Stroke

ORIGINAL CONTRIBUTION

Delayed Neurological Improvement After Full Endovascular Reperfusion in Acute Anterior Circulation Ischemic Stroke

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BACKGROUND AND PURPOSE: We aimed to determine the prevalence and predictors of delayed neurological improvement (DNI) after complete endovascular reperfusion in anterior circulation acute ischemic stroke (AIS).

METHODS: Retrospective analysis of an online multicenter prospective reperfusion registry of patients with consecutive anterior circulation AIS treated with endovascular thrombectomy (EVT) from January 2018 to June 2019 in tertiary stroke centers of the NORDICTUS (NORD-Spain Network for Research and Innovation in ICTUS) network. We included patients with AIS with a proximal occlusion in whom a modified Thrombolysis in Cerebral Infarction 3 reperfusion pattern was obtained. DNI was defined if, despite absence of early neurological improvement during the first 24 hours, patients achieved functional independence on day 90. Clinical and radiological variables obtained before EVT were analyzed as potential predictors of DNI.

RESULTS: Of 1565 patients with consecutive AIS treated with EVT, 1381 had proximal anterior circulation occlusions, 803 (58%) of whom achieved a modified Thrombolysis in Cerebral Infarction 3. Of these, 628 patients fulfilled all selection criteria and were included in the study. Mean age was 73.8 years, 323 (51.4%) were female, and median baseline National Institutes of Health Stroke Scale was 16. Absence of early neurological improvement was observed in 142 (22.6%) patients; 32 of these (22.5%) achieved good long-term outcome and constitute the DNI group. Predictors of DNI in multivariable-adjusted logistic regression were male sex (odds ratio, 6.4 [95% CI, 2.1–22.3] P=0.002), lower pre-EVT National Institutes of Health Stroke Scale score (odds ratio, 1.4 [95% CI, 1.2–1.5], P<0.001), and intravenous thrombolysis (odds ratio, 9.1 [95% CI, 2.7–30.90], P<0.001).

CONCLUSIONS: One-quarter of patients with anterior circulation AIS who do not clinically improve within the first 24 hours after complete cerebral endovascular recanalization will achieve long-term functional independence, regardless of the poor early clinical course. Male sex, lower initial clinical severity, and use of intravenous thrombolysis before EVT predicted this clinical pattern.

GRAPHIC ABSTRACT: An online graphic abstract is available for this article.

Key Words: brain ■ ischemic stroke ■ outcome ■ reperfusion ■ thrombectomy

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Nonstandard Abbreviations and Acronyms

AIS	anterior circulation acute ischemic stroke
CT	computed tomography
DNI	delayed neurological improvement
ECASS-2	European Cooperative Acute Stroke Study
ENI	early neurological improvement
EVT	endovascular thrombectomy
mRS	modified Rankin Scale
mTICI	modified Thrombolysis in Cerebral Infarction
NIHSS	National Institutes of Health Stroke Scale
OR	odds ratios
TOAST	Trial of ORG 10172 in Acute Stroke Treatment
tPA	tissue-type plasminogen activator

Acute ischemic stroke (AIS) is a major worldwide cause of mortality and morbidity.[1] Brain reperfusion therapies contribute decisively to improving stroke outcomes. Their ultimate aim is to restore blood flow as soon as possible to rescue the ischemic cerebral tissue at risk of becoming infarcted, thereby minimizing irreversible brain damage and consequently, reducing or avoiding the neurological sequelae in stroke patients.[2] The rates of complete early arterial recanalization have increased dramatically thanks to the development of endovascular reperfusion therapies. Complete arterial recanalization is often followed by early clinical improvement, and this pattern of clinical response to reperfusion therapies has been shown to be a strong predictor of good long-term clinical outcome.[3–5] However, patients sometimes fail to respond clinically within the first hours after complete arterial recanalization has been achieved, which can be very discouraging for their medical team.[5]

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Nevertheless, lack of an early clinical response after cerebral arterial recanalization does not necessarily have to imply a poor long-term outcome. Over 15 years ago in the intravenous thrombolysis literature, Alexandrov et al[6] (2004) first described a pattern of delayed neurological improvement (DNI) that occurred in patients treated with tPA (tissue-type plasminogen activator); in the absence of neurological improvement during the first 24 hours after complete arterial recanalization, these patients still achieved clinical recovery and good long-term clinical outcome. They called this phenomenon stunned brain and suggested several mechanisms to try to explain it, such as relatively late but still nutritious recanalization, resolving brain edema, delayed improvement in microcirculation in ischemic tissues, and neuronal reorganization.[6]

However, although this phenomenon has been well characterized after intravenous thrombolysis, it does not appear to have been sufficiently studied after endovascular thrombectomy (EVT).[7] There are important differences in the process of arterial recanalization after intravenous and endovascular reperfusion therapies that could determine early clinical response to them. Endovascular therapy is associated with a higher rate of complete recanalization, which occurs more abruptly than intravenous thrombolysis-induced arterial recanalization.[8] Hence, we consider it clinically relevant to study this phenomenon in patients undergoing EVT. Our aim was therefore to analyze the prevalence and predictors of DNI after complete endovascular reperfusion in anterior circulation ischemic stroke.

METHODS

Study Design and Setting

We performed a retrospective observational analysis of an online multicenter prospective reperfusion registry of patients with consecutive AIS treated with EVT in tertiary stroke centers of the NORDICTUS (NORD-Spain Network for Research and Innovation in ICTUS) network from January 1, 2017 to June 30, 2019; 13 of these centers included patients eligible for this study. NORDICTUS is a network for research and innovation in cerebrovascular diseases that brings together all public hospitals with stroke units in the North-West of Spain, with a global catchment area of 11.5 million inhabitants.

Personal, clinical, and radiological data obtained in the registry were processed in accordance with the Spanish law on Personal Data Protection. The study was approved by the Ethics Committee of the coordinating center (HCUV- CASVE PI 20-1793). The database is available for other researchers upon reasonable request. This study is reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology statement.

Participants

Patients were eligible if they fulfilled the following criteria: (1) absence of previous relevant disability evaluated by the modified Rankin Scale (mRS) score ≤2; (2) patients with an AIS affecting the proximal anterior cerebral circulation considered eligible for EVT. Selection criteria for EVT included substantial neurological deficit and confirmed intracranial large vessel occlusion affecting either the intracranial internal carotid artery, the first segment of the middle cerebral artery, or the dominant middle cerebral artery segment M2. Patients also had to meet conventional brain plain computed tomography (CT) and CT perfusion criteria. With respect to the plain CT scan, patients with an intracranial hemorrhage or extended early signs of ischemia, as defined by an Alberta Stroke Program Early CT Score <5 were excluded from EVT. In patients presenting beyond 6 hours, EVT was indicated following CT perfusion mismatch

criteria[9]; (3) intravenous thrombolysis was offered to selected patients presenting within the first 4.5 hours from onset, according to international guidelines[2]; (4) pretreatment and 24-hour National Institutes of Health Stroke Scale (NIHSS) scores available; and (5) mRS score on day 90 available.

Clinical Variables

Clinical management of all patients before, during, and after reperfusion therapy was performed in accordance with the institutional protocols of recruiting centers, which are based on up-to-date national and international guidelines. Clinical variables included in our Reperfusion Registry were sex, age, presence of hypertension, diabetes, dyslipidemia, smoking or alcohol consumption, previous antiplatelet or anticoagulant treatment, baseline stroke severity evaluated by the NIHSS scale, and last seen normal time. We also collected information about time from onset to door, door to first neuroimaging, door-groin puncture time, and time from stroke onset to last angiographic series (time from onset to reperfusion). Whenever possible, patients were admitted to NORDICTUS center Stroke Units after completing the endovascular treatment.

Once admitted to the Stroke Unit, patients underwent clinical surveillance and multiparametric noninvasive monitoring. Serial NIHSS assessments were conducted by protocol, and the 24-hour NIHSS score was used to evaluate the early neurological course. A decrease of ≥4 points in patients with a baseline NIHSS score >4, or 24-hour NIHSS score of 0 to 1 in those with a baseline NIHSS score ≤4, were considered indicative of early neurological improvement (ENI). With respect to systemic complications occurring during admission, a diagnosis of respiratory infection by the stroke team was also recorded. Finally, after conventional diagnostic workup, stroke subtypes were categorized according to the TOAST (Trial of ORG 10172 in Acute Stroke Treatment) classification.[10]

Neuroimaging Variables

Admission Imaging

Acute neuroimaging was performed upon admission and included noncontrast CT, CT-angiogram, and CT perfusion when indicated. The extent of early ischemic changes was assessed using the Alberta Stroke Program Early CT Score in pretreatment noncontrast CT, and the site of arterial occlusion was visualized on the CT-angiogram and categorized into intracranial internal carotid artery, M1 or M2 occlusion. Reperfusion status was assessed in the final cerebral angiogram series and graded according to the modified Thrombolysis in Cerebral Infarction (mTICI) scale. Complete reperfusion was defined as an mTICI 3 grade and was considered a mandatory inclusion criterion.

Follow-Up Neuroimaging

A repeat brain CT was performed 24 hours after treatment (or earlier in the event of clinical deterioration) and was used to diagnose the presence and extent of hemorrhagic transformation. Different hemorrhagic transformation subtypes were categorized according to the ECASS-2 (European Cooperative Acute Stroke Study)[11] definition into hemorrhagic infarction types 1 and 2, and parenchymal hematoma types 1 and 2.[12] Symptomatic hemorrhage was defined as hemorrhagic transformation associated with significant neurological worsening, as defined by an increase of four or more points on the NIHSS scale within the first 24 hours.[13] Brain CT was repeated at 48 to 72 hours to differentiate between hemorrhagic transformation and radiological

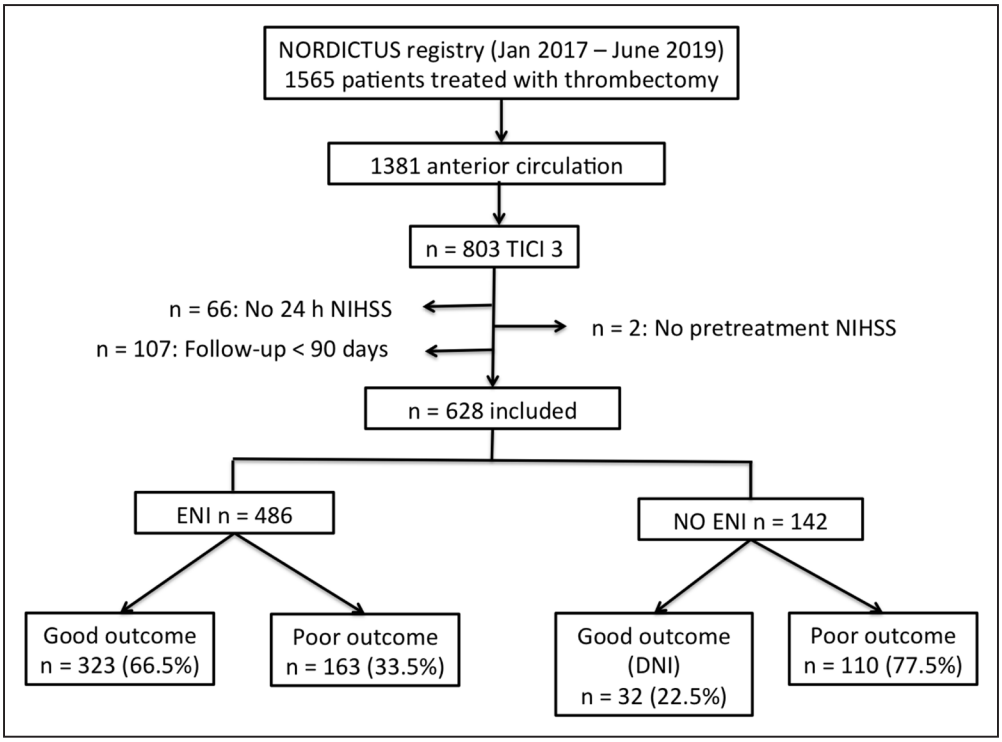

Figure. Study flowchart.
DNI indicates delayed neurological improvement; ENI, early neurological improvement; TICI, Thrombolysis in Cerebral Ischemia; NIHSS, National Institutes of Health Stroke Scale; and NORDICTUS, NORD-Spain Network for Research and Innovation in ICTUS.

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contrast retention when the 24-hour CT scan was considered inconclusive in this respect. The presence of cerebral edema with midline shift ≥5 mm at 24 hours was also recorded.

Primary Outcome Variable

Included patients were clinically followed up until day 90, when the mRS score was evaluated. The mRS was assessed by a stroke neurologist during a physical visit to our stroke prevention clinic, or by telephone, if the patient belonged to remote referral areas. The occurrence of DNI was defined by the achievement of functional independence at day 90 (mRS score, 0–2) despite absence of ENI at 24 hours.

Statistical Methods

Statistical analyses were carried out using SPSS Statistics version 24 (Chicago, IL) and R v4.0.2 (R Core Team [2013]. R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL http://www.R-project.org/). Baseline continuous variables were described using their mean ± SD or median (interquartile range), as appropriate. Discrete variables were expressed as number of cases and their percentage. 95% CI of mean and median values and percentages were also obtained. The Kolmogorov-Smirnov test was used to evaluate if the variables followed a normal distribution. Bivariate analyses were performed to detect baseline and intermediate (recorded during admission) variables associated with the occurrence of DNI. Comparison between baseline variables was conducted using univariate logistic regressions corrected by age and sex, expressed by their odds ratios (OR) and corresponding 95% CI. Comparison between intermediate variables was performed using the χ^2 test or Fisher exact test. A multivariable logistic regression model to predict DNI occurrence was fitted. Variable selection for this model was conditioned by the requirement of using no more variables than the least common outcome events (DNI, 32) divided by ten. The model was built following the classical proposal by Hosmer, Lemeshow, and Sturdivant. After eliminating the variable location of occlusion, whose level of significance was close to 0.05, we achieved a 3-variable model including sex, baseline NIHSS, and tPA treatment. This model also was identified as the best when applying elastic net penalization for variable selection. Besides, the performance of this model was almost identical than the one achieved by the more complex including additionally age and location of occlusion because the correlation coefficients between predicted probabilities (in the logit scale) given by both models were around 0.95. For the final fitted logistic regression model, we provided adjusted OR and their 95% CI. Additionally, we included measures of the predictive performance of this model obtained by bootstrap: Area under ROC curve and its CI and pairs of sensitivity and specificity values for some chosen rules derived from it. Statistical significance was defined as a $P<0.05$.

RESULTS

From January 1, 2017 to June 30, 2019, 1565 patients with AIS underwent EVT at the tertiary centers of the NORDICTUS network and were included in the registry. Of these, 1381 had an anterior circulation occlusion, of whom 803 (58%) achieved an mTICI 3 score. Complete baseline and 24-hour NIHSS and 90 day-mRS data were available in 628 patients, who constitute the final study sample. The reasons for exclusion of the remaining 175 patients were lack of 24-hour NIHSS score due to general anesthesia and prolonged intubation or early death (n=66), absence of pretreatment NIHSS due to the need for intubation before or during the ambulance transportation (n=2), and uncompleted follow-up at 3 months (n=107). Study flowchart is shown on the Figure. We performed an exploratory analysis comparing the included 628 patients with the 175 who were excluded, and both groups were comparable in terms of most baseline variables, only male sex and diabetes were more frequent among the excluded patients (data not shown). The main baseline characteristics of the final study sample are shown in Table 1. Mean age was 73.8 years, 323 (51.4%) were female, and median baseline NIHSS was 16.

Regarding the early neurological course after EVT, 142 (22.6%) patients did not show ENI, 32 of whom (22.5%) achieved a long-term outcome and constitute the DNI group. As expected, the probability of achieving long-term independence was significantly higher in the ENI group ($P<0.0001$). Among the patients experiencing ENI after mTICI 3, 323 (66.5%) had a good long-term outcome, and the remaining 163 (33.5%) did not.

Table 1. Baseline Characteristics of the Study Sample

Variables	Sample (N=628)
Age, y	73.8±12.7
Sex (women)	323 (51.4%)
Prior mRS	0 (0–1)
Hypertension	405 (64.9%)
Diabetes	106 (16.9%)
Dyslipidemia	325 (52.1%)
Current smoking habit	103 (16.7%)
Atrial fibrillation	296 (47.6%)
On anticoagulants	132 (21.7%)
On antiplatelets	162 (27%)
Known onset time	433 (68.9%)
Baseline NIHSS	16 (1–20)
Laterality, left	318 (50.6%)
TICA occlusion	108 (17.2%)
Baseline ASPECTS	9 (8–10)
tPA treatment	193 (30.7%)
No. of thrombectomy passes	1 (1–2)
Time onset-reperfusion, min	304.5±186.6
Cause: cardioembolic	336 (53.8%)

Continuous data are expressed as mean±SD or as median and interquartile range. Categorical data are expressed as no. of cases (n) and percentage. ASPECTS indicates Alberta Stroke Program Early CT Score; CT, computed tomography; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; TICA, terminal internal carotid artery; and tPA, tissue-type plasminogen activator.

In contrast, 32 (22.5%) patients in the non-ENI group achieved a good functional outcome versus 110 (77.5%) who did not. Comparison of baseline variables between the ENI and non-ENI groups is shown on Table 2.

Tables 3 and 4 show the main results of the bivariate analysis of baseline (pre-EVT) and intermediate (during admission) variables potentially associated with DNI among the group of patients not showing ENI at 24 hours. Among pre-EVT variables, as shown in Table 3, those significantly associated with DNI were a lower prior mRS, sex (male), no atrial fibrillation, lower baseline NIHSS, a more distal artery occlusion, and the use of tPA. Regarding subsequent variables, significant associations were found for presence of symptomatic and parenchymal hematoma–type intracranial hemorrhages, cerebral edema with midline shift ≥5 mm, and respiratory infection, as shown in Table 4.

The fitted multivariable logistic regression model for DNI identified the following variables as baseline predictors: male sex (OR, 6.4 [95% CI, 2.1–22.3] P=0.002), lower pre-EVT NIHSS score (OR, 1.4 [95% CI, 1.2–1.5]), P<0.001) and tPA treatment (OR, 9.1 [95% CI, 2.7–30.90], P<0.001). The predictive capacity of this selected model is shown by an area under the ROC curve of 90.9% (95% CI, 83.5%–98.1%) and by the sensitivity and specificity values obtained for 2 chosen cutoff points (sensitivity, 79%; specificity, 87% and sensitivity, 83%; specificity, 81%).

DISCUSSION

The main finding of this multicenter study, performed in consecutive patients with anterior circulation AIS who achieved complete cerebral recanalization after mechanical thrombectomy, was that around one-quarter of patients who did not respond early to endovascular recanalization experienced DNI and still achieved long-term functional independence. This observation may have relevant clinical implications because the probability of delayed clinical recovery after a lack of significant neurological improvement during the first 24 hours after EVT is not inconsiderable,[3–5] and a proactive attitude towards patients should, therefore, be maintained regardless of their early clinical course. Second, we were able to identify several baseline predictors of this clinical pattern, which could be used by stroke teams to guide their diagnostic and therapeutic approach to patients not responding early to full endovascular reperfusion.

The pattern of delayed clinical recovery also occurs after EVT-driven complete recanalization. Our observed DNI prevalence is somewhat lower than the 37% reported in the first description by Alexandrov et al.[6] Interestingly,

Table 2. Comparison Between Groups With and Without ENI

Variables	ENI (n=486)	No-ENI (n=142)	OR (95% CI) for no-ENI
Age, y	72.8±13 (71.6–73.9)	77.1±11 (75.3–79)	1.03 (1.01–1.05)
Sex (women)	249/52% (47.3%–56.4%)	74/54% (45%–62.6%)	0.92 (0.62–1.36)
Prior mRS	0 (0–1) (1.5–2)	0 (0–2) (2–2)	1.27 (1.04–1.54)
Hypertension	310/64% (59.7%–68.5%)	95/67% (59%–75%)	1.01 (0.66–1.55)
Diabetes	78/16% (13%–19.7%)	28/20% (13.5%–27.2%)	1.0 (0.66–1.8)
Dyslipidemia	256/53% (48.5%–57.6%)	69/49% (40.1%–57.1%)	0.81 (0.55–1.19)
Current smoking habit	86/18% (14.4%–21.4%)	17/12% (7.1%–18.5%)	0.9 (0.48–1.67)
Atrial fibrillation	228/47.% (42.9%–52%)	66/48% (39%–56.1%)	0.8 (0.53–1.19)
On anticoagulants	103/22% (17.6%–25.1%)	29/21% (14.1%–28%)	0.8 (0–52–1.36)
On antiplatelets	138/28% (24.4%–32.6%)	50/35% (27.4%–43.7%)	1.35 (0.9–2.02)
Known onset time	343/71% (66.3%–74.6%)	90/63% (54.9%–71.3%)	0.74 (0.49–1.11)
Baseline NIHSS	16 (11–20) (15–16)	16 (9–21) (14–16)	0.99 (0.95–1.02)
Laterality, left	234/48% (43.6%–52.7%)	84/59% (50.6%–67.3%)	1.48 (1–2.18)
TICA occlusion	76/16% (12.5%–19.2%)	32/23% (16%–30.3%)	1.75 (1.08–2.83)
Baseline ASPECTS	9 (8–10) (9–9)	8 (7–10) (8–9)	0.82 (0.71–0.93)
tPA treatment	147/30% (26.2%–34.5%)	46/32% (24.8%–40.8%)	1.18 (0.78–1.79)
Thrombectomy passes	1 (1–2) (1–2)	1 (1–2) (2–2)	1.34 (1.11–1.63)
Time onset-reperfusion, min	299.9±185 (283.1–316.7)	320.5±191 (287.9–353)	1.03 (0.97–1.09)
Cause: cardioembolic	261/54% (49.2%–58.2%)	75/54% (44.3%–61.2%(	0.81 (0.54–1.2)

Continuous data are expressed as mean±SD or as median and interquartile range plus corresponding 95% CI. Categorical data are expressed as no. of cases (n)/percentage (95% CI for percentages). Last column shows OR for no-ENI adjusted by age and sex and corresponding 95% CI. Numerical variables were entered in their corresponding logistic regressions as continuous variables using their usual scale, with the exception of Time onset-reperfusion, where a specific scale based on 60 min intervals was used. ASPECTS indicates Alberta Stroke Program Early CT Score; CT, computed tomography; ENI, early neurological improvement; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio; TICA, terminal internal carotid artery; and tPA, tissue-type plasminogen activator.

Table 3. Bivariate Analysis of Pretreatment Variables Potentially Associated With DNI

Variables	DNI; n=32	No DNI n=110	OR (95% CI) for no DNI
Age	75.1±9.8 (71.9%–76.4%)	77.7±11.4 (72.5%–74.7%)	1.01 (0.97–1.05), *P*=0.715
Prior mRS	0 (0–0) (1–2)	1 (0–2) (1–2)	2.14 (1.19–3.83), *P*=0.009
Sex-women	9/30% (14.7%–49.4%)	65/61% (50.8%–70%)	3.44 (1.38–8.54), *P*=0.006
Hypertension	23/72% (53.3%–86.3%)	72/66.1% (56.4%–74.9%)	0.66 (0.25–1.69), *P*=0.385
Diabetes	7/22% (9.3%–40%)	21/19% (12.2%–27.7%)	0.9 (0.31–2.61), *P*=0.832
Dyslipidemia	19/59% (40.6%–76.3%)	50/46% (35.9%–55.2%)	0.54 (0.23–1.28), *P*=0.165
Current smoking habit	5/16% (5.3%–32.8%)	12/11% (5.8%–18.3%)	0.88 (0.24–3.31), *P*=0.843
Atrial fibrillation	5/16% (5.5%–33.7%)	39/36% (27.1%–45.9%)	3.32 (1.04–10.61), *P*=0.042
On anticoagulants	3/10% (2%–25%)	26/25% (16.1%–32.7%)	4.05 (0.88–18.6), *P*=0.067
On antiplatelet	15/47% (29.1%–65.3%)	35/32% (23.3%–41.4%)	0.57 (0.24–1.35), *P*=0.193
Known time of onset	21/66% (46.8%–81.4%)	69/63% (53%–71.8%)	1.24 (0.51–2.99), *P*=0.661
Baseline NIHSS	9 (5–11) (8–9)	18 (12–21) (16–18)	1.29 (1.17–1.43), *P*<0.001
Laterality of the stroke-left	20/63% (43.7%–78.9%)	64/58% (48.4%–67.5%)	0.76 (0.32–1.81), *P*=0.552
Pretreatment ASPECTS	9 (8–10) (8–9)	8 (7–10) (9–9)	0.66 (0.47–0.92), *P*=0.012
Site of occlusion–MCA-M2	13/41% (23.7%–59.4%)	16/15% (8.5%–22.5%)	0.19 (0.07–0.51), *P*<0.001
tPA treatment	19/59% (40.6%–76.3%)	27/24% (16.8%–33.7%)	0.22 (0.09–0.53), *P*<0.001
Thrombectomy passes	1 (1–2) (1–1.5)	1 (1–2) (1–1.5)	0.98 (0.65–1.5), *P*=0.943
Onset to reperfusion, min	319±169 (270–324)	321±199 (289–324)	0.99 (0.86–1.14), *P*=0.902
Cause, cardioembolic	19/59% (40.6%–76.3%)	56/52% (41.2%–60.6%)	0.56 (0.23–1.39), *P*=0.209

Continuous data are expressed as mean±SD or as median and interquartile range plus corresponding 95% CI. Categorical data are expressed as no. of cases (n)/percentage (95% CI for percentages). Last column shows OR for no-ENI adjusted by age and sex and corresponding 95% CI. Numerical variables were entered in their corresponding logistic regressions as continuous variables using their usual scale, with the exception of Time onset-reperfusion, where a specific scale based on 60 min intervals was used. ASPECTS indicates Alberta Stroke Program Early CT Score; CT, computed tomography; DNI, delayed neurological improvement; ENI, early neurological improvement; MCA-M2, middle cerebral artery segment M2; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio; and tPA, tissue-type plasminogen activator.

they studied this clinical phenomenon in patients who had achieved arterial recanalization within two hours of starting intravenous thrombolysis infusion; thus complete arterial recanalization occurred very early in that study, within a time window paralleling the time course of endovascular recanalization.[6] According to our results, DNI may occur less frequently after EVT-driven complete arterial recanalization. The important distinct features of the arterial recanalization process in both treatment modalities may translate into a difference in the probability of DNI after complete recanalization. However, we did not perform serial cerebral perfusion imaging and cortical activity monitoring after complete recanalization, which may be needed to optimally identify the stunned brain phenomenon as the main contributor to DNI. Therefore, more studies are needed to clarify the specific mechanisms and causal pathways leading to DNI after EVT.

Male sex, lower baseline NIHSS score, and the use of intravenous thrombolysis before EVT emerged as baseline predictors of DNI in our series. The association between DNI and the initial neurological clinical severity was an expected finding, since the NIHSS score is known to correlate with the site of arterial occlusion, the capacity of collateral circulation, and, therefore, with the brain's ischemic penumbra and infarct volumes.[5,7] A more intriguing finding was that women had a significantly lower probability of achieving long-term recovery than men if they had not improved within the first 24 hours after complete arterial recanalization. This is in line with previous studies showing poorer outcomes for women after stroke in general and also after endovascular therapy.[14,15] In our case, this was not explained by differences in arterial recanalization or in-hospital complications.[16,17]

Table 4. Bivariate Analysis of Variables Obtained During Admission (Intermediate Variables) Potentially Associated With DNI

Variables	DNI; n=32	No DNI; n=110	*P* value
Symptomatic hemorrhage	0	15 (14%)	0.024
All hemorrhages			
HI1	3 (9.7%)	5 (4.8%)	1.000
HI2	3 (6.1%)	6 (5.8%)	0.172
PH1	0	14 (13%)	0.017
PH2	0	15 (14.4%)	0.010
Remote or SAH	0	7 (6.7%)	0.098
Respiratory infection	1 (3.6%)	34 (33%)	0.001
Edema with midline shift (> 5 mm)	0	22 (22%)	0.005

Categorical data are expressed as no. of cases (n)/percentage (95% CI for percentages). DNI indicates delayed neurological improvement; HI, hemorrhagic infarction; PH, parenchymal hematoma; and SAH, subaracnoidal hemorrhage.

Our study design did not allow us to assess some relevant factors that could help us understand why this occurred in our cohort, such as marital status, socioeconomic conditions, or the quality of care received during the first months after stroke.[18] Moreover, given the small number of patients with DNI, we cannot rule out that the association found is due to an artifact or to an unexplored selection bias, and therefore this finding needs to be confirmed in future EVT studies. Finally, it was also interesting to note that the use of intravenous thrombolysis before EVT predicted the DNI clinical pattern. This finding supports the hypothesis that tPA could continue to act on persistent microcirculation and distal occlusions not visible on cerebral mTICI3 angiograms, thus helping to achieve more complete and nutritive reperfusion to the brain tissue. In this setting, there are several randomized clinical trials that attempt to ascertain whether intravenous thrombolysis should still be given before EVT in candidates for EVT, and our results support the pertinence of this scientific question.[16,19]

Our study also revealed interesting associations between DNI probability and some intermediate outcome variables occurring during admission, such as the development of parenchymal hematoma–type hemorrhagic transformation or the occurrence of respiratory infections. These associations may also have important practical implications for the clinical management of those patients who do not respond clinically to complete arterial recanalization. If the follow-up brain CT scan does not explain the lack of clinical improvement at 24 hours, then the stroke team may need to actively look for systemic factors that could be hampering clinical recovery, such as respiratory infections, which are gaining increasing attention as determinants of higher morbidity and mortality in stroke patients.[20]

This study has several limitations. First, the need to assess pretreatment and 24-hour NIHSS to evaluate the early clinical course forced us to exclude patients who needed to remain intubated during this time window, who tend to have a worse outcome.[21] However, the stunned brain, as initially described, is a clinical phenomenon. Second, due to our retrospective design, we were unable to systematically assess other potentially correctable factors that could contribute to generating this clinical pattern, such as toxic-metabolic disorders, or abnormalities in brain electric activity that could potentially delay clinical improvement.[22,23] Third, the resulting predictive model lacks a validation in an independent cohort, although we performed several alternative statistical methodologies to show that the proposed model is real and is not derived from spurious associations. Finally, although we assessed the extent of early ischemic changes as a surrogate for infarct core, the infarct volume on follow-up CT was not systematically calculated in all centers, and this intermediate value is also known to be a predictor of poor outcome after EVT.

CONCLUSIONS

In conclusion, one-quarter of patients with anterior circulation AIS who do not clinically improve within the first 24 hours after an mTICI 3 endovascular reperfusion grade will still achieve long-term functional independence. Being male, lower pretreatment clinical severity and the use of intravenous thrombolysis before EVT emerged as independent predictors of delayed clinical recovery after full arterial recanalization. Replication of these findings in larger prospective studies is needed.

ARTICLE INFORMATION

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Disclosures

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Supplemental Materials

NORDICTUS Investigators

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