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# Unfavorable clinical outcomes in patients with good collateral scores following endovascular treatment for acute ischemic stroke of the anterior circulation: The UNCLOSE study

**Arturo Consoli[1,2], Marco Pileggi[1,3], ATM Hasibul Hasan[1,4], Mohammad H Rahman[1,4], Alice Venier[1], Alessandro Sgreccia[1], Silvia Pizzuto[1], Oguzhan Coskun[1], Federico Di Maria[1], Luca Scarcia[1,5], Bertrand Lapergue[6], Georges Rodesch[1], Serge Bracard[2,7] and Bailiang Chen[2]**

**Abstract**

**Background:** Patients with acute ischemic stroke secondary to large vessel occlusions and good collaterals are frequently associated with favorable outcomes after mechanical thrombectomy, although poor outcomes are observed also in this subgroup. We aimed to investigate the factors associated with unfavorable outcomes (modified Rankin Scale3–6) in this specific subgroup of patients.

**Methods:** In total, 219 patients (117 females) with anterior circulation stroke and good collaterals (American Society for Interventional and Therapeutic Neuroradiology/Society of Interventional Radiology grades 3–4), treated by mechanical thrombectomy between 2016 and 2021 at our institution were included in this study. Clinical files and neuroimaging were retrospectively reviewed. Univariate and multivariate analyses were performed to identify the predictors of unfavorable outcomes in the overall population (primary endpoint). Secondary endpoints focused on the analysis of the predictors of unfavorable outcomes in the subgroup of successfully recanalized patients, mortality, and symptomatic intracerebral hemorrhages in the overall population.

**Results:** Poor outcome was observed in 47% of the patients despite the presence of good collaterals. Older age ($p < 0.001$), higher baseline National Institute of Health stroke scale ($p < 0.001$), no intravenous thrombolysis administration ($p = 0.004$), > 3 passes ($p = 0.01$), and secondary transfers ($p < 0.001$) were associated with the primary endpoint. The multivariate analysis showed a predictive effect of modified treatment in cerebral infarction 2b-3 and of first pass effect on symptomatic intracerebral hemorrhage.

**Conclusions:** Despite good collaterals, defined through the American Society for Interventional and Therapeutic Neuroradiology/Society of Interventional Radiology scale, poor outcomes occurred in almost half of the patients. Patients with good collaterals not receiving intravenous thrombolysis were significantly associated with unfavorable outcomes, whereas first pass effect was not significantly correlated with clinical outcome in this specific cohort of patients. Different methods to assess collaterals should also be investigated.

**Keywords**

Collaterals, stroke, clinical outcome, mechanical thrombectomy

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[1]Interventional and Diagnostic Neuroradiology Department, Foch Hospital, Suresnes, France
[2]CIC-IT IADI Laboratory, Université de Lorraine, CHRU de Nancy, Nancy, France
[3]Diagnostic and Interventional Neuroradiology, Neurocenter of Southern Switzerland, EOC, Lugano, Switzerland
[4]National Institute of Neurosciences and Hospital, Dhaka, Bangladesh
[5]Institute of Radiology, Università Cattolica del Sacro Cuore, Rome, Italy
[6]Department of Neurology and Stroke Unit, Foch Hospital, Suresnes, France
[7]Interventional and Diagnostic Neuroradiology Department, CHRU de Nancy, Nancy, France

*shared first co-authorship

**Corresponding author:**
Arturo Consoli, Interventional and Diagnostic Neuroradiology Department; Foch Hospital, 40 rue Worth, 92151 Suresnes, France.
Emails: onemed21@gmail.com; a.consoli@hopital-foch.com

## Introduction

Good collaterals represent a hemodynamic reservoir for ischemic areas due to large vessel occlusions (LVOs). Their role has been widely described in the literature in terms of association with favorable clinical outcome,[1,2] of the modulation between "slow" and "fast progressors"[3,4] and of the reduction of the hemorrhagic transformation after mechanical thrombectomy (MT).[5] Therefore, patients with good collaterals are considered the most suitable candidates for MT, although poor clinical outcomes are observed also in patients with a good collateral profile. The aim of this paper was to analyse the factors associated with poor clinical outcomes in patients with a potentially favorable profile based on the presence of a good collateral circulation.

## Materials and methods

### Study cohort

All consecutive patients with acute ischemic stroke of the anterior circulation who underwent MT from January 1, 2016 to December 31st 2021 at our institution were retrospectively analyzed from a prospectively collected, web-based registry (ETIS Registry, NCT03776877).

### Variables and definitions

In the present study, the following data were reviewed and analyzed: age, sex, cardiovascular risk factors, baseline modified Rankin Scale (mRS), baseline National Institute of Health stroke scale (NIHSS) score, presence of hemorrhage or acute FLAIR signal abnormalities at baseline CT or MRI, CT or DWI-Alberta Stroke Program Early CT Score (ASPECTS), arterial occlusion site, patient's direct admission to our comprehensive stroke center or to a primary stroke center with secondary transfer (drip and ship), time metrics [onset-to-groin, onset-to-recanalization (OTR), groin-to-recanalization (GTR)], intravenous thrombolysis (IVT) administration, type of anesthesia, MT technique, number of passes, first pass effect (FPE) procedural complications, recanalization grade according to the modified treatment in cerebral infarction (mTICI) scale, 24 h-NIHSS and ASPECTS, hemorrhagic transformation and symptomatic intracerebral hemorrhage (sICH) according to the ECASS definition and 90-days mRS score. Standard recanalization grades definitions were used: Partial (mTICI 0-2a), adequate (mTICI 2b-3) and almost complete/complete (mTICI 2c-3). Patients at admission were mainly images by MRI (>90%). Ethical approval was obtained from the institutional review board.

### Inclusion and exclusion criteria

Inclusion criteria were age ≥ 18, acute LVO in the anterior circulation (intracranial internal carotid and M1 or proximal M2 segments of the middle cerebral artery), and good collateral circulation which was defined as grades 3 and 4 of the American Society for Interventional and Therapeutic Neuroradiology/Society of Interventional Radiology (ASITN/SIR) scale.[6]

Patients with tandem or multiple occlusions, with significant pre-stroke disability defined as mRS > 2, and patients with incomplete and unavailable follow-up data were excluded.

### Collateral circulation assessment

Interventional images were retrospectively reviewed by an interventional neuroradiologist and an interventional neurologist with ≥5 years of experience in the neurointerventional field. Collateral circulation was assessed in the pre-thrombectomy angiographic study, with injection from ipsilateral ICA (for M1 and proximal M2 occlusions) or contralateral ICA and posterior circulation (for intracranial ICA occlusions). The ASITN/SIR scale was used for the evaluation. A third neurointerventionalist with >10 years of experience reviewed all the angiograms and resolved the disagreements. Kappa inter- and intra-observer agreement was calculated per grade and per dichotomization (grades 1–2 vs grades 3–4). Patients without an adequate pre-thrombectomy angiographic study to assess collateral circulations were excluded.

### Endpoints

The primary endpoint was to investigate the factors associated with unfavorable outcomes defined as the lack of the achievement of functional independence (mRS 3–6) at 90-days outpatient visit or telephone interview. Clinical evaluations were performed by certified stroke neurologists.

Secondary outcomes included the analysis of those factors associated with: unfavorable outcomes in patients adequately recanalized (defined as mTICI 2b-3), all-causes mortality at 90-days and post-procedural sICH in the overall population.

Supplemental specific analyses, such as the subgroup of patients recanalized with mTICI 2c-3, were performed in order to help with the interpretation of the results.

### Statistical analysis

Statistical analysis was performed using descriptive evaluation with the median [interquartile] or mean ± standard deviation for continuous variables and frequency and percentage for categorical variables. Student's T-tests or Wilcoxon tests were performed for continuous variables depending to the number of patients in groups. For categorical variables, chi-square test or Fisher's test were used when the expected value was less than 5. Those variables associated with the outcome in univariate analysis with a significance level below 0.2 were included in a multivariate logistic regression model, which was adjusted for confounding factors. The odds ratios between factors and outcomes of their respective 95% confidence intervals were calculated. Stepwise backward multiple regression was performed to identify statistically significant predictors. All tests were bilateral with a 5% degree of significance. The area under the curve (AUC) was calculated to assess the statistical validity for each model. Variance inflation factor (VIF) was calculated to assess multicollinearity. Statistical analysis was performed with the SAS 9.4 software.

## Results

We reviewed 1419 patients with acute ischemic stroke due to LVO in the anterior circulation treated by MT and 219 (females: 53.4%, mean age: $70.6 \pm 16$ y.o.) patients were included in the final population following the inclusion criteria. A flowchart of the study is provided in Figure 1. Kappa intra- and inter-observer agreement were 0.61 and 0.69, respectively, per ASITN/SIR grade and 0.72 and 0.82 per dichotomization (grades 1–2 vs 3–4). An unfavorable outcome was observed in 103 patients (47%). The results of the univariate analysis related to the primary and secondary endpoints are summarized in Table 1 and Table 2, respectively, whereas Table 3 reports the multivariate analyses. Supplementary analyses are reported in Supplemental Tables 1–3. VIF was 2.5 showing a low level of multicollinearity between the investigated variables.

### Primary endpoint

In our population, a statistically significant correlation with an unfavorable clinical outcome was observed for patients with older age ($p < 0.001$), baseline mRS2 ($p < 0.001$), higher baseline NIHSS ($p < 0.001$), longer OTR ($p = 0.03$) and GTR ($p = 0.004$), IVT administration ($p = 0.004$), number of passes <3 ($p = 0.01$), a partial mTICI score (TICI 0-2a; $p = 0.002$), a higher 24h-NIHSS and lower 24h-ASPECTS ($p < 0.001$) and sICH ($p < 0.001$). The multivariate analysis (AUC = 0.81) showed an independent correlation between unfavorable outcomes and older age, higher baseline NIHSS, no-IVT administration, higher number of passes and secondary transfers ("drip and ship" model).

### Secondary endpoints

Factors associated with unfavorable outcomes in patients with adequate recanalization are shown in Table 2 and did not differ from those identified for the primary endpoint at the univariate analysis, except for the OTR and the procedural time, which were not significantly associated as well as the number of passes which were not retained in the multivariate analysis.

In the sub-analysis performed on all-cause mortality at 90 days we observed that although older age ($p < 0.001$), baseline mRS, baseline and 24h-NIHSS and 24h-ASPECTS ($p < 0.001$), IVT administration ($p = 0.02$) and adequate recanalization ($p = 0.01$) were significantly correlated, only baseline mRS and NIHSS and the final mTICI 2b-3 resulted independent predictors at the adjusted multivariate analysis (Table 3).

Furthermore, sICH were significantly correlated to baseline ASPECTS, longer procedures, FPE, a higher number of maneuvers, recanalization failures, and

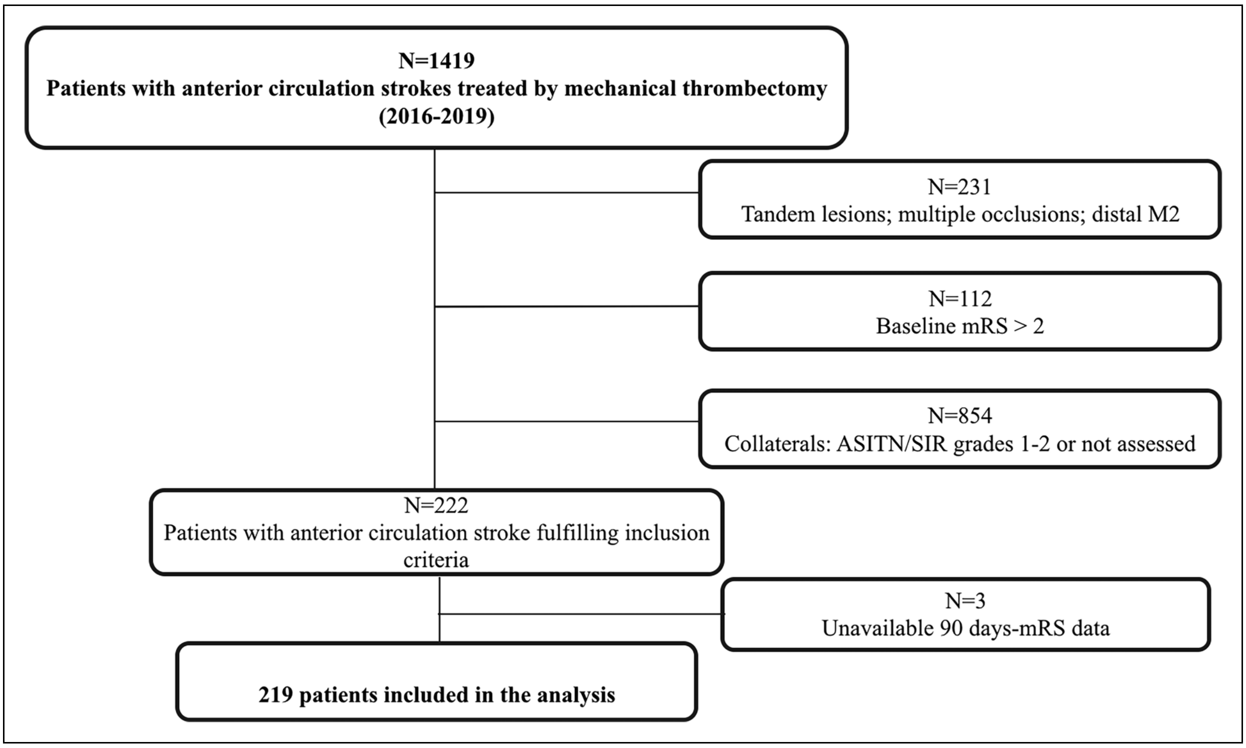


**Figure 1.** Flowchart of the study.

**Table 1.** Overall study population data and univariate analysis (primary endpoint).

| | Overall *(N = 219)* | Favorable outcome *(N = 116)* | Unfavorable outcome *(N = 103)* | p |
|---|---|---|---|---|
| *Females, N(%)* | 117 (53.4) | 56 (48) | 46 (45) | 0.59 |
| *Age, mean ± SD* | 70.6 ± 16 | 65.3 ± 16.9 | 76.6 ± 12.9 | <0.001 |
| *Baseline mRS, N(%)* | | | | |
| 0 | 181 (82) | 105 (91) | 76 (74) | <0.001 |
| 1 | 23 (10) | 11 (9) | 12 (12) | |
| 2 | 15 (7) | 0 | 15 (14) | |
| *Baseline NIHSS, median (IQR)* | 15 (9–19.25) | 12 (7–17) | 18 (14–21) | <0.001 |
| *Occlusion site, N(%)* | | | | |
| ICA terminus | 14 (6) | 6 (5) | 8 (8) | 0.21 |
| M1-MCA | 165 (74) | 83 (72) | 82 (79) | |
| Proximal M2 | 40 (18) | 27 (23) | 13 (13) | |
| *Side, N(%)* | | | | |
| Left | 115 (53) | 62 (53) | 53 (51) | 0.76 |
| Right | 104 (47) | 54 (47) | 50 (50) | |
| Baseline ASPECTS, median (IQR) | 8 (7–9) | 8 (7–9) | 8 (7–9) | 0.1 |
| Secondary transfer, *N*(%) | 132 (60) | 63 (54) | 69 (67) | 0.06 |
| Onset-to-groin, mean ± SD | 230.12 ± 113.09 | 225.5 ± 82.8 | 239.7 ± 87.1 | 0.22 |
| Onset-to-recanalization, mean ± SD | 288.3 ± 117.3 | 270.4 ± 93 | 299.4 ± 96 | 0.03 |
| Groin-to-recanalization, mean ± SD | 53.8 ± 41.1 | 46.3 ± 32.7 | 63.1 ± 47.6 | 0.004 |
| IVT, *N*(%) | 116 (53) | 72 (62) | 44 (43) | 0.004 |
| *Anesthesia protocol, N(%)* | | | | |
| General anesthesia | 38 (17) | 16 (14) | 22 (21) | 0.12 |
| Conscious sedation | 157 (72) | 90 (78) | 67 (65) | |
| Local anesthesia | 24 (11) | 10 (9) | 14 (14) | |
| BGC used, *N*(%) | 61 (28) | 38 (33) | 23 (22) | 0.09 |
| *First-line strategy, N(%)* | | | | |
| Aspiration | 137 (63) | 69 (59) | 68 (66) | 0.08 |
| Stent retriever/combined | 82 (37) | 47 (41) | 35 (34) | |
| First pass effect | 89 (41) | 50 (43) | 39 (38) | 0.43 |
| No of passes, mean ± SD | 2.3 ± 2 | 2 ± 1.3 | 2.7 ± 2.5 | 0.01 |
| *mTICI, N(%)* | | | | |
| 2b-3 | 194 (89) | 109 (94) | 85 (82) | 0.002 |
| 2c-3 | 153 (70) | 89 (77) | 64 (62) | |
| Complications, *N*(%) | 26 (12) | 15 (13) | 11 (11) | 0.63 |
| 24h-NIHSS, median (IQR) | 8 (3–17) | 4 (2–8) | 16.5 (11–20.75) | <0.001 |
| 24h-ASPECTS, median (IQR) | 7 (6–8) | 7 (5–8) | 6 (3–8) | <0.001 |
| PH1/PH2 | 30 (13.6) | 10 (8.6) | 20 (20) | 0.02 |
| sICH, *N*(%) | 13 (6) | 0 | 13 (13) | <0.001 |
| Recurrent stroke, *N*(%) | 11 (5) | 3 (3) | 8 (8) | 0.09 |

BGC: balloon guiding catheter; ICA: internal carotid artery; IQR: interquartile range; IVT: intravenous thrombolysis; MCA: middle cerebral artery; mRS: modified Rankin Scale; SD: standard deviation; sICH: symptomatic intracerebral hemorrhage; PH1/PH2: parenchymal hemorrhage type 1 and 2 according to the ECASS-III classification; ASPECTS: DWI-Alberta Stroke Program Early CT Score; mTICI: modified treatment in cerebral infarction.

24h-NIHSS, whereas only age, baseline ASPECTS and FPE proved a statistical correlation at the multivariate analysis.

## Discussion

Patients with good collaterals could be described as the best candidates for MT. However, a non-negligible part of patients treated by MT does not reach functional independence after the endovascular treatment,[7] although patients with unfavorable outcomes show more frequently a poor collateral profile.[8] In our cohort, age (OR: 1.05, IC95%[1.02–1.09], $p = 0.001$) and higher 24-h NIHSS (OR: 1.23, IC95%[1.14–1.32], $p < 0.001$) were some of the main predictors of poor clinical outcome (Table 1), which is in line with previously published papers.[9] However, some Authors argued that age could have a different behavior which would be in favor of a preserved collateral status.[10] The mean age of this cohort was 70.6 ± 16 y.o., which could be considered slightly higher than in other acute stroke cohorts. We aimed to analyze the impact of other factors that could explain the unfavorable clinical results in this specific subgroup of patients with good collaterals.

### *Collaterals and recanalization*

The adequate recanalization of the occluded artery is widely known as an independent predictor of favorable clinical outcome, although about half of the patients

**Table 2.** Secondary endpoints.

| | *Recanalized patients (2b-3)* | | | *Mortality* | | | *sICH*[a] | | |
|---|---|---|---|---|---|---|---|---|---|
| | Favorable outcome *(mRS 0–2, N = 110)* | *Unfavorable outcome (mRS 3–6, N = 84)* | *p* | *Survival (N = 189)* | *Death (N = 30)* | *p* | *No sICH (N = 198)* | *sICH (N = 13)* | *p* |
| *Sex (female), N(%)* | 58 (53) | 46 (55) | 0.78 | 102 (54) | 15 (50) | 0.6 | 105 (54) | 7 (54) | 0.9 |
| *Age, mean ± SD* | 64.8 ± 17.1 | 75.9 ± 13.7 | <0.001 | 68.9 ± 16.5 | 81.2 ± 8,0 | <0.001 | 69.9 ± 16.4 | 78.8 ± 7,7 | 0.06 |
| *Baseline mRS, N(%)* | | | | | | | | | |
| 0 | 99 (90) | 64 (76) | <0.001 | 163 (86) | 18 (60) | <0.001 | 168 (84) | 9 (70) | 0.13 |
| 1 | 11 (10) | 7 (8) | | 19 (10) | 4 (13) | | 20 (10) | 2 (15) | |
| 2 | 0 | 13 (16) | | 7 (4) | 8 (27) | | 12 (6) | 2 (15) | |
| *Baseline NIHSS, median (IQR)* | 12 (7–17) | 18 (15–21) | <0.001 | 8 (15–19) | 19 (14.5–21.5) | 0.002 | 15 (9–19) | 19 (15–21) | 0.05 |
| Occlusion site | | | | | | | | | |
| ICA terminus | 5 (4) | 6 (7) | 0.08 | 139 (74) | 26 (86) | 0.21 | 154 (77) | 8 (61) | 0.34 |
| M1-MCA | 80 (73) | 69 (82) | | 38 (20%) | 2 (7%) | | 34 (17%) | 4 (31%) | |
| Proximal M2-MCA | 25 (23) | 9 (11) | | 12 (6%) | 2 (7%) | | 12 (6%) | 1 (8%) | |
| *Side, N(%)* | | | | | | | | | |
| Left | 59 (54) | 46 (55) | 0.87 | 97 (51) | 18 (60) | 0.37 | 105 (53) | 7 (54) | 0.95 |
| Right | 51 (46) | 38 (45) | | 92 (49) | 12 (40) | | 93 (47) | 6 (46) | |
| Baseline ASPECTS, median (IQR) | 8 (7–9) | 8 (7–9) | 0.24 | 8 (7–9) | 7 (7–8) | 0.17 | 8 (7–9) | 7 (5.75–8) | 0.03 |
| Secondary transfers, *N*(%) | 59 (54) | 58 (69) | 0.03 | 115 (61) | 17 (57) | 0.66 | 119 (60) | 8 (62) | 1 |
| Onset-to-groin, mean ± SD | 218.7 ± 71.6 | 234 ± 80 | 0.18 | 233.5 ± 88.1 | 223.7 ± 62.6 | 0.83 | 233.2 ± 87.3 | 218.2 ± 64.6 | 0.63 |
| Onset-to-recanalization, mean ± SD | 263.8 ± 80 | 287.1 ± 91.8 | 0.07 | 283.1 ± 97.8 | 286.7 ± 77.6 | 0.53 | 282.2 ± 97.9 | 300.8 ± 64.3 | 0.14 |
| Groin-to-recanalization, mean ± SD | 45.1 ± 32.2 | 52.7 ± 39 | 0.16 | 51.7 ± 37,8 | 69.0 ± 56.5 | 0.35 | 51.8 ± 39.5 | 82.5 ± 51.3 | 0.03 |
| IVT | 70 (64) | 38 (45) | 0.01 | 106 (57) | 10 (33) | 0.02 | 108 (54) | 4 (31) | 0.1 |
| *Anesthesia protocol, N (%)* | | | | | | | | | |
| General anesthesia | 15 (14) | 17 (20) | 0.26 | 32 (17) | 6 (20) | 0.91 | 36 (18) | 2 (15) | 0.81 |
| Conscious sedation | 85 (77) | 56 (67) | | 136 (72) | 21 (70) | | 142 (71) | 9 (70) | |
| Local anesthesia | 10 (9) | 11 (13) | | 21 (11) | 3 (10) | | 22 (11) | 2 (15) | |
| Use of BGC, *N*(%) | 36 (33) | 20 (24) | 0.17 | 55 (29) | 6 (20) | 0.3 | 60 (30) | 1 (8) | 0.12 |
| *First-line strategy* | | | | | | | | | |
| Aspiration | 65 (59) | 57 (68) | 0.08 | 119 (63) | 17 (59) | 0.07 | 122 (61) | 10 (77) | 0.51 |
| Stent retriever/Combined | 45 (41) | 27 (32) | | 70 (37) | 12 (41) | | 77 (39) | 3 (23) | |
| First pass effect, *N*(%) | 50 (45) | 39 (46) | 0.89 | 79 (42) | 10 (33) | 0.38 | 86 (43) | 1 (8) | 0.01 |
| No of passes, mean ± SD | 1.9 ± 1.3 | 2.2 ± 1.6 | 0.11 | 2.2 ± 1.6 | 3.0 ± 3.6 | 0.36 | 2.3 ± 2.0 | 3.5 ± 2.0 | 0.01 |
| mTICI | | | | | | | | | |
| 0-2a | - | - | - | *17 (9)* | *8 (27)* | *0.01* | *20 (10)* | *5 (38)* | *0.01* |
| 2b-3 | - | - | | *172 (91)* | *22 (73)* | | *180 (90)* | *8 (62)* | |

(continued)

**Table 2.** Continued.

| | Recanalized patients (2b-3) | | | Mortality | | | sICH[a] | | |
|---|---|---|---|---|---|---|---|---|---|
| | Favorable outcome *(mRS 0–2, N = 110)* | *Unfavorable outcome (mRS 3–6, N = 84)* | *p* | *Survival (N = 189)* | *Death (N = 30)* | *p* | *No sICH (N = 198)* | *sICH (N = 13)* | *p* |
| Complications, *N*(%) | 15 (13) | 11 (10) | 0.63 | 22 (12) | 4 (13) | 0.9 | 23 (12) | 3 (23) | 0.2 |
| 24h-NIHSS, median (IQR)[b] | 4 (2–7) | 16 (9.5–20) | <0.001 | 7 (2–14) | 20 (16.75–24.25) | <0.001 | 7 (3–16) | 20 (22–26) | <0.001 |
| 24h-ASPECTS, median (IQR)[b] | 8 (7–9) | 6 (5–8) | <0.001 | 8 (7–9) | 5 (3–6) | <0.001 | 7 (5–9) | 5 (3–6) | <0.001 |
| sICH[a], *N*(%) | 0 | 8 (10) | <0.001 | 8 (4) | 5 (17) | 0.03 | - | - | - |
| Stroke recurrence[b], *N*(%) | 3 (3) | 8 (10) | 0.06 | 5 (3) | 6 (21) | 0.001 | 11 (6) | 0 | 0.001 |

BGC: balloon guiding catheter; ICA: internal carotid artery; IQR: interquartile range; IVT: intravenous thrombolysis; MCA: middle cerebral artery; mRS: modified Rankin Scale; SD: standard deviation; sICH: symptomatic intracerebral hemorrhage; ASPECTS: DWI-Alberta stroke program early CT score; mTICI: modified treatment in cerebral infarction.

[a]Data available for 211/219 patients.

[b]Data available for 204/219 patients.

**Table 3.** Multivariate analysis for primary and secondary endpoints.

| | *P* value | OR [IC 95%] |
|---|---|---|
| *Primary endpoint–Unfavorable outcome in overall population* | | |
| Age | 0.001 | 1,06 [1.03–1.09] |
| Baseline NIHSS | <0.001 | 1.15 [1.08–1.22] |
| Secondary transfers | 0.005 | 2.91 [1.39–6.04] |
| IVT | 0.019 | 0.42 [0.20–0.87] |
| Number of passes | 0.021 | 1.29 [1.04–1.61] |
| Adjusted for: Age, side, baseline ASPECTS, baseline mRS, baseline NIHSS, occlusion site, anesthesia protocol, OTR, procedure time (Groin-to-recanalization), IV thrombolysis, final mTICI, number of passes, complications, secondary transfers, use of BGC. | | |
| *Secondary endpoints* | | |
| ***Unfavorable outcome in adequately recanalised patients (mTICI 2b-3)*** | | |
| Age | 0.002 | 1.05 [1.03–1.08] |
| Baseline NIHSS | <0.001 | 1.15 [1.07–1.22] |
| Secondary transfers | 0.005 | 2.95 [1.38–6.33] |
| IVT | 0.022 | 0.41 [0.19–0.88] |
| Adjusted for: Age, side, baseline ASPECTS, baseline mRS, baseline NIHSS, occlusion site, OTR, procedure time (groin-to-recanalization), IV thrombolysis, final mTICI, number of passes, complications, secondary transfers, use of BGC | | |
| | ***Mortality*** | |
| *Baseline mRS* | 0.003 | |
| 1 vs 0 | 0.534 | 1.57 [0.38–6.47] |
| 2 vs 0 | <0.001 | 10.67 [2.78–41.02] |
| Baseline NIHSS | 0.003 | 1.17 [1.05–1.27] |
| Final mTICI 2b-3 | 0.012 | 0.18 [0.05–0.69] |
| Adjusted for: Age, side, baseline ASPECTS, baseline mRS, baseline NIHSS, occlusion site, anesthesia protocol, OTR, procedure time (groin-to-recanalization), IV thrombolysis, final mTICI, number of passes, complications, secondary transfers, use of BGC | | |
| | **sICH** | |
| Age | 0.039 | 1.08 [1.07–1.29] |
| Baseline ASPECTS | 0.005 | 0.53 [3.87–106.34] |
| First pass effect | 0.033 | 0.10 [0.01–0.83] |
| Adjusted for: Age, side, baseline ASPECTS, baseline mRS, baseline NIHSS, occlusion site, anesthesia protocol, OTR, procedure time (groin-to-recanalization), IV thrombolysis, final mTICI, first pass effect, number of passes, complications, secondary transfers, use of BGC | | |

Only variables with significant differences are shown. IVT: intravenous thrombolysis; sICH: symptomatic hemorrhage; ECASS-PH1/PH2: European Cooperative Stroke Study/Parenchymal Hemorrhage type 1 and type 2; NIHSS: National Institute of Health stroke scale; mRS: modified Rankin Scale; ASPECTS: DWI-Alberta Stroke Program Early CT Score; OTR: onset-to-recanalization; mTICI: modified treatment in cerebral infarction; BGC: balloon guide catheter.

with adequate-to-complete recanalization do not achieve functional independence.[11] Our results showed that an adequate recanalization grade remains a strong predictor of favorable clinical outcomes in patients with good collaterals. The interaction between the recanalization grade and collaterals had already been investigated previously showing that collaterals enhance the effect of the recanalization, improving the clinical outcomes of recanalized patients.[12]

When we compared patients with favorable clinical outcomes and those with unfavorable ones, the rates of mTICI 2b-3 were high in both subgroups but significantly lower in the subgroup of patients with an unfavorable outcome (82% vs 95%, $p = 0.002$; Table 1) independently from the endovascular technique used. Interestingly, neither the FPE nor the mTICI grade resulted as independent predictor of favorable outcome or a protective factor for mortality at the multivariate analysis (Table 3), however, that could be explained by the selected population and the high recanalization rates in both subgroups. Thus, we observed similar results when we considered patients with mTICI 2c-3 grades (Supplemental Table 1). These results are in line with the physiopathological concept that collaterals supply the microcirculation in the ischemic territory during the arterial occlusion,[13] maintaining a sort of "hemodynamic reserve."[14]

Other possible explanations of the effectiveness of the association between collaterals and recanalization could be related to the mitigation of the ischemic vascular injury the better exposition to thrombolytics agents[15] or to the higher chance of dislodgment of the clot.[12,16] Nevertheless, complete recanalizations may have a favorable impact on the collateral circulation itself, allowing the removal of the thrombotic material in the pial arterioles and in the capillary bed providing a proper supply of the microcirculation.[17]

Furthermore, we did not observe any differences concerning the type of anesthesia or the use of a balloon guide catheter (BGC) whereas the potential detrimental effect of general anesthesia was described in patients with poor or intermediate collaterals[18] and the BGC had previously been correlated with improved outcomes[19] unless a combined technique (stent retriever + aspiration) was used as a first-line strategy.[20] Moreover, intraprocedural complications were not associated with worse clinical outcomes since these were neither frequent nor clinically relevant in most of the cases. Indeed, mechanical vasospasm represented more than half of the reported complications without clinical consequences.

### *Collaterals and time*

In our cohort, patients with unfavorable clinical outcomes were recanalized later with almost a 30-min difference in terms of onset-to-reperfusion (299.4 vs 270.4 min, $p = 0.03$; Table 1). Secondary transfers resulted, significantly associated with unfavorable outcomes (OR: 2.91, IC95%[1.39–6.04], $p = 0.002$), at the multivariate analysis whereas no differences were shown in terms of OTG. The most significant difference was observed in terms of procedure time, which was longer in patients with unfavorable outcomes (63.1 vs 46.3 min, $p = 0.004$), although no differences were shown in terms of first-line endovascular technique or occlusion site. This datum could be explained by the higher number of passes performed in patients with poor clinical outcomes (2.7 vs 2, $p = 0.01$, Table 1) or sICH (3.5 vs 2.3 min, $p = 0.01$, Table 1), which is in line with previously reported series.[21] These results could suggest that despite good collaterals, a fast and complete recanalization must remain the goal of MT. Therefore, good collaterals should not be considered as a "time machine" that would provide a certain tolerance for long procedures.

The effect of the collateral circulation to maintain cerebral perfusion during ischemia also in late temporal windows has already been described[22] as well as its role of modulator of the progression of the ischemia.[23] Moreover, in our population we did not observe any significant difference in terms of clinical outcome between patients treated before and beyond 6 h (mRS0-2: 56% vs 44%, $p = 0.19$, Supplemental Table 2) although higher recanalization grades were obtained before 6 h, which supports the hypothesis of a neuroprotective effect of good collaterals on the brain tissue in both early and late windows.

### *Collaterals and thrombolysis*

The role of IVT on collateral circulation remains still debated. Some Authors did not find any correlation between IVT and collaterals[24] while other papers had underlined the role of both fibrin[25] and platelets[26,27] in the development of the in situ thrombotic phenomena that can occur within the collateral vessels, particularly in the venous side.[17] IVT (mainly Alteplase according to the inclusion period) was significantly associated with favorable clinical outcomes with a protective effect observed at the multivariate analysis (OR:0.42, IC95%[0.20–0.87], $p = 0.019$). There is currently no evidence that IV thrombolysis may have an effect on collateral circulation, and these results could be explained by the significantly higher rate of patients with mTICI 2b-3 among those who received IV thrombolysis prior to MT (Supplemental Table 3). The SWIFT DIRECT Trial[28] has recently shown that the association IVT + MT provided better clinical outcomes compared to MT alone. However, in our cohort secondary transfers were significantly associated with unfavorable outcomes and it could be hypothesized that the transfer delays may be due to the IVT administration. Nevertheless, only 60% of the patients secondarily transferred to our institution had received IV thrombolysis at the Primary Stroke Centers (unpublished data).

### *Collaterals and hemorrhagic transformation*

The rate of sICH was low (5.9%, 13/219) as one could expect in a selected population with good collateral scores. Indeed, poor collaterals are frequently associated with higher hemorrhagic rates after endovascular treatment.[5,29] In this cohort, older age (OR: 1.08 IC95%[1.07–1.29], $p = 0.039$) and lower baseline ASPECTS were independent predictors of sICH, whereas partial or unsuccessful recanalizations (mTICI 0-2a) and longer procedures were associated with a higher rate of sICH only at the univariate analysis. Furthermore, FPE had a protective effect on sICH at the multivariate analysis (OR:0.1 IC95%[0.01–0.83], $p = 0.033$). These results are in line with previously published papers[30,31] which highlighted a sort of protective effect of collaterals to slowdown the extension of the ischemia and of FPE in preventing sICH.

## Limitations

The retrospective nature of the analysis represents the main limitation of this study. However, we acknowledge also the fact that since the collateral circulation was assessed using the ASINT/SIR[6] scale and that the inter- and intra-observer agreement for this score could be quite poor,[8] although in this cohort we considered a dichotomous parameter since we included only patients with ASITN/SIR grades 3 and 4 and an excellent interobserver agreement was recorded.

Furthermore, although the predictors of unfavorable outcome did not differ from those observed in overall stroke populations and already described in literature, this study represents, to the best of our knowledge, the first analysis specifically focused on this subgroup of patients, providing findings that could be potentially hypothesis generating. Indeed, these results could be conditioned by the limited value of the ASITN/SIR in assessing the effectiveness of the collateral circulation despite its extension.[32]

## Conclusions

Unfavorable clinical outcomes were observed in 47% of patients following MT despite good collaterals according to the ASITN/SIR classification. Although a good collateral circulation could allow to achieve functional independence, also in patients treated in late temporal windows, partial recanalizations and secondary transfers were associated with poor outcomes. FPE was significantly correlated with mortality but not with functional independence, therefore a complete and fast recanalization remains the goal also in thus subgroup of patients. IVT increases the chance to achieve a good clinical outcome in patients with good collaterals without increasing the risk of hemorrhagic transformation. Furthermore, a thoughtful reflection on the angiographic tools and scales to assess collaterals should be encouraged.

### Data availability statement

Data are available upon reasonable request to the corresponding author.

### Declaration of conflicting interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

### Ethics approval statement

The local Institutional Review Board approved the data collection and analysis for this study.

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### ORCID iDs

Arturo Consoli https://orcid.org/0000-0001-6640-8541
Marco Pileggi https://orcid.org/0000-0002-7691-8999
ATM Hasibul Hasan https://orcid.org/0000-0002-9355-6758
Serge Bracard https://orcid.org/0000-0001-9423-6660

### Supplemental material

Supplemental material for this article is available online.

### References

1. Gersing AS, Schwaiger BJ, Kleine JF, et al. Clinical outcome predicted by collaterals Depends on technical success of mechanical thrombectomy in middle cerebral artery occlusion. *J Stroke Cerebrovasc Dis* 2017; 26: 801–808.
2. Qian J, Fan L, Zhang W, et al. A meta-analysis of collateral status and outcomes of mechanical thrombectomy. *Acta Neurol Scand* 2020; 142: 191–199.
3. Rocha M and Jovin TG. Fast versus slow progressors of infarct growth in large vessel occlusion stroke: Clinical and research implications. *Stroke* 2017; 48: 2621–2627.
4. Mohammaden MH, Haussen DC, Pisani L, et al. Characterizing fast and slow progressors in anterior circulation large vessel occlusion strokes. *Interv Neuroradiol* 2022; 159101992210831.
5. Cao R, Ye G, Wang R, et al. Collateral vessels on 4D CTA as a predictor of hemorrhage transformation after endovascular treatments in patients with acute ischemic stroke: A single-center study. *Front Neurol* 2020; 11: 60.
6. Higashida RT and Furlan AJ. Trial design and reporting standards for intra-arterial cerebral thrombolysis for acute ischemic stroke. *Stroke* 2003; 34: e109–e137.
7. van Horn N, Kniep H, Leischner H, et al. Predictors of poor clinical outcome despite complete reperfusion in acute ischemic stroke patients. *J NeuroIntervent Surg* 2021; 13: 14–18.
8. Ben Hassen W, Malley C, Boulouis G, et al. Inter- and intraobserver reliability for angiographic leptomeningeal collateral flow assessment by the American Society of Interventional and Therapeutic Neuroradiology/Society of Interventional Radiology (ASITN/SIR) scale. *J Neurointerv Surg* 2019; 11: 338–341.
9. Arsava EM, Vural A, Akpinar E, et al. The detrimental effect of aging on leptomeningeal collaterals in ischemic stroke. *J Stroke Cerebrovasc Dis* 2014; 23: 421–426.
10. Agarwal S, Scoffings DJ, Jones PS, et al. Interaction of age with the ischaemic penumbra, leptomeningeal collateral circulation and haemodynamic variables in acute stroke: A pilot study. *J Neurol Neurosurg Psychiatry* 2013; 84: 271–276.
11. Goyal M, Menon BK, van Zwam WH, et al. Endovascular thrombectomy after large-vessel ischaemic stroke: A meta-analysis of individual patient data from five randomised trials. *Lancet* 2016; 387: 1723–1731.
12. Leng X, Fang H, Leung TWH, et al. Impact of collateral Status on successful revascularization in endovascular treatment: A systematic review and meta-analysis. *Cerebrovasc Dis* 2016; 41: 27–34.
13. Kunz A and Iadecola C. Chapter 14 cerebral vascular dysregulation in the ischemic brain. In: *Handbook of clinical neurology*. Edinburgh: Elsevier, 2008, pp.283–305.
14. Consoli A, Andersson T, Holmberg A, et al. CT Perfusion and angiographic assessment of pial collateral reperfusion in acute ischemic stroke: The CAPRI study. *J NeuroIntervent Surg* 2016; 8: 1211–1216.
15. Seners P, Roca P, Legrand L, et al. Better collaterals are independently associated with post-thrombolysis recanalization before thrombectomy. *Stroke* 2019; 50: 867–872.
16. Liggins JTP, Mlynash M, Jovin TG, et al. Interhospital variation in reperfusion rates following endovascular treatment for acute ischemic stroke. *J NeuroIntervent Surg* 2015; 7: 231–233.
17. Tong L, Guo Z, Ou Y, et al. Cerebral venous collaterals: A new fort for fighting ischemic stroke? *Prog Neurobiol* 2018; 163–164: 172–193.
18. Liu D, Nie X, Pan Y, et al. Adverse outcomes associated with higher mean blood pressure and greater blood pressure variability immediately after successful embolectomy in those with acute ischemic stroke, and the influence of pretreatment collateral circulation status. *JAHA* 2021; 10: e019350.
19. Blasco J, Puig J, Daunis-i-Estadella P, et al. Balloon guide catheter improvements in thrombectomy outcomes persist despite advances in intracranial aspiration technology. *J NeuroIntervent Surg* 2021; 13: 773–778.
20. Bourcier R, Marnat G, Labreuche J, et al. Balloon guide catheter is not superior to conventional guide catheter

when stent retriever and contact aspiration are combined for stroke treatment. *Neurosurg* 2021; 88: E83–E90.
21. Bourcier R, Saleme S, Labreuche J, et al. More than three passes of stent retriever is an independent predictor of parenchymal hematoma in acute ischemic stroke. *J NeuroIntervent Surg* 2019; 11: 625–629.
22. Liebeskind DS, Saber H, Xiang B, et al. Collateral circulation in thrombectomy for stroke after 6 to 24 hours in the DAWN trial. *Stroke* 2022; 53: 742–748.
23. Anadani M, Finitsis S, Clarençon F, et al. Collateral status reperfusion and outcomes after endovascular therapy: Insight from the endovascular treatment in ischemic stroke (ETIS) registry. *J NeuroIntervent Surg* 2021; 14: 551–557.
24. Anadani M, Januel A-C, Finitsis S, et al. Effect of intravenous thrombolysis before endovascular therapy on outcome according to collateral status: Insight from the ETIS registry. *J NeuroIntervent Surg* 2023; 15: 14–19.
25. Jeanneret V and Yepes M. The plasminogen activation system promotes dendritic spine recovery and improvement in neurological function after an ischemic stroke. *Transl Stroke Res* 2017; 8: 47–56.
26. Xu H, Ping Y, Lin H, et al. Antiplatelet strategies and outcomes in patients with noncardioembolic ischemic stroke from a real-world study with a five-year follow-up. *Transl Stroke Res* 2017; 8: 228–233.
27. Yao Z, Wang L, Wu X, et al. Enhanced procoagulant activity on blood cells after acute ischemic stroke. *Transl Stroke Res* 2017; 8: 83–91.
28. Fischer U, Kaesmacher J, Strbian D, et al. Thrombectomy alone versus intravenous alteplase plus thrombectomy in patients with stroke: An open-label, blinded-outcome, randomised non-inferiority trial. *Lancet* 2022 Jul 9; 400: 104–115. PMID: 35810756.
29. Hao Y, Yang D, Wang H, et al. Predictors for symptomatic intracranial hemorrhage after endovascular treatment of acute ischemic stroke. *Stroke* 2017; 48: 1203–1209.
30. Broocks G, Kemmling A, Faizy T, et al. Effect of thrombectomy on oedema progression and clinical outcome in patients with a poor collateral profile. *Stroke and Vascular Neurology* 2021; 6: 222–229.
31. Ducroux C, Piotin M, Gory B, et al. ASTER Trial investigators. First pass effect with contact aspiration and stent retrievers in the Aspiration versus Stent Retriever (ASTER) trial. *J Neurointerv Surg* 2020 Apr; 12: 386–391. Epub 2019 Aug 30. PMID: 31471527; PMCID: PMC7146919.
32. Consoli A, Pizzuto S, Sgreccia A, et al. Angiographic collateral venous phase: A novel landmark for leptomeningeal collaterals evaluation in acute ischemic stroke. *J Neurointerv Surg* 2022.