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Predictors of good functional outcome in ischaemic stroke patients without delayed neurological improvement after mechanical thrombectomy

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ABSTRACT

Introduction. This study aimed to identify predictors of 90-day good functional outcome (GFO) in patients with acute ischaemic stroke (AIS) who were treated with mechanical thrombectomy but did not achieve a delayed neurological improvement (DNI).

Clinical rationale for the study. In-hospital neurological improvement in patients with AIS is consistently associated with long-term GFO. Patients who experience neither early nor delayed neurological improvement can still achieve long-term GFO, but predictors of such an outcome have not been studied.

Material and methods. This single-centre retrospective study involved 307 patients with anterior circulation AIS treated with mechanical thrombectomy. Multiple clinical, biochemical, radiological, and treatment-related variables were collected and analysed. DNI on day 7 was defined as at least a 10-point reduction in the National Institutes of Health Stroke Scale (NIHSS) score or NIHSS score < 2. GFO on day 90 was defined as a modified Rankin Scale (mRS) score ≤ 2. We compared the characteristics of patients with and without DNI, with special attention paid to patients who achieved 90-GFO despite a lack of DNI. Multivariate analyses were then performed to establish independent predictors of 90-day GFO among patients without DNI.

Results. DNI occurred in 150 out of 307 patients (48.7%) and significantly increased the odds for 90-day GFO (odds ratio [OR]: 13.99; p < 0.001). Among patients without DNI, 41.4% achieved 90-day GFO. Younger age (OR: 0.96; 95% confidence interval [CI]: 0.93–0.99; p = 0.008), lower baseline NIHSS score (OR: 0.80; 95% CI: 0.73–0.89; p < 0.001), treatment with intravenous thrombolysis (OR: 3.06; 95% CI: 1.25–7.49; p = 0.014), lack of an undetermined aetiology (OR: 0.40; 95% CI: 0.16–0.998; p = 0.050), lack of pneumonia (OR: 0.08; 95% CI: 0.02–0.31; p < 0.001), and higher haemoglobin concentration on admission (OR: 1.31; 95% CI: 1.04–1.69; p = 0.024) were identified as predictors of 90-day GFO in this subgroup.

Conclusion. Almost half of patients with AIS in anterior circulation treated with mechanical thrombectomy experience DNI, which is a good predictor of 90-day GFO. Furthermore, 40% of patients without DNI achieve 90-day GFO which can be independently predicted by younger age, lower baseline NIHSS score, treatment with intravenous thrombolysis, higher haemoglobin concentration on admission, lack of undetermined ischaemic stroke aetiology, and lack of pneumonia.

Keywords: acute ischaemic stroke, mechanical thrombectomy, early neurological improvement, delayed neurological improvement

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Introduction

The proven evidence-based safety and efficacy of mechanical thrombectomy in the management of acute ischaemic stroke have provoked interest in a search for any variables that would predict patients' long-term prognosis after modern recanalisation procedures. Initially, early neurological improvement was proposed as an accurate predictor of a favourable long-term outcome in stroke patients treated with intravenous thrombolysis or mechanical thrombectomy [1, 2]. Most studies, however, define early neurological improvement as an improvement achieved 24 hours after the recanalisation procedure, and it can be argued that the patient's condition at that time is still relatively unstable. More recently, it has been shown that the National Institutes of Health Stroke Scale (NIHSS) score assessed seven days, rather than 24 hours, after intervention can provide more meaningful information about patients' long-term prognosis, most likely because it includes the time when most of the complications occur [3–6]. Unsurprisingly, a significant decrease in neurological deficit observed on day 7, a feature known as delayed neurological improvement (DNI), predicts 90-day good functional outcome (GFO) more accurately than does early neurological improvement [3].

Clinical rationale for the study

Although many patients with acute ischaemic stroke achieve neither early nor delayed neurological improvement, their long-term outcome may still be favourable. Whereas several predictors of 90-day GFO, including male sex, smaller neurological deficit, and the use of intravenous thrombolysis, have been identified among patients without early neurological improvement [7], factors contributing to long-term GFO in the absence of DNI have not previously been studied.

The identification of these factors would increase clinicians' confidence in early prognostication, guide therapeutic and rehabilitation decisions in long-term care, and allow caregivers to make better informed judgements about the adjustments needed to meet the patient's needs in the future.

Thus, our primary goal was to identify predictors of 90--day GFO among patients with acute ischaemic stroke who were treated with mechanical thrombectomy but who did not achieve DNI. In addition, we assessed the impact of DNI as a predictor of 90-day GFO in all patients with ischaemic stroke treated with mechanical thrombectomy.

Material and methods

Study population

We conducted a retrospective analysis of data collected prospectively from patients with acute ischaemic stroke admitted to the Comprehensive Stroke Centre at the University Hospital in Krakow, Poland from January 2019 to December 2021. We included patients who met the following criteria: (1) age ≥ 18 years; (2) diagnosis of ischaemic stroke consistent with the AHA/ASA definition [8]; (3) substantial neurological deficit on admission, defined as NIHSS score ≥ 6; (4) large vessel occlusion of the internal carotid artery, M1 or M2 segment of the middle cerebral artery, or tandem occlusion diagnosed with the use of computed tomography angiography or magnetic resonance angiography; (5) mechanical thrombectomy performed within six hours from symptom onset, or between six and 24 hours from time last known to be well before their stroke according to the ESO-ESMINT guidelines on mechanical thrombectomy in acute ischaemic stroke [9]; and (6) availability of NIHSS score on day 7 after intervention.

Inclusion criteria were met by 342 of 593 patients treated during the study period. We further excluded six patients due to a lack of 90-day follow-up, 21 patients due to nondiagnostic RAPID software evaluation (caused mainly by movement artifacts), and eight patients due to incomplete laboratory data.

All patients were treated according to the selection and eligibility criteria of the current European Stroke Organisation (ESO) guidelines on intravenous thrombolysis and mechanical thrombectomy in acute ischaemic stroke [9, 10]. All procedures were performed in accordance with the Declaration of Helsinki [11].

The protocol of this study was approved by the Jagiellonian University Ethical Committee (KBET/54/B/2007 and 1072.6120.118.2020)

Data collection

The following data was collected from all patients: age, sex, time last known to be well before their stroke, chronic antiplatelet or anticoagulant use, risk factors for stroke i.e. hypertension, diabetes mellitus, coronary artery disease, atrial fibrillation (AF), smoking status (smokers were defined as those who were either smoking when they were recruited into the study or those who had smoked in the past), history of stroke or transient ischaemic attack (TIA), hyperlipidaemia, obesity, and alcohol abuse. NIHSS score on admission and on day 7 was used to assess stroke severity. Blood tests on admission included white blood cell (WBC) count, platelet count, serum concentrations of glucose, haemoglobin and creatinine, plasma fibrinogen concentration, activated partial thromboplastin time, and international normalised ratio. Fasting blood tests on day 1 consisted of C-reactive protein (CRP), triglyceride and cholesterol concentrations. Stroke aetiology was classified according to the Trial of ORG 10,172 in Acute Stroke Treatment (TOAST) criteria [12]. Medical complications that occurred after mechanical thrombectomy were diagnosed as described elsewhere [13].

Patients with acute ischaemic stroke qualified for mechanical thrombectomy underwent the following protocol of imaging studies: non-contrast computed tomography

(Alberta Stroke Programme Early CT Score — ASPECT), computed tomography angiography, computed tomography perfusion with post-processing analysis with RAPID software (volume of cerebral blood flow [CBF] less than 30% [infarct volume], time to peak concentration-more-than-6-second volume ($T6_{max}$), and volume of $T6_{max}$ minus CBF < 30% [penumbra]). Follow-up non-contrast computed tomography was performed 24 hours after mechanical thrombectomy (Siemens Somatom Definition Edge 64-detector scanner).

Immediate recanalisation was graded according to the modified Thrombolysis in Cerebral Infarction (mTICI) criteria: grade 0 — no perfusion; grade 1 — penetration with minimal perfusion; grade 2a — partial perfusion < 50%; grade 2b — partial perfusion ≥ 50–99%; and grade 3 — no flow constraint and complete perfusion.

The following parameters related to mechanical thrombectomy were recorded: site of the occlusion, time from stroke onset to groin puncture, time from groin puncture to recanalisation, presence of intracerebral haemorrhage on non-contrast computed tomography performed 24 h after mechanical thrombectomy, and successful recanalisation after mechanical thrombectomy, defined as a mTICI score of 2b or 3.

DNI was defined as either a 10-point reduction in the NIHSS score from baseline to day 7 or an NIHSS score < 2 on day 7 [3]. Disability 90 days after ischaemic stroke onset was assessed using the modified Rankin scale (mRS) during scheduled visits in an outpatient clinic or via telephone interviews with patients or their family members or caregivers. 90-day GFO was defined as mRS score ≤ 2.

Statistical analysis

Descriptive statistics were provided for the entire studied population and for subgroups defined according to the presence or absence of DNI. Categorical variables were expressed as counts and percentages, whereas continuous variables were characterised by median and interquartile range (IQR) because of the lack of normality shown in the Shapiro–Wilk test.

Firstly, univariate analysis of differences between subgroups with and without DNI was performed. The significance of differences between the groups was assessed with a χ^2 test for categorical variables and a Mann-Whitney U-test for continuous variables. Multivariate analysis of the predictors of 90-day GFO in all patients was performed. Two models were proposed — the first one did not account for DNI, and the second one included DNI. To compare the predictive accuracy of the two models (before and after inclusion of the DNI), we constructed a receiver operating characteristic (ROC) curve and calculated 95% confidence intervals (CI) and p-values for the areas under the curve for each model (baseline *vs.* baseline + DNI).

Subsequently, we performed univariate analysis of the differences between two subgroups of patients without DNI (with and without 90-day GFO). The analysis of independent predictors of 90-day GFO (dependent variable) was performed by logistic regression modelling. The initial model included all variables that differed at $p < 0.1$ in univariate analysis and was refined with stepwise removal of nonsignificant variables until the final model of independent predictors was achieved at $p < 0.05$. We have provided an adjusted odds ratio (OR) and 95% CI for each variable. A two-sided p-value of less than 0.05 was considered significant.

Statistical analysis was conducted using IBM SPSS Statistics 29 and StataSE 18.

Results

Our study sample consisted of 307 patients, including 161 (52.4%) females. Median age was 71 years. All baseline characteristics are set out in Supplementary Table 1.

Characteristics of DNI and non-DNI patients

All baseline characteristics of DNI and non-DNI patients and the results of univariate analysis of differences between these subgroups are set out in Supplementary Table 2. In general, DNI patients had a higher rate of successful recanalisation and a shorter time from symptom onset to groin puncture; they received intravenous thrombolysis more frequently and had lower rates of stroke-related complications (pneumonia, urinary tract infection and haemorrhagic transformation). Both WBC count and glucose concentration were lower among patients with DNI. These patients had lower infarct volume in RAPID computed tomography perfusion evaluation, and had internal carotid artery/tandem occlusion less frequently. Moreover, they spent less time in hospital and were more likely to achieve 90-day GFO. In addition, 90-day fatalities were lower in the DNI group. However, patients with and without DNI were similar regarding other baseline characteristics such as age, medical history before stroke, ASPECT score, and other laboratory measures. All variables mentioned in the 'Data collection' section but not included in the tables were similar in both groups.

Utility of DNI in predicting 90-day GFO

Ninety-day GFO was achieved by 192 (61.9%) patients. The multivariate model (adjusted by sex) identified younger age ($p < 0.001$), lower baseline NIHSS score ($p < 0.001$), lack of pneumonia ($p < 0.001$), treatment with intravenous thrombolysis ($p = 0.018$), and successful recanalisation ($p = 0.022$) as independent predictors of 90-day GFO, and these variables were included in the baseline model. Inclusion of DNI showed its role as an independent predictor of 90-day GFO, increasing odds for GFO by almost 14 times ($p < 0.001$) (Suppl. Tab. 3). In ROC analysis, DNI inclusion significantly improved the predictive accuracy of the baseline model in prognosing 90-day GFO ($p = 0.0007$) (Fig. 1).

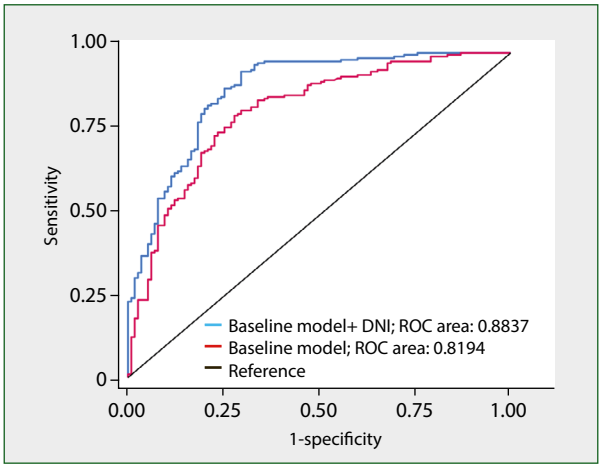

Figure 1. Receiver operating characteristic curve of two models predicting 90-day good functional outcome in all patients. Red: baseline model (age, sex, baseline NIHSS score, intravenous thrombolysis, successful recanalisation, pneumonia) without DNI as an independent variable (AUC: 0.8194, 95% CI [0.77–0.87]); blue: baseline model after inclusion of DNI (AUC 0.8837, 95% CI [0.84–0.92]); p = 0.0007 (*vs.* baseline model). AUC — area under curve; CI — confidence interval; DNI — delayed neurological improvement; NIHSS — National Institutes of Health Stroke Scale

Factors associated with 90-day GFO in non-DNI patients

Although more than half of the patients (n = 157) did not achieve DNI, 65 of them (41.4%) had a 90-day GFO. Details of the univariate analysis of differences between patients with and without 90-day GFO are set out in Table 1. Patients with 90-day GFO were younger, more frequently male, and had a lower baseline NIHSS score. They also had lower serum glucose and CRP concentrations, higher haemoglobin concentration, lower WBC count, and smaller penumbra volume. Patients with 90-day GFO suffered from pneumonia less frequently, and their ischaemic stroke was less likely to have an undetermined aetiology (Tab. 1).

Multivariate analysis revealed the following independent predictors of 90-day GFO among non-DNI patients; younger age (p = 0.008), lower baseline NIHSS score (p < 0.001), treatment with intravenous thrombolysis (p = 0.018), lack of pneumonia (p < 0.001), higher haemoglobin concentration (p = 0.024), and lack of undetermined ischaemic stroke aetiology (p = 0.050). Details of the final model are set out in Table 2.

Discussion

This study confirmed the significance of DNI as a predictor of long-term prognosis, expressed as 90-day GFO. More importantly, we have shown that GFO could be achieved by more than 40% of patients without DNI. Such an outcome can be predicted by younger age, lower baseline NIHSS score, treatment with intravenous thrombolysis, higher haemoglobin concentration on admission, lack of undetermined ischaemic stroke aetiology, and lack of pneumonia.

The presence of GFO despite a lack of early neurological improvement (with different definitions of this variable) has been noted and studied before, but we focused on predictors of good outcome among those patients who did not achieve DNI (assessed on day 7 after stroke). To the best of our knowledge, this has not been studied before.

Younger age is broadly recognised as a crucial prognostic factor in ischaemic stroke treatment [14]. We did not find an association between younger age and DNI, but younger age did predict better outcomes among non-DNI patients. It is probable that elderly subjects develop additional complications or suffer from exacerbations of their comorbidities in the period after ischaemic stroke. The risk of subsequent vascular events in these patients is also higher than among younger ones. Accordingly, Desai et al. [15] found that younger age was associated with so called delayed functional independence (i.e. 90-day GFO in a group without early functional independence, defined as GFO at discharge), but not with early functional independence itself. Some authors (e.g. Jadhav et al. [16]) have identified age as a predictor of both early and delayed functional independence. Nevertheless, our findings suggest that even though age may not impact upon the clinical course during hospitalisation, it is still pertinent to the patient's long-term prognosis.

We identified lower baseline NIHSS score and treatment with intravenous thrombolysis as other independent predictors of GFO, and that finding was consistent with the study by Talavera et al. [7] which identified male sex, lower baseline NIHSS score, and treatment with intravenous thrombolysis, as predictors of GFO with an absence of early neurological improvement. A higher baseline NIHSS score has been consistently associated with poor functional outcomes, as it correlates with ischaemic stroke severity and complications [17, 18]. The impact of treatment with intravenous thrombolysis on 90-day GFO in non-DNI patients might be considered to be a surprising result. It could be expected that thrombolytic treatment would primarily affect the short-term outcome. We hypothesise that this could be explained by patient eligibility to receive such a treatment, as patients burdened with specific conditions (i.e. recent major surgery, malignancy, disordered coagulation) often do not receive thrombolytic treatment [19]. Such a burden may affect their longer-term prognosis after ischaemic stroke and lack of thrombolytic treatment could merely be a marker of significant comorbidities.

Our results also indicate that a higher haemoglobin concentration may have a positive impact on 90-day GFO. A recent meta-analysis showed that admission anaemia was associated with higher mortality in acute ischaemic stroke [20], and another study demonstrated that a lower haemoglobin concentration was linked to worse functional outcomes [21].

Table 1. Comparison of baseline characteristics between patients with and without 90-day good functional outcome (GFO) among subjects without delayed neurological improvement

	Patients with 90-day GFO (n = 65)	Patients without 90-day GFO (n = 92)	P-value
Demographics			
Age [years]; median (IQR)	65 (57–76)	74.5 (66–84)	0.004
Females, *n* (%)	28 (43.1)	56 (60.9)	0.028
Stroke risk factors			
Hypertension, *n* (%)	44 (67.7)	68 (73.9)	0.396
Diabetes mellitus, *n* (%)	14 (21.5)	21 (22.8)	0.849
Ischaemic heart disease, *n* (%)	6 (9.2)	9 (9.8)	0.908
Atrial fibrillation, *n* (%)	17 (26.2)	25 (27.2)	0.887
Hypercholesterolaemia, *n* (%)	10 (15.4)	16 (17.4)	0.739
Smoking, *n* (%)	18 (27.7)	16 (17.4)	0.123
History of stroke or TIA, *n* (%)	9 (13.8)	12 (13)	0.884
Clinical characteristics			
Baseline NIHSS score, median (IQR)	12 (9–16)	18 (14–21)	< 0.001
Time from onset to puncture [minutes], median (IQR)	315 (255–388)	306.5 (218–379)	0.457
Intravenous thrombolysis, *n* (%)	40 (61.5)	43 (46.7)	0.067
Successful recanalisation, (mTICI ≥ 2b), *n* (%)	57 (87.7)	71 (77.2)	0.094
Occlusion of ICA or tandem occlusion, *n* (%)	19 (29.2)	24 (26.1)	0.664
Blood glucose [mmol/L], median (IQR)	5.7 (5.04–6.75)	6.86 (5.9–8.79)	< 0.001
Haemoglobin [g/dL], median (IQR)	14 (12.25–14.65)	12.95 (11.3–14.08)	0.007
WBC count [10^9/L], median (IQR)	9 (6.93–11.15)	9.95 (7.6–12.9)	0.031
C-reactive protein [mg/L], median (IQR)	5.6 (2.09–13)	9 (2.98–27.5)	0.024
NIHSS score on day 7, median, (IQR)	6 (3–10)	16 (12–19)	< 0.001
Use of antiplatelets, *n* (%)	18 (27.7)	18 (19.6)	0.233
Use of anticoagulants, *n* (%)	14 (21.5)	26 (28.3)	0.341
Radiological examination			
Baseline ASPECT score, median, IQR	8 (7–9)	8 (7–9)	0.619
Penumbra volume [mL], median (IQR)	92 (50–119)	104 (63.75–143.8)	0.045
Infarct volume (CBF < 30%) [mL], median (IQR)	13 (0–29.5)	12.5 (0–36.5)	0.345
Stroke-related complications			
Pneumonia, *n* (%)	4 (6.2)	44 (47.8)	< 0.001
Urinary tract infection, *n* (%)	17 (26.2)	25 (27.2)	0.887
Haemorrhagic transformation, *n* (%)	13 (20)	28 (30.4)	0.143
Stroke aetiology			
Cardioembolic, *n* (%)	27 (41.5)	35 (38)	0.003
Large vessel disease, *n* (%)	13 (20)	11 (12)	
Rare, *n* (%)	0	6 (9.2)	
Undetermined, *n* (%)	19 (29.2)	46 (50)	

ASPECT — Alberta Stroke Programme Early CT Score; CBF — cerebral blood flow; ICA — internal carotid artery; IQR — interquartile range; mTICI — modified Thrombolysis in Cerebral Infarction; NIHSS — National Institutes of Health Stroke Scale, TIA — transient ischaemic attack; WBC — white blood cells

Table 2. Independent predictors of 90-day good functional outcome among patients without delayed neurological improvement (logistic regression model R2 = 0.546; p < 0.001)

	Odds ratio	95% confidence interval	P-value
Age	0.957	0.926–0.989	0.008
Baseline NIHSS score	0.803	0.727–0.887	< 0.001
Intravenous thrombolysis	3.062	1.252–7.490	0.014
Undetermined aetiology	0.402	0.162–0.998	0.050
Haemoglobin concentration	1.315	1.037–1.687	0.024
Pneumonia	0.085	0.025–0.313	< 0.001

Odds ratios denote change by 1 year (age), by 1 point in NIHSS, by 1 g/dL (haemoglobin concentration), or change from 'no' to 'yes' in cases of dichotomised variables (intravenous thrombolysis, undetermined aetiology, pneumonia). NIHSS — National Institutes of Health Stroke Scale

It is not entirely clear why low haemoglobin concentrations portend a worse prognosis in ischaemic stroke patients, but at least two mechanisms can be suggested. A low haemoglobin level can impair oxygen supply to the ischaemic tissue and impair cerebral vascular regulation [22]. Moreover, low haemoglobin can be a result of inflammation [23], and some inflammatory markers adversely impact upon functional outcomes [24].

Finally, we showed that stroke-related pneumonia and undetermined ischaemic stroke aetiology also decrease the odds for achieving 90-day GFO in the non-DNI group. The detrimental neurological effect of ischaemic stroke complications is well known [25], and pneumonia has been consistently linked to poor functional outcomes [26]. The negative impact of undetermined ischaemic stroke aetiology on the long-term prognosis can be further explained by the following associations. Firstly, we suppose that some of these patients might actually be suffering from an undiagnosed cardioembolism from AF, which is a quite common underlying cause in patients with cryptogenic stroke [27]. All our patients underwent 72-hour cardiac monitoring; moreover, Holter-ECG was monitored either for 48–72 hours (among patients younger than 60) or for 24 hours (in older patients). We are aware that such monitoring may be insufficient to reveal all cases of ischaemic stroke associated with AF. Jabaudon et al. [28] have shown that Holter-ECG monitoring for seven days can detect AF in 5.7% of patients without AF in standard ECG. Furthermore, two randomised controlled trials monitored patients for even longer periods: in the EMBRACE study (30-Day Cardiac Event Monitor Belt for Recording Atrial Fibrillation After a Cerebral Ischaemic Event), AF was detected in almost 16% of patients with acute ischaemic stroke of undetermined aetiology at 30 days of monitoring [29]; and in the CRYSTAL-AF trial (Study of Continuous Cardiac Monitoring to Assess Atrial Fibrillation After Cryptogenic Stroke), the AF detection rate after three years of monitoring was 30% [30]. Moreover, undiagnosed (and therefore untreated) AF in ischaemic stroke patients is generally associated with a worse prognosis [31, 32]. It is also possible that patients with an undetermined stroke aetiology might actually have two or more potential stroke aetiologies; therefore, they are heavily burdened with conditions potentially resulting in a poor prognosis. An undetermined aetiology of ischaemic stroke also means that no specific secondary prevention is instituted, and the rate of recurrent strokes might be higher.

Importantly, we did not obtain data regarding some MT-related complications, such as malignant cerebral oedema and infarct volume progression — both of which have been closely linked to patient prognosis [33]. Desai et al. [15] showed that lower follow-up infarct volume does indeed portend delayed functional independence; we could not collect data to confirm this finding in our study, because infarct assessment was made on admission only — it was not associated with DNI. Moreover, considering the severity of cerebral oedema and the generally poor conditions of such patients, we suspect that they would be less likely to achieve DNI. Also, we did not specifically classify patients into a hyperglycaemia group, which again could contribute to patient outcomes [34]. Rather than doing that, we treated serum glucose level as a continuous variable, as this approach is generally thought to be more statistically robust.

We recognise some other limitations in the interpretation of our results. Firstly, the generalisability of our results is somewhat hampered by the single-centre nature and retrospective design of the study. However, the characteristics of our study sample are similar to those of most populations of patients with acute ischaemic stroke reported in Europe. Secondly, the number of non-DNI patients with 90-day GFO was relatively small, and further studies with larger samples are needed to confirm our findings. Additionally, the patients' pre-stroke functional status was not available. On the other hand, our study benefited from uniform patterns of diagnostic procedures, including extensive data on computed tomography perfusion, which is rarely reported in such a large group of patients.

Clinical implications and future directions

Our results show that DNI is obtained in almost half of patients and portends a good long-term prognosis. Furthermore, 90-day GFO was still obtained by a considerable fraction of

the non-DNI group and could be predicted by several simple variables. Identification of these predictors allows clinicians to provide a more accurate longer-term prognosis in patients after ischaemic stroke; it can also guide the most effective use of resources. Nonetheless, our findings should be replicated in independent cohorts of ischaemic stroke patients and applied prospectively to confirm their predictive accuracy and applicability.

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