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Role of Favorable Perfusion Imaging in Predicting the Outcome of Patients with Acute Ischemic Stroke due to Large Vessel Occlusion Undergoing Effective Thrombectomy: A Single-Center Study

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Keywords
Ischemic stroke · Perfusion CT · Thrombectomy · Modified Rankin Scale · Outcome

Abstract
Introduction: We sought to verify the predicting role of a favorable profile on computed tomography perfusion (CTP) in the outcome of patients with acute ischemic stroke (AIS) due to large vessel occlusion (LVO) undergoing effective mechanical thrombectomy (MT). ***Methods:*** We retrospectively enrolled 25 patients with AIS due to LVO and with a CTP study showing the presence of ischemic penumbra who underwent effective MT, regardless of the time of onset. The controls were 25 AIS patients with overlapping demographics and clinical and computed tomography angiography features at admission who had undergone successful MT within 6 h from onset and without a previous CTP study. The outcome measure was the modified Rankin Scale (mRS) score at 90 days. ***Results:*** Sixty-four percent of the study patients had an mRS score of 0–1 at 90 days versus 12% of the control patients ($p < 0.001$). Patients of the study group had a more favorable distribution of disability scores (median mRS [IQR] score of 0 [0–2] vs. 2 [2–3]). Multivariate analysis showed that the selection of patients based on a favorable CTP study was strongly associated ($p < 0.001$) with a better neurological outcome. ***Conclusions:*** In our small-sized and retrospective study, the presence of ischemic penumbra was associated with a better clinical outcome in patients with AIS due to LVO after MT. In the future, a larger and controlled study with similar criteria of enrollment is needed to further validate the role of CTP in patient selection for MT, regardless of the time from the onset of symptoms.

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Introduction

Treatment of acute ischemic stroke (AIS) is based on the timely restoration of blood flow to the ischemic brain tissue by intravenous thrombolysis (IVT) and/or mechanical thrombectomy (MT). Eligibility to treatment is

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based on the time from onset of symptoms, that is up to 4.5 h for IVT and 6 h for MT in AIS due to large vessel occlusion (LVO) [1–4]. These time boundaries were established after the results of randomized clinical trials where the presence of salvageable brain tissue (the so-called ischemic penumbra [5, 6]) was not considered. More recent studies have shown the effectiveness of recanalization therapies in patients selected based on the presence of ischemic penumbra even beyond the current time limits and using dedicated contrast-based computed tomography (CT) or magnetic resonance imaging (MRI) protocols [7–11]. CT perfusion (CTP) appears the most practicable neuroimaging protocol to outline the infarct tissue and the ischemic penumbra in the setting of AIS management, in comparison to MRI, which requires a longer time and complete patient cooperation [12, 13]. We sought to verify whether the selection of AIS patients based on a favorable CTP profile is associated, after successful MT, with a better clinical outcome than the simple time-based selection.

Methods

This is a retrospective observational single-center study conducted at our high-volume tertiary stroke center that enrolled 2 cohorts of AIS patients from January 2016 to December 2019. Patients with LVO in the anterior circulation and CTP showing the presence of ischemic penumbra who had undergone effective MT were selected and compared for outcome measures to matched control patients who had undergone successful MT without being subjected to CTP. The present study was approved by the local Ethics Committee.

Patient Selection

Study patients were retrospectively selected according to the following criteria: (1) being at least 18 years of age; (2) first-ever stroke; (3) a pre-event modified Rankin Scale (mRS) score of 0; (4) AIS due to the occlusion of internal carotid artery (ICA) and/or middle cerebral artery (MCA), tract M1-M2, diagnosed using CT angiography (CTA); (5) CTP showing the presence of ischemic penumbra; (6) had received successful MT, either preceded or not by IVT. An equal number of control patients were then retrospectively selected among those with AIS due to LVO that were not subjected to CTP and met the following criteria: (1) having baseline demographic, clinical, and CTA features similar to those of study patients; (2) had received successful MT, either preceded or not by IVT. A flow diagram of patient selection is provided in Figure 1a. Experienced stroke physicians collected clinical data from a dedicated database.

Imaging Analysis

The CT protocol included; (1) a basal scan with assessment of early ischemic changes using the Alberta Stroke Program Early CT score (ASPECT) [14], followed by (2) multiphase CTA, and (3) CTP. For CTP, 50 mL of iodinated contrast (370 mgI/mL) were power-injected at a rate of 4.5 mL/s followed by a saline flush of 50 mL at 5 mL/s. The protocol included 2 phases (scan type: axial-shuttle; slice thickness: 5 mm; kV: 80; mA: 200; rotation time: 0.5 s): the first phase, starting 5 s after contrast injection of 22 repeated acquisitions on the same 8-cm section (total scan duration: 60.6 s) and the second performed after 15 s and consisting of 1 acquisition on the same section (total scan duration: 15 s). CT images were processed using delay-insensitive deconvolution software (CT Perfusion 4D; GE Healthcare, Waukesha, WI). Absolute maps of T_{max} (seconds) were obtained by the deconvolution of tissue time-density curves. The T_{max} maps were post-processed using 2 different thresholds: (1) between 16 and 25 s for the ischemic core ($T_{16–25smax}$), and (2) between 9.5 and 25 s for the hypoperfused area ($T_{9.5–25smax}$), as previously described [15]. The areas with altered perfusion on different maps were manually outlined to obtain $T_{16–25smax}$ and $T_{9.5–25smax}$ volumes and to calculate the core-penumbra mismatch (Fig. 1b). For the selection of patients, we considered an initial infarct volume ≤70 mL and a ratio of the volume of ischemic tissue to infarct volume ≥1.8, as previously described [8]. An experienced neuroradiologist blinded to clinical outcome retrospectively reviewed the diagnostic radiological data of all patients.

Recanalization Procedure

The treatment strategy (stent-retriever vs. thromboaspiration or a combination of both) was at the discretion of the treating neurointerventionist. Flow restoration at the end of each procedure was graded by the neurointerventionist using the modified Treatment In Cerebral Infarction (mTICI) scale [16]. All patients of both groups had a flow restoration score of 2b–3, corresponding to almost complete (2b) or complete (3) recanalization. Angiographic data of all patients were reviewed by an experienced neurointerventional radiologist blinded to the clinical outcome. No procedural complications were recorded.

Clinical Assessment and Outcome

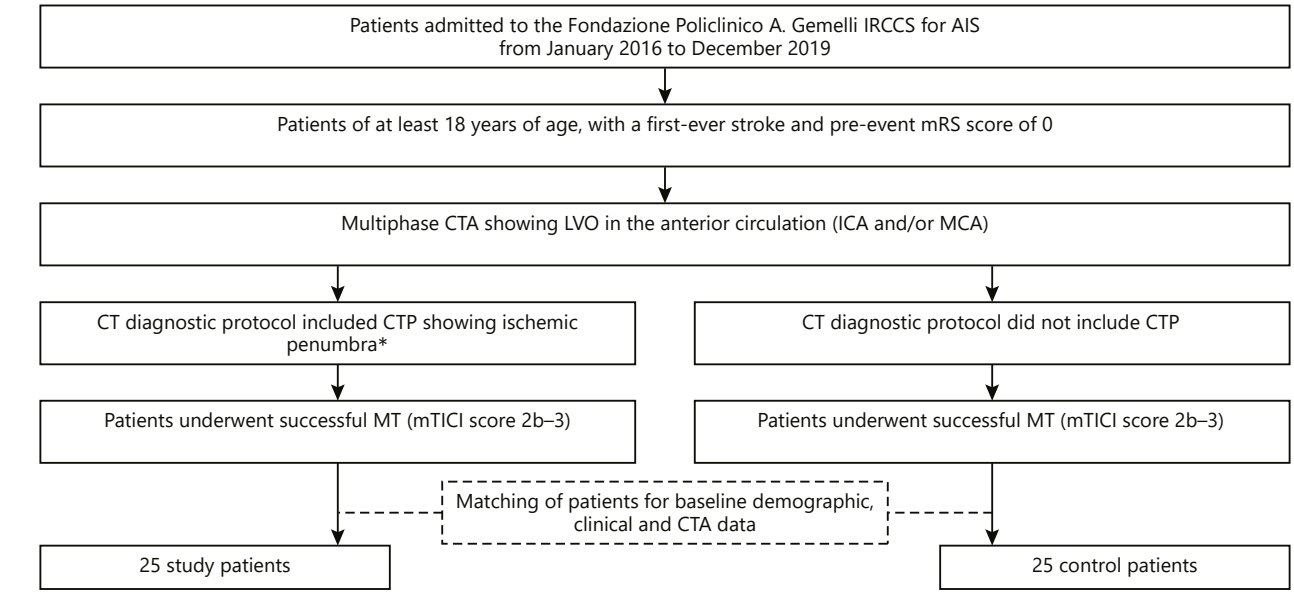
Stroke severity at admission was assessed using the National Institute of Health Stroke Scale (NIHSS). The primary outcome measure was an mRS score of 0–1 (excellent functional outcome) at 90 days, assessed through a structural interview, either in person or on the telephone. Safety outcomes were: (1) brain bleeding events following recanalization therapies, assessed by CT or MRI scan at 72 h and classified using the ECASS II criteria [17], and (2) death within 90 days after stroke. For our analysis we included demographic data (age and sex), cardiovascular risk factors (hypertension, diabetes, atrial fibrillation), and previous antithrombotic therapy.

Statistical Analysis

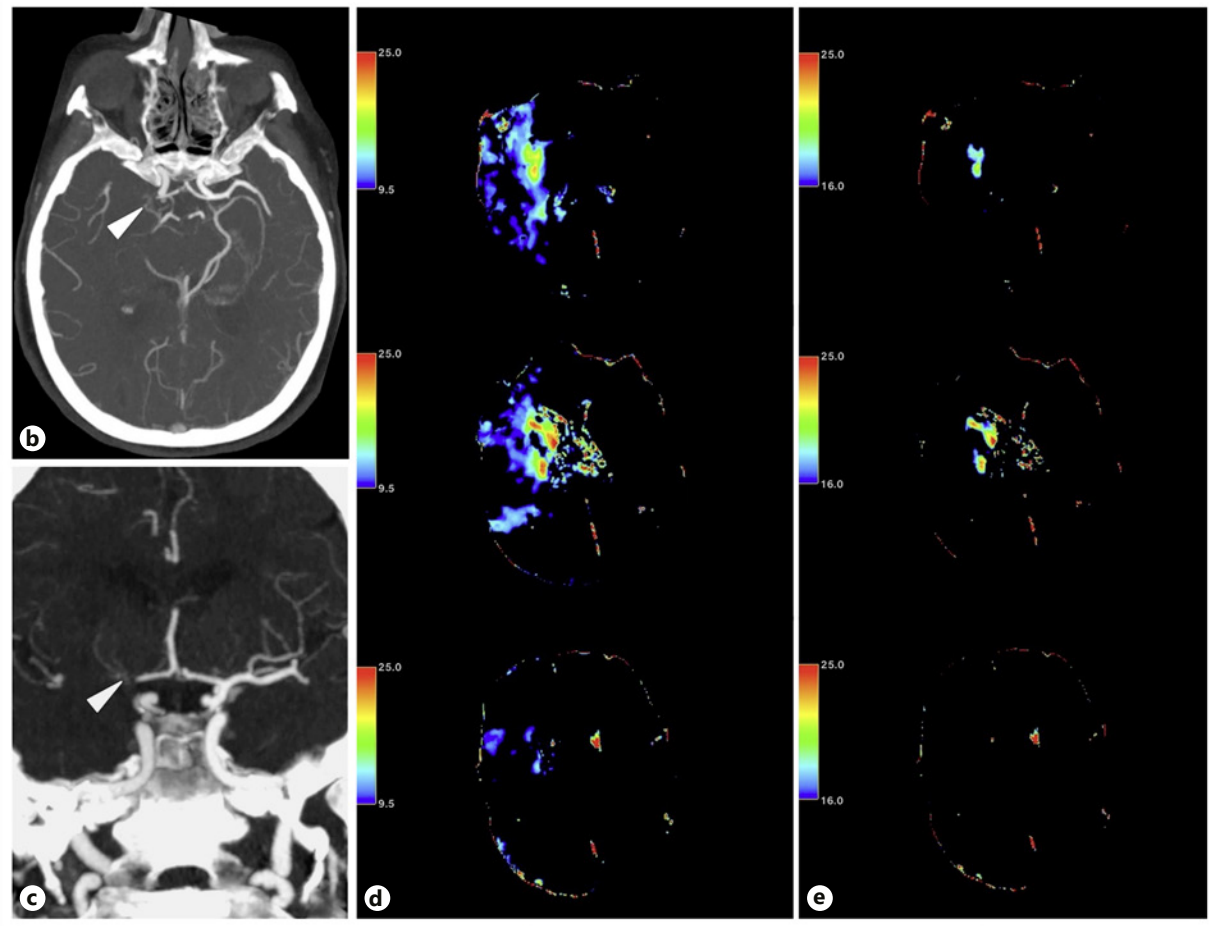
We described the general characteristics of the population with summary statistics and used the Mann-Whitney U test and Pearson χ^2, as appropriate, to test differences between the 2 groups. For data not normally distributed the median and interquartile range (IQR)

Fig. 1. a Flow diagram of patient selection. * Initial infarct volume ≤70 mL and a ratio of the volume of ischemic tissue to infarct volume ≥1.8. **b–e** Representative case of a study patient. Axial (**b**) and coronal (**c**) CTA multiplanar reconstruction demonstrating ICA terminus occlusion (arrowheads). CTP shows a large area of penumbra involving the right cerebral hemisphere ($T_{9–25smax}$, **d**), with a relatively small ischemic core ($T_{16–25smax}$, **e**).

(For figure see next page.)


Patients admitted to the Fondazione Policlinico A. Gemelli IRCCS for AIS from January 2016 to December 2019
Patients of at least 18 years of age, with a first-ever stroke and pre-event mRS score of 0
Multiphase CTA showing LVO in the anterior circulation (ICA and/or MCA)
CT diagnostic protocol included CTP showing ischemic penumbra*
CT diagnostic protocol did not include CTP
Patients underwent successful MT (mTICI score 2b–3)
Patients underwent successful MT (mTICI score 2b–3)
Matching of patients for baseline demographic, clinical and CTA data
25 study patients
25 control patients

a


b
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25.0
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1

Table 1. Patient data

	Study patients (n = 25)	Control patients (n = 25)
Female/male	14/11	14/11
Age, years,	74 (68–81)	74 (68–80)
Atrial fibrillation	13 (52)	13 (52)
Diabetes	4 (16)	4 (16)
Hypertension	4 (16)	4 (16)
Previous antiplatelet therapy	3 (12)	9 (36)
Previous anticoagulant therapy	9 (36)	9 (36)
NIHSS score at admission	13 (10–18)	13 (10–18)
ASPECT score at admission	8 (7–9)	9 (8–10)
Site of arterial occlusion		
ICA	5 (20)	2 (8)
MCA (including MCA + ICA)	20 (80)	23 (92)
CTP study	Performed	Not performed
Infarct core volume shown by CTP analysis, cm^3	10.6 (1.9–33.2)	Not available
Mismatch volume shown by CTP analysis, cm^3	59.2 (42.2–76.6)	Not available
Ratio of ischemic tissue volume to infarct volume	3.8 (2.6–7)	Not available
Intravenous thrombolysis	7 (28)	8 (32)
Onset-to-groin time		
≤6 h	6 (24)	25 (100)
≥6 h	12 (48)	None
Minutes	480±180	Not available
Unknown onset-to-groin time (wake-up stroke)	7 (28)	None
mTICI score 2b-3, %	100	100

Data are presented as n (%), the median (IQR), or the mean ± SD. NIHSS, National Institute of Health Stroke Scale; ASPECT, Alberta Stroke Program Early CT score; ICA, internal carotid artery; MCA, middle cerebral artery; CTP, computed tomography perfusion; mTICI, modified treatment in cerebral infarction.

were calculated. We therefore evaluated univariate associations between groups of patients with a favorable or unfavorable outcome at 90 days, respectively. A multivariate analysis was performed with a logistic regression model using a favorable functional outcome (mRS score 0–1) as the dependent variable. Despite age and sex, only the variables with a p value ≤0.1 in the univariate analysis were included in the multivariate model. The significance threshold was set at 5%. Statistical analysis was performed with SPSS version 25 (IBM).

Results

Twenty-five patients with AIS due to occlusion of ICA and/or MCA and a favorable CTP profile were retrospectively selected. Because in our stroke center a CTP protocol has been adopted as an eligibility criterion for MT in patients admitted between 6 and 24 h from onset or with undetermined onset according to current guidelines [18], the majority of study patients had been treated beyond the 6-h time window. On the contrary, the 25 AIS control patients, selected to match the study patients for demographics and baseline clinical and CTA features, were eligible for MT on the basis of the time-from-onset criterion and therefore CTP had not been performed. All relevant data of the patients included in this study are reported in Table 1. IVT was always performed within 4.5 h from onset either in our hospital or in a spoke hospital that later referred the patient for MT.

The percentage of patients with an mRS score of 0–1 at 90 days was 64% in the study group (16 patients) and 12% in the control group (3 patients; $p < 0.001$). Dichotomization of mRS scores of 0–2 (functional independence) versus 3–6 (poor outcome) showed a higher rate of favorable outcomes in study patients compared to the control patients (72 vs. 56%, respectively); however, this was below the significance threshold ($p = 0.051$; Fig. 2). Overall, study patients had a more favorable distribution of disability scores with a median (IQR) mRS score of 0 (0–3) vs. 2 (2–3) for controls ($p = 0.019$). The rate of non-symptomatic hemorrhagic transformation of the ischemic brain tissues was higher in the study group than in con-

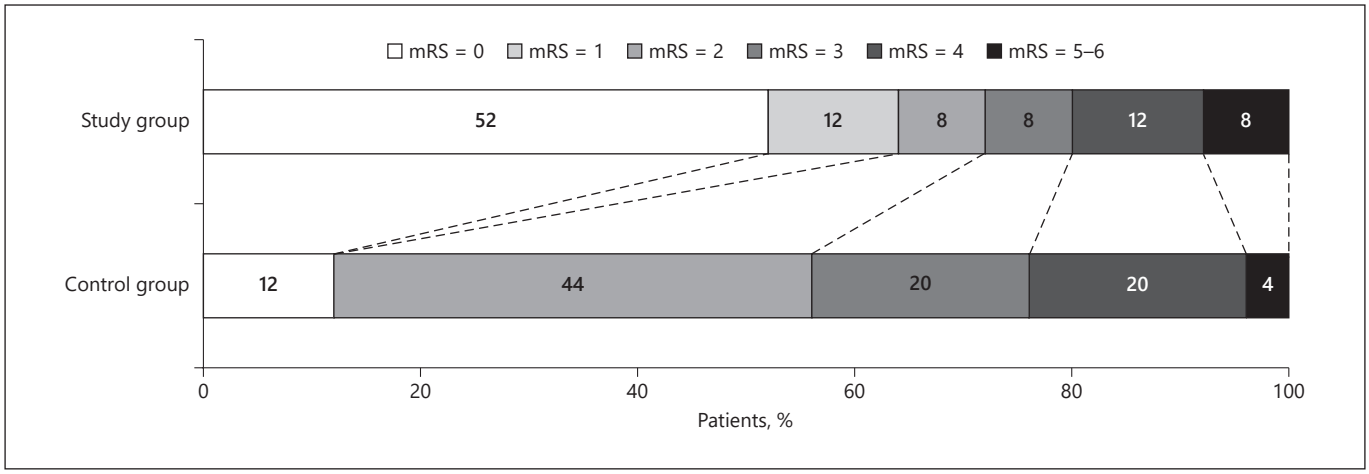

Fig. 2. Distribution of mRS scores at 90 days. Scores of 5 and 6 were aggregated into a single worst-outcome group. The percentage of patients with an mRS score of 0–1 was 64% in the study group, compared with 12% in the control group ($p < 0.001$).

trols (52 vs. 28%, respectively) without reaching statistical significance ($p = 0.083$). The only case of non-symptomatic hematoma occurred in the control group. There was no significant difference in mortality rate.

Baseline demographics and clinical and procedural characteristics were compared between patients of both groups with mRS scores of 0–1 at 90 days and those with an mRS score of 2–6. Univariate analysis showed that lower age ($p = 0.043$) and a favorable CTP imaging profile ($p < 0.001$) were associated with an excellent neurological outcome, whereas there was no significant association with cardiovascular risk factors, previous antithrombotic therapy, and IVT. In addition, IVT did not significantly affect the outcome in any of the 2 groups of patients. Age, sex, NIHSS score at onset, and selection of patients based on favorable CTP data were entered into a multivariate logistic regression analysis for predictors of mRS scores of 0–1. This showed that a lower NIHSS score at onset (OR 1.22; 95% CI 1.00–1.48; $p = 0.042$) and selection of patients based on a favorable CTP imaging (OR 30.00; 95% CI 4.45–202.08; $p < 0.001$) were associated with excellent outcomes, whereas younger age was not (OR 1.09; 95% CI 0.99–1.20; $p = 0.062$). All results are reported in Table 2.

Discussion

Recent studies have shown that recanalization therapies can be extended up to 24 h from the onset of symptoms when the selection of patients is done through multimodal CT or MRI protocols that verify the presence of ischemic penumbra [8–10, 19]. In the hectic setting of AIS treatment decision making, this has added a pathophysiological criterion to the simple determination of the time elapsed from the onset of symptoms. Since 2018 a CTP protocol has been adopted in our high-volume tertiary stroke center for MT eligibility in patients admitted between 6 and 24 h after onset, according to current guidelines [4, 18], and it is also frequently performed in patients under 6 h from onset.

In this retrospective observational study, we intended to evaluate whether the selection of AIS patients based on a favorable CTP profile is associated, after effective MT, with a better clinical outcome at 3 months more consistently than the simple time-based selection. The outcome results in our control patients were largely in line with those of the STAR trial, which described 57.9% of patients with an mRS score of 0–2 at 90 days after almost 80% had successful recanalization procedures (mTICI score 2b–3), and higher than those of the MR CLEAN study, in which the effective recanalization rate was 58.7% [1, 20]. Conversely, the selection of patients based on a favorable CTP dataset resulted in a more favorable distribution of mRS disability scores, with 52% more patients in our study group having an mRS score of 0–1 compared to the control group. Such differences are possibly dependent on the fact that a variable proportion of our control patients did not have salvageable ischemic tissue already before 6 h from onset [7, 12, 21]. Although on a smaller scale, the outcome results in our study patients are better

Table 2. Study results

	Study patients	Control patients		*p* value
Difference of outcome measures between groups				
Patients, *n*	25	25		
mRS score of 0–1 at 90 days	16 (64)	3 (12)		<0.001
mRS score of 0–2 at 90 days	18 (72)	14 (56)		0.051
mRS score at 90 days	0 (0–3)	2 (2–3)		0.019
Hemorrhagic transformation type 1 and 2	13 (52)	6 (24)		0.083
Parenchymal hematoma type 1	0 (0)	1 (4)		0.16
Mortality at 90 days	2 (8)	1 (4)		0.16
	Overall	mRS 0–1	mRS 2–6	*p* value
Baseline, procedural and outcome parameters at 90 days of follow-up				
Patients, *n*	50	19	31	
Age, years	74 (68–81)	68 (59–77)	76 (69–82)	0.043
Female	28 (56)	9 (47.4)	19 (61.3)	0.336
NIHSS score at admission	13 (10–18)	12 (8–15)	14 (11–20)	0.093
ASPECT score at admission	9 (7–10)	9 (7–10)	9 (7–10)	0.953
Favorable CTP profile	25 (50)	16 (84)	9 (29)	<0.001
Intravenous thrombolysis	15 (30)	6 (31)	9 (29)	0.849
Hemorrhagic transformation	20 (40)	8 (28.6)	12 (39)	0.787
Previous antiplatelet therapy	12 (24)	5 (26.3)	7 (22.6)	0.764
Previous anticoagulant therapy	18 (36)	5 (26.3)	13 (41.9)	0.264
Diabetes	8 (16)	3 (15.8)	5 (16.1)	0.975
Hypertension	34 (68)	13 (68.4)	21 (67.7)	0.960
Atrial fibrillation	26 (52)	7 (36.8)	19 (61.3)	0.093
	Odds ratio	95% CI		*p* value
Multivariate logistic regression for predictors of favorable outcome at 90 days (mRS 0–1 vs. 2–6)				
Age (younger)	1.09	0.99–1.20		0.062
Sex (female)	1.24	0.22–6.83		0.803
NIHSS score at admission (lower)	1.22	1.00–1.48		0.042
Favorable CTP profile	30.00	4.45–202.08		<0.001
Atrial fibrillation	1.26	0.20–7.77		0.796

Data are presented as *n* (%) or the median (IQR). mRS, modified Rankin Scale; NIHSS, National Institute of Health Stroke Scale; ASPECT, Alberta Stroke Program Early CT score; CTP, computed tomography perfusion.

that those reported in the DEFUSE 3 trial, where MT performed between 6 and 16 h from onset in patients with favorable perfusion imaging resulted in 26% of them having an mRS score of 0–1 at 90 days [8]. This difference possibly relies on the fact that patients enrolled in the DEFUSE 3 trial had a pre-event mRS score of 0–2 and the effective recanalization rate after MT was 69%. Conversely, our results are similar to those reported in the EXTEND-IA trial, where an extremely high rate of successful MT was associated with 52% of patients having an mRS score of 0–1 and 71% having a score of 0–2 at 90 days [7]. However, it is noteworthy that in the EXTEND-IA trial MT was always initiated within the 6-h time window, whereas 76% of our study patients received MT beyond 6 h.

The main limitation of our single-center study is the small number of patients. In addition, this is a retrospective observational study that can be influenced by the fact that clinical information was not collected within the more rigid criteria of a clinical trial. We are also aware of the fact that the strict criteria of selection of patients in our study do not reflect real world experience for endovascular treatment. Despite these limitations, our study supports the hypothesis that selection of patients based on the presence of ischemic penumbra, rather than solely on the time from onset, could be a reliable predictor of

good outcome after effective MT. This does not scale back the importance of a timely intervention in AIS as the infarct volume increases over time together with a progressive reduction of salvageable brain tissue [22–24].

Conclusion

A growing body of evidence suggests that the presence of ischemic penumbra is associated, after effective MT, with a better clinical outcome in patients with AIS due to LVO. With all the limitations of a small-sized and retrospective study, our results support a future controlled study of adequate size to further validate CTP imaging as an eligibility criterion for MT, regardless the time from the onset of symptoms.

Statement of Ethics

The study fully adheres to the ethical principles of the Declaration of Helsinki as well as GCP guidelines. Approval was granted by the Ethics Committee of the Fondazione Policlinico Universitario A. Gemelli IRCCS (ref. No. 6410/20 ID:3004). Informed consent was obtained from each patient included in the study.

Conflict of Interest Statement

The authors have nothing to disclose.

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Author Contributions

A.B. contributed to the conception or design of the work, analysis and interpretation of data, and writing the draft of the manuscript. R.D.I., F.P., A.L., I.V., S.G., G.F., P.P., S.C., A.A., P.C., R.M., E.L., F.D., A.P., and G.D.M. contributed to the collection and interpretation of the data. C.C. and P.C. contributed to the interpretation of the data. All authors critically reviewed the manuscript and approved the final version.

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