ).

**Conclusion:** The claw sign is an angiographic imaging factor that might predict FPE after MT for anterior circulation acute ischemic stroke.

**Keywords:** Acute ischemic stroke, Angiography, Claw sign, First pass, Mechanical thrombectomy

### INTRODUCTION

As a result of recent major clinical trials, mechanical thrombectomy (MT) has been established as the standard treatment in patients with acute intracranial large vessel occlusion (LVO).<sup>[1,2]</sup> In recent years, achieving complete recanalization with a single procedure that does not require additional treatment has been defined as the first-pass effect (FPE) and has been shown to be associated with good functional prognosis.<sup>[2,25]</sup> FPE is considered to lead to good prognosis by

reducing procedural time and periprocedural complications such as arterial endothelial injury. FPE is currently the best angiographic goal in MT, and several procedural techniques are being developed to achieve it.<sup>[10,18,21]</sup>

Zaidat *et al.* reported that FPE was more likely to be obtained in cases with balloon guide catheter use and noninternal carotid artery (ICA) occlusion.<sup>[25]</sup> However, there have been few subsequent reports on preoperative factors that predict FPE. Intraprocedural angiographic morphological characteristics of the clot at the occlusion site have been the focus of attention in recent years.<sup>[16]</sup> Proximal protrusions of the thrombus, called the claw sign<sup>[24]</sup> or clot meniscus sign,<sup>[4]</sup> have been known to be useful in predicting recanalization and stroke subtype. The aim of this study was, thus, to investigate whether perioperative imaging findings, including claw sign, are predictive of FPE in patients with anterior circulation LVO treated by MT.

## MATERIALS AND METHODS

### Study design and data collection

We retrospectively examined 130 consecutive patients who underwent MT at our hospital from January 2014 to December 2019. During this period, 121 cases were treated for acute intracranial LVO in the ICA or proximal portion of the middle cerebral artery (MCA M1-2). After excluding patients with tandem occlusion and extensive infarction defined as Alberta Stroke Program Early Computed Tomography (CT) Score <6 on diffusion-weighted imaging, 91 patients were finally analyzed [Figure 1]. Vascular risk factors were recorded for each patient and defined as follows: (1) hypertension: a history of antihypertensive drug use, a systolic blood pressure of  $\geq 140$  mmHg, or a diastolic blood

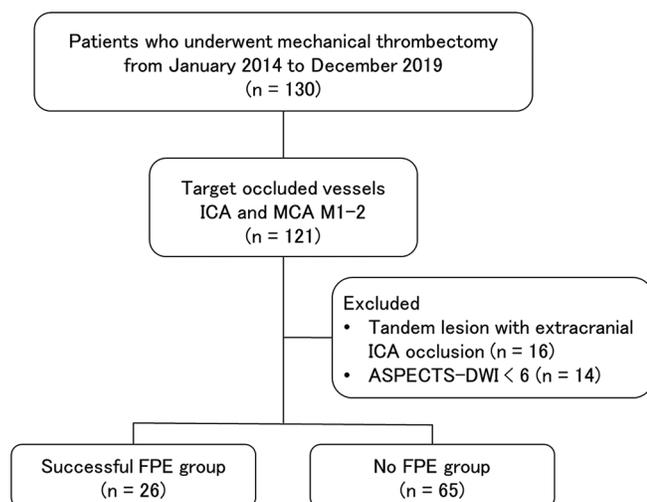
pressure of  $\geq 90$  mmHg at hospital discharge; (2) diabetes mellitus: current hypoglycemic drug use, a random glucose level of  $\geq 200$  mg/dL, or a glycosylated hemoglobin level of  $\geq 6.5\%$  at the time of admission.

Diagnosis of acute cerebral LVO was performed using magnetic resonance imaging (MRI). MT was performed either alone or with intravenous recombinant tissue plasminogen activator (IV-TPA), depending on the adaptation. According to our institutional protocol, patients with eligibility for IV-TPA were administered this at a dose of 0.6 mg/kg within 4.5 h of onset.<sup>[22]</sup> Either a stent retriever or aspiration catheter, or both, was used for MT by the choice of the operator. Balloon guiding catheters were used in all cases. After the procedure, recanalization results were assessed according to the modified Thrombolysis in Cerebral Infarction (mTICI) grading scale. In this study, FPE was defined as the achievement of mTICI 2c or 3<sup>[9]</sup> with a single procedure pass regardless of device type, such as stent retriever, direct aspiration, or combination of them. Functional outcome was evaluated using the modified Rankin scale (mRS) scores at 90 days after onset. Additional clinical outcomes included National Institute of Health Stroke Scale (NIHSS) at discharge, hospitalization days. Symptomatic intracranial hemorrhage (ICH) was classified according to the second European-Australasian Acute Stroke Study classification,<sup>[13]</sup> as any ICH with an increase of NIHSS  $\geq 4$  within 24 h.

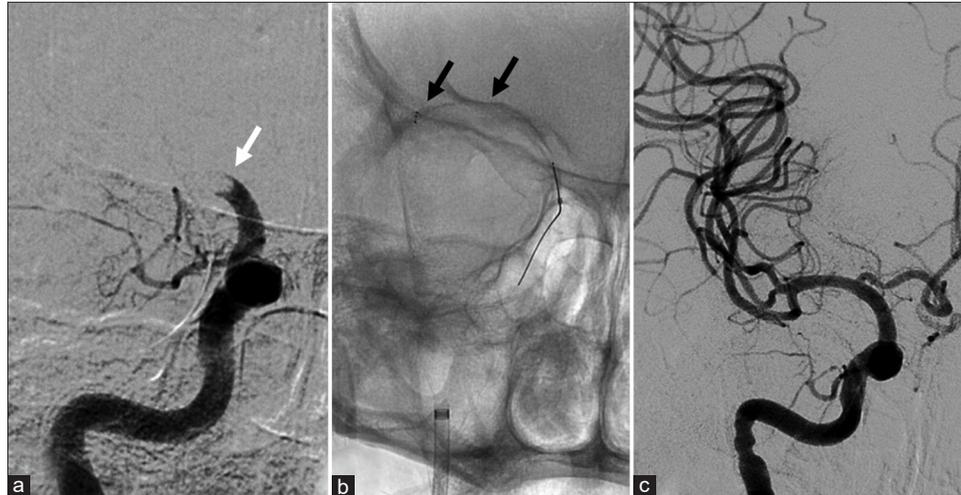
Susceptibility vessel sign (SVS), two-layered SVS (TL-SVS), and claw sign were selected as candidates for perioperative imaging factors that predict FPE. SVS was defined as a hypointense signal exceeding the size of the contralateral arterial diameter on MRI T2\*-weighted image in a vessel cistern. TL-SVS was defined as SVS with a low-intensity core and higher intensity signal around the core.<sup>[5,23]</sup> The claw sign was defined as a contrast morphology of the occlusion site in which a convexity protruded to the proximal side with a protrusion length that was more than half of the arterial vessel diameter<sup>[24]</sup> [Figures 2 and 3]. The claw sign was considered positive if it was observed in either the anterior-posterior or lateral views on digital subtraction angiography (DSA), using a biplane Philips AlluraClarity machine (Philips Healthcare, Best, the Netherlands). All imaging findings were retrospectively evaluated by a neurologist who was not informed of other patient information.

### Statistical analyses

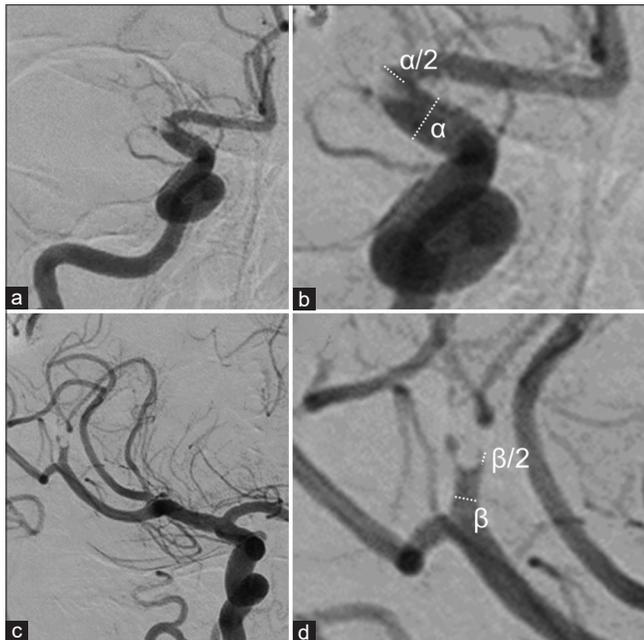
Results are expressed as means  $\pm$  standard deviations or as medians (minimum-maximum) for quantitative variables and as count and percentages for categorical variables. Univariate analyses were performed with the Mann-Whitney U-test for continuous or ordinal variables and the  $\chi^2$  test for categorical variables. A one-way analysis of variance was used to compare the difference of variables



**Figure 1:** Study flowchart. ASPECTS-DWI: Alberta Stroke Program Early CT Score on diffusion-weighted imaging, FPE: First-pass effect, ICA: Internal carotid artery, MCA: Middle cerebral artery.



**Figure 2:** Positive case of claw sign. A 91-year-old man with the right internal carotid artery (ICA) occlusion. (a) Angiography reveals proximal protrusion of the thrombus (white arrow) at the terminus of ICA. (b) After lesion passing through a microcatheter, stent retriever (black arrows) (Solitaire 2, Medtronic, Dublin, Ireland) is deployed. (c) After retrieving of stent, angiography shows complete recanalization of ICA.



**Figure 3:** Angiograms with the claw sign. (a) A case of proximal middle cerebral artery occlusion. (b) The thrombus protrudes proximally by more than half of the diameter of vessel. (c) A case of middle cerebral artery M2 occlusion. (d) The thrombus protrudes proximally by more than half of the diameter of vessel.

among the three groups (the Bonferroni correction was used as *post hoc* analysis). All statistical tests were two sided, and the significance ( $P$ ) level was set at 0.05. Multivariate analysis was performed including non-ICA terminus occlusion as a known FPE predictor and preoperative factors with  $P < 0.05$  obtained by univariate analysis. All statistical analyses were performed with SPSS 26.0 (IBM, Armonk, New York).

## RESULTS

### Basic characteristics and clinical outcomes

We included and analyzed data from 91 consecutive patients (50 females; mean age:  $75.6 \pm 11.0$  years). The baseline characteristics of patients are summarized in Table 1. Overall, 28.1% (26/91) achieved FPE. Comparing the groups with and without FPE, female sex (73.1% vs. 47.7%;  $P = 0.028$ ), not smoking (80.8% vs. 58.5%;  $P = 0.044$ ), and the presence of claw sign (53.8% vs. 30.8%;  $P = 0.040$ ) were significantly observed more often in the successful FPE group. The claw sign was positive in 37.4% (34/91) of all patients. Of these positive cases, 41.2% (14/34) of successful FPE cases and 88.2% (30/34) of final recanalization (mTICI  $>2b$ ) were observed. There were no differences between the two groups in the presence of SVS and TL-SVS.

Procedural outcomes significantly demonstrated a smaller number of passes (median, 1 vs. 2;  $P < 0.01$ ) and shorter puncture to reperfusion time (33 min vs. 76 min;  $P < 0.01$ ) in the FPE group. Clinical outcomes showed a lower NIHSS at discharge (median, 0 vs. 8;  $P < 0.01$ ) and a better mRS score at 90 days after onset (mRS 0–1, 57.7% vs. 29.2%;  $P = 0.11$ ) in the FPE group [Table 2].

### Predictors of FPE

The multivariate analysis included non-ICA terminus occlusion as a known FPE predictor and the preoperative factors (presence of claw sign, female sex, and not smoking) for which there were significant differences identified in the univariate analysis [Table 3]. Only the presence of claw sign was significantly associated with successful FPE, with an odds ratio of 2.67 (95% CI = 1.01–7.06;  $P = 0.047$ ).

**Table 1:** Baseline characteristics.

	Successful FPE (n=26) (%)	No FPE (n=65) (%)	P
Age, years	77.9±9.1	74.6±11.7	0.21
Sex, female	19 (73.1)	31 (47.7)	0.028*
Past ischemic stroke	6 (23.1)	16 (24.6)	0.88
Coronary artery disease	5 (19.2)	11 (16.9)	0.77
Hypertension	18 (69.2)	33 (50.8)	0.11
Diabetes mellitus	5 (19.2)	15 (23.1)	0.69
Not smoking	21 (80.8)	38 (58.5)	0.044*
Atrial fibrillation on the ECG	12 (46.2)	25 (38.5)	0.50
Baseline mRS score	0 (0-5)	0 (0-5)	0.40
Systolic blood pressure, mmHg	153±27	153±32	0.98
Diastolic blood pressure, mmHg	89±16	84±19	0.32
Heart rate,/min	88±22	80±20	0.10
NIHSS on admission	13.5 (2–31)	17 (2–35)	0.48
IV-TPA	12 (46.2)	32 (49.2)	0.79
ASPECTS-DWI	8.5 (6–11)	9 (6–11)	0.69
TL-SVS	12 (46.2)	21 (32.3)	0.22
SVS	15 (57.7)	29 (44.6)	0.26
Claw sign	14 (53.8)	20 (30.8)	0.040*
Occlusion vessel			
ICA	9 (34.6)	26 (40.0)	0.88
MCA M1	13 (50.0)	29 (44.6)	
MCA M2	4 (15.4)	10 (15.4)	

ASPECTS-DWI: Alberta Stroke Program Early CT Score on diffusion-weighted imaging, ECG: Electrocardiogram, FPE: First-pass effect, ICA: Internal carotid artery, IV-TPA: Intravenous recombinant tissue plasminogen activator, NIHSS: National Institutes of Health Stroke Scale, MCA: Middle cerebral artery, mRS: Modified Rankin scale, SVS: Susceptibility vessel sign, TL-SVS: Two-layered susceptibility vessel sign

## DISCUSSION

In this study, we selected SVS, TL-SVS, and claw sign as imaging candidates to predict FPE after MT for anterior circulation acute ischemic stroke. Univariate analysis showed that female sex, not smoking, and the presence of claw sign were significantly more frequently seen in the successful FPE group. From multivariate analysis in which non-ICA occlusion was added to these three factors, claw sign emerged as an independent predictor of FPE with an odds ratio of 2.67.

In recent years, several studies have described the morphological characteristics of clots observed on angiography during MT<sup>[3,4,11,19,24]</sup> [Table 4]. Baik *et al.* examined 89 patients who underwent MT for acute basilar artery occlusion and reported a clot meniscus sign in 62.9%, with a higher successful recanalization rate (89.3%) and successful FPE rate (32.1%) in the clot meniscus sign-positive group than in the negative group.<sup>[4]</sup> The judgment of the clot meniscus sign is based on the macroscopic subjectivity, the definition of claw sign uses a proximal protrusion of more than half of the diameter of the mother vessel as an objective index. There are small differences, however, both can be considered equivalent in essence. In our study, successful recanalization rate (88.1%) and successful FPE rate (41.2%) in the claw sign-positive group

were similarly high, and the positive claw sign may be used as a predictor of procedural success. By contrast, the positive rate of claw sign in this study was 41.2%, which is lower than that in the previous report. One reason may be the difference in target occlusion vessels, including the ICA and MCA M1-2. When evaluating the clot morphology, it is necessary to observe the longitudinal axis of the target vessel from the lateral direction. This may cause false negatives when detecting the claw sign in tortuous vessels like the terminal ICA. The basilar artery, which runs along the craniocaudal axis of the body, can be observed in both anterior-posterior and lateral images of DSA, while the MCA M1 is usually observed only in anterior-posterior images. Although claw sign is a useful predictor of FPE, its detection requires evaluation of the occluded vessel from an appropriate angle.

Consoli *et al.* classified the morphological phenotype of the occlusion site in the M1 segment of the MCA into regular and irregular.<sup>[7]</sup> Baik *et al.* reported that contact aspiration showed higher complete recanalization rates compared with a stent retriever in patients with the clot meniscus sign.<sup>[3]</sup> These suggests that selecting treatment devices depending on the morphological features of the clot may improve recanalization rate and patients' clinical outcomes. In our study, there was no difference in FPE

**Table 2:** Clinical outcomes.

	Successful FPE (n=26) (%)	No FPE (n=65) (%)	P
Number of passes	1 (1-1)	2 (2-6)	<0.01*
mTICI grade			
0	0 (0.0)	4 (6.2)	<0.01*
1	0 (0.0)	3 (4.6)	
2a	0 (0.0)	10 (15.4)	
2b	0 (0.0)	23 (35.4)	
2c	3 (11.5)	5 (7.7)	
3	23 (88.5)	20 (30.8)	
Onset to puncture time, min	228 (60-945)	235 (85-1135)	0.30
Puncture to reperfusion time, min	33 (13-105)	76 (22-160)	<0.01*
Device for the first pass			
Combination	6 (23.1)	11 (16.9)	0.34
Direct aspiration	8 (30.8)	31 (47.7)	
Stent retriever	12 (46.2)	23 (35.4)	
Etiology			
Cerebral embolism	20 (76.9)	43 (66.2)	0.22
Large artery atherosclerosis	2 (7.7)	15 (23.1)	
Others	4 (15.4)	7 (10.8)	
ICAD	0 (0.0)	16 (24.6)	0.004*
sICH	0 (0.0)	3 (4.6)	0.56
Hospital days	14.5 (4-30)	15 (2-36)	0.83
NIHSS at discharge	0 (0-13)	8 (0-42)	<0.01*
mRS score of 0-2 at 90 days	15 (57.7)	19 (29.2)	0.011*

FPE: First-pass effect, ICAD: Intracranial atherosclerotic disease, NIHSS: National Institutes of Health Stroke Scale, mRS: Modified Rankin scale, mTICI: Modified thrombolysis in cerebral infarction, sICH: Symptomatic intracerebral hemorrhage

**Table 3:** Multivariate analysis of predictors for FPE.

	Odds ratio	95% CI	P
Positive claw sign	2.67	1.01-7.06	0.047*
Sex, female	2.39	0.62-9.20	0.21
Not smoking	1.56	0.37-6.63	0.55
Not ICAO	0.97	0.35-2.71	0.95

CI: Confidence interval, ICAO: Internal carotid artery occlusion

achievement depending on the device used in the first pass; however, this was a retrospective study, and the procedure was not performed in the same manner in all patients. Recently, the usefulness of a combination technique using both a stent retriever and aspiration catheter has also been reported for successful FPE.<sup>[4,6]</sup> Further research is needed to investigate the relationship between the morphological

features of the clot and treatment outcome of each thrombectomy device.

Yamamoto *et al.* investigated 73 patients who underwent MT for ICA, MCA M1-2, and VA-BA occlusion and found claw sign in 29 patients (40.0%). It was also reported that infarction with an embolic mechanism was more frequent (93.1% vs. 72.7%) in the claw sign-positive group than in the -negative group.<sup>[24]</sup> It is thought that one of the reasons for the formation of the claw sign is that the shape of the spherical embolus is projected by contrast medium. In this study, claw sign was found in 3 of 16 cases (19%) that were finally diagnosed with intracranial atherosclerotic disease (ICAD) as the cause of acute LVO. In the previous reports, there is evidence that angiographic tapered appearance more frequently indicate ICAD.<sup>[11]</sup> However, in acute exacerbations of ICAD, *in situ* thrombi cause acute vessel occlusion,<sup>[14]</sup> in which case, the morphology of the occlusion site may appear to protrude proximally. LVO from ICAD sometimes requires adjunctive treatments such as balloon angioplasty and stenting, which can lead to complexity, longer procedure times, and poorer clinical outcomes.<sup>[1]</sup> Using angiographic findings alongside, the findings of other imaging modalities may be effective for early identification of ICAD; however, this needs to be assessed further in the future studies.

SVS is a hypointense signal exceeding the diameter of the contralateral artery on MRI T2\*-gradient echo imaging sequences.<sup>[17]</sup> TL-SVS has been reported to more specifically predict cardioembolism.<sup>[5,23]</sup> Positive SVS has been reported to be associated with FPE and has a good short-term prognosis,<sup>[8]</sup> while others report that SVS and FPE are not related.<sup>[6,15,20]</sup> In this study, no significant correlation was found between SVS/TL-SVS and FPE. However, the presence or absence of SVS provides us with information on thrombotic properties. SVS is observed when red blood cell dominant clots are present, whereas a lack of SVS is indicative of clots with a higher fibrin content.<sup>[17]</sup> The recanalization rate of the MT using stent retriever alone is reported to be better for SVS-positive clots than SVS-negative clots.<sup>[6]</sup> Combining morphological features such as claw sign with information on thrombotic properties may allow for more effective treatment choices.

There are some potential limitations of this study. First, this study was performed in a single center and followed a retrospective design. Further investigations are needed with a larger sample size to validate our results. The procedure technique and the devices were not unified in advance and were left to the operator. Finally, in some cases, the proximal end of the thrombus might not be accurately evaluated due to tortuous nature of the vessels or inadequate contrast injection.

**Table 4:** Predictive studies of mechanical thrombectomy by angiographic appearance of thrombus.

Study	Clot signs	Definition of clot signs	Number of patients	Occlusion vessels	Predictive outcomes of procedure	Other predictive meanings
Garcia-Bermejo, 2019	Tapered	No definition: two neurointerventionists retrogradely reviewed	131	ICA, MCA M1-2, ACA, and VA/BA	No differences in reperfusion rates	Intracranial atherosclerosis etiology
Yamamoto, 2019	Claw	A convexity protruded to the proximal side with a protrusion length that was more than half of the arterial vessel diameter	73	ICA, MCA M1-2, and VA/BA	mTICI 2b or 3	Occlusions due to embolic thrombus
Baik, 2020	Meniscus	Meniscoid/edge-like appearance at the proximal occlusion site, or tram-track-like appearance/antegrade side wall contrast opacification distal to thrombus	89	BA	FPE	
Baik, 2021	Meniscus	Same as above	161	BA	Higher complete recanalization rate with contact aspiration compared to stent retriever	
Mönch, 2021	Cutoff, tapered, and meniscus/tram-track	Cutoff: a well-demarcated line between the contrast-opacified antegrade blood flow and the occluded downstream arteries with no opacity	144	MCA M1-2	Higher number of maneuvers in the cutoff cohort	
The present study	Claw	Same as above	91	ICA and MCA M1-2	FPE	

ACA: Anterior cerebral artery, BA: Basilar artery, FPE: First-pass effect, ICA: Internal carotid artery, MCA: Middle cerebral artery, mTICI: Modified thrombolysis in cerebral infarction, VA: Vertebral artery

## CONCLUSION

The claw sign is an angiographic imaging factor that predicts FPE after MT for anterior circulation acute ischemic stroke. Angiographical clot protruding features at the occlusion site can predict treatment outcomes and stroke subtypes and may be useful in the future for procedure and device selection.

## Ethics approval and consent to participate

The study protocol was approved by the local research ethics committee and consent for publication was obtained from all participants.

## Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

## Financial support and sponsorship

Nil.

## Conflicts of interest

There are no conflicts of interest.

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