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Original Paper

Importance of Reperfusion Status after Intra-Arterial Thrombectomy for Prediction of Outcome in Anterior Circulation Large Vessel Stroke

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Keywords
Ischemic stroke · Intra-arterial thrombectomy · Prognosis · Predictor · Reperfusion

Abstract
Background: Reperfusion status after intra-arterial thrombectomy (IAT) is a critical predictor of functional outcome after acute ischemic stroke. However, most prognostic models have not included a detailed assessment of reperfusion status after IAT. ***Objective:*** The aim of this work was to assess the association between successful reperfusion and clinical outcome. ***Methods:*** Clinical, radiological, and procedural variables of patients treated with IAT were extracted from our prospective stroke registry. The association with functional outcome using the modified Rankin Scale (mRS) after 3 months was assessed using multivariable logistic regression. An extension of the modified TICI score, eTICI, was used to classify reperfusion status. The prognostic value of reperfusion status after IAT in addition to age, stroke severity, imaging characteristics, treatment with intravenous thrombolysis, and time from symptom onset to the end of IAT was assessed with logistic regression and summarized with receiver operating characteristic curves. ***Results:*** In total, 119 patients were included (mean age 66 years). In multivariable analysis, age >80 years (OR 6.8, 95% CI 1.2–39.8), NIHSS at presenta-

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tion >15 (OR 7.3, 95% CI 2.3–23.5), and incomplete reperfusion status (eTICI score <2C; OR 10.3, 95% CI 3.5–30.6) were the strongest predictors of a poor outcome (mRS 3–6). Adding reperfusion status to the model improved the prognostic accuracy (AUC 0.88, 95% CI 0.91–0.94). Our results indicate a large difference between using an eTICI cutoff of ≥2C versus ≥2B: a cutoff ≥2C improved the predictive value for a good clinical outcome (2C: positive predictive value, PPV, 0.78; 2B: PPV 0.32). ***Conclusion:*** Our results promote using reperfusion status for assessing prognosis in ischemic stroke patients treated with IAT. A model using eTICI ≥2C had greater PPV than eTICI ≥2B and could improve prognostic accuracy.

Introduction

Approximately 12 million people worldwide are annually diagnosed with ischemic stroke [1]. Functional outcome after a proximal intracranial occlusion of the anterior circulation may be improved by intra-arterial thrombectomy (IAT), which is currently widely implemented as the standard care for acute ischemic stroke [2–7].

Knowledge of prognostic factors improves evidence-based patient management. Information on prognosis is crucial to both patients and their family, and aids in determining appropriate rehabilitation programs. However, predicting outcome after ischemic stroke remains difficult due to its heterogeneous nature and the various factors affecting the disease course [8–18].

Patient selection for IAT has been studied extensively [2, 6–8], whereas prognostication after IAT is relatively understudied [8–11]. Previous studies designed prediction models for outcome after ischemic stroke; however, the degree of reperfusion status was often not accounted for [19–23].

This study aims to assess the prognostic value of reperfusion status, including an extension of the currently used modified TICI score (eTICI; extended Treatment in Cerebral Ischemia), in addition to other clinical and radiological characteristics on functional outcome in anterior circulation stroke patients treated with IAT.

Methods

Patients

All patients with any form of stroke admitted to the Haaglanden Medical Center, The Hague, are systematically documented. Patients diagnosed with ischemic stroke between April 2014 and November 2016 were extracted from this prospective registry for further analysis.

Inclusion criteria for this study were: prestroke modified Rankin Scale (mRS) ≤2, proximal occlusion in the anterior circulation, and treatment with IAT. A proximal occlusion was defined as an occluded distal internal carotid artery (ICA), M1 or M2 segment of the middle cerebral artery, or A1 or A2 segment of the anterior cerebral artery with or without tandem occlusion of the ICA. Local guidelines stipulate intravenous thrombolysis (IVT) initiated within 4.5 h and IAT within 6 h after symptom onset [6, 7]. However, exceptions could be made at the physician's discretion and therefore the time from stroke onset to treatment was not used as an exclusion criterion. Based on findings from previous prediction models for IVT and IAT [8–24], the following variables were extracted from the registry: age, prestroke mRS, National Institutes of Health Stroke Scale (NIHSS) at presentation, Alberta Stroke Program Early CT Score (ASPECTS) for early ischemic changes [12], the Tan score for collateral supply [15], treatment with IVT, time from symptom onset to the end of IAT (i.e., sheath from groin), reperfusion status assessed with the eTICI score, and functional outcome. The eTICI score ranges from grade 0 (no reperfusion) to grade 3 (complete reperfusion) and was assessed after intervention by digital subtraction angiography. Previously, a modified TICI (mTICI) score of 2B (reperfusion of more than half of the previously occluded target artery ischemic territory) or 3 was classified as successful. However, recent studies

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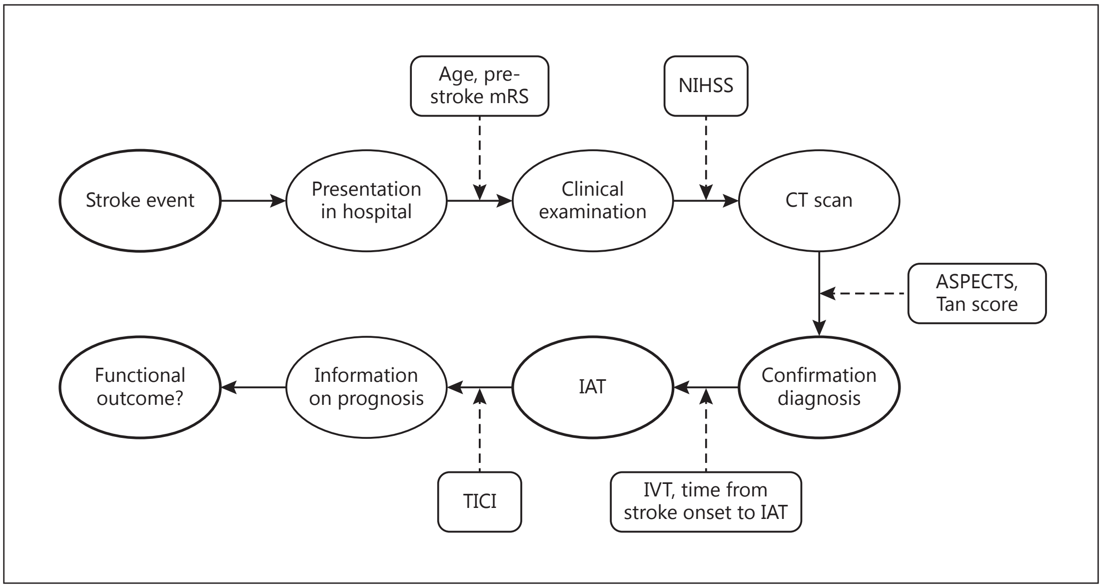

Fig. 1. Flowchart of stroke workup and feature selection.

have reported an extension of mTICI (i.e., eTICI), adding a 2C score which indicates a near complete perfusion except for slow flow in a few distal cortical vessels or presence of distal cortical emboli [25, 26]. The effect of successful reperfusion on prognosis, either defined by eTICI ≥2B or ≥2C, was also assessed. The primary outcome was mRS at the 3-month follow-up. The mRS is a 7-point scale ranging from 0 (no symptoms) to 6 (death). A score above 2 points indicates functional dependence, i.e., poor functional outcome [27].

CT Imaging Protocol

Noncontrast CT and CT angiography (CTA) were evaluated by a stroke imaging researcher (H.H.). Patients were scanned using either a 16- or 64-slice CT scanner (Brightspeed S or Lightspeed VCT, respectively; General Electric Medical Systems, Hatfield, UK) with a tube voltage of 120 kV and the gantry angled to the orbitomeatal line. The mean current was 335 mA and 100 mA for CT and CTA, respectively. For CTA, 50 mL of Visipaque iodine contrast material (General Electric Healthcare, Hatfield, UK) was injected intravenously and image acquisition was triggered automatically at the time of contrast passage through the aortic arch. Multiplanar reconstructions and 10-mm axial maximum intensity projection images were generated using Vitrea 6.8 (Vital Images, Minnetonka, MN, USA).

Ethical Considerations

The study protocol was approved by the local ethical committee of the Haaglanden Medical Center and the Medical Ethical Review Board of South-West Holland.

Statistical Analysis

Continuous variables are expressed as the mean with 95% confidence interval (CI) or median with interquartile range (IQR). Discrete variables were expressed as counts (n) and percentages. Independent variables were dichotomized, with age at >80 versus ≤80 years, NIHSS at presentation >15 versus ≤15, use of IVT or not, ASPECTS ≤7 versus 8–10, Tan collateral score <2 versus ≥2, time from symptom onset to the end of IAT >360 versus ≤360 min, and eTICI score either 0–2A versus 2B-3 or 0–2B versus 2C-3. Prestroke mRS was not included in the analyses due to its skewed distribution. These cutoff values are mostly based on previous studies [12, 16, 17, 24, 28–30].

The association between aforementioned factors and poor clinical outcome after 3 months, i.e., mRS >2, was analyzed with univariate logistic regression models. Multivariate logistic regression models were subsequently computed with a forced entry autoregressive covariance matrix, applying a multiple-block structure reflecting the timeframe of the clinical process of stroke patients (Fig. 1). Given a sample size of 119 patients, we were confident of maintaining sufficient statistical power for a total of 7 predictors [31].

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Table 1. Reasons for no IVT treatment

	n
Presentation at stroke center >4.5 h after onset	15
Use of anticoagulants	6
INR >1.7	3
IVT in past 24–48 h	3
Recent surgery	2
Hypertension	2
Recent intracranial hemorrhage	2
Physicians choice for immediate IAT	2
Trauma	1
Recent stroke	1
Allergy to alteplase	1

IAT, intra-arterial thrombectomy; IVT, intravenous thrombolysis; INR, international normalized ratio.

The timeline of ischemic stroke patients from presentation in the emergency department up to treatment with IAT was systematically followed. Figure 1 depicts this process, including the time-points at which different variables were evaluated. Block 1 included age as the baseline characteristic. Block 2 included the NIHSS score (clinical information collected at presentation). Block 3 included the ASPECTS and Tan collateral score reflecting radiological variables during the diagnostic phase. Block 4 included co-treatment with IVT and time from the onset of symptoms to the end of IAT. Finally, block 5 included reperfusion status using the eTICI score reflecting radiological outcome after IAT. Odds ratios (OR) with 95% CI were calculated.

To determine the discriminative properties of our model, a receiver operating characteristic (ROC) curve was plotted to assess the area under the curve (AUC). SPSS software (version 22.0; IBM SPSS, Chicago, IL, USA) was used for the statistical analyses. A p value <0.05 was considered significant.

Results

Patients and Outcomes

Overall, 119 patients treated with IAT fulfilled the inclusion criteria. The mean age was 65 years (range 20–94 years) and 59 (49.6%) were female. The median NIHSS at presentation was 15, median ASPECTS was 9, and 90 patients (75.6%) had a good collateral supply. Eighty-one patients (68.1%) were additionally treated with IVT. The reasons for refraining from IVT are detailed in Table 1.

Successful reperfusion was achieved in 90 patients (75.6%) with a mean time from symptom onset to the end of IAT of 339 min. At the 3-month follow-up, 47 patients (40.2%) had a good clinical outcome, 49 patients (41.1%) were alive but had a poor clinical outcome, 21 patients (17.9%) had died, and 2 patients were lost to follow-up. The demographic, clinical, radiological, and procedural characteristics are shown in Table 2.

Univariate Analyses

Predictors of poor clinical outcome at the 3-month follow-up were: age (OR 4.0, 95% CI 1.1–14.7), NIHSS at presentation (OR 7.1, 95% CI 3.0–16.7), and ASPECTS (OR 2.2, 95% CI 1.0–4.7). Both the eTICI score with a cutoff <2B (OR 10.4, 95% CI 3.4–32.3) and with a cutoff <2C (OR 11.4, 95% CI 4.6–28.2) were strong predictors of a poor clinical outcome (Table 3).

Multivariate Analyses

In multivariate analyses, the reperfusion status was dichotomized at a cutoff ≥2C as this yielded a larger regression coefficient compared to a cutoff at ≥2B. Age (OR 6.8, 95% CI

Table 2. Demographic, clinical, radiological, and procedural characteristics

	Total (*n* = 119)
Age, years	65.5±15.3
Female	59 (49.6)
History of ischemic stroke or TIA	18 (15.1)
NIHSS at presentation	15 (11–19)
Prestroke mRS >2	14 (11.8)
Occlusion sites	
M1	68 (57.1)
M2	13 (10.9)
M3	2 (1.7)
Intracranial ICA	34 (28.6)
MCA and ACA without ICA	2 (1.7)
Extracranial involvement of ICA	
No	94 (79.0)
Carotid occlusion or stenosis >70%	14 (11.8)
Dissection	7 (5.9)
Pseudo-occlusion	4 (3.4)
ASPECTS	9 (6–10)
Tan collateral score ≥2	90 (75.6)
Treatment with IVT	81 (68.1)
Time from symptom onset to end of IAT, min	339±180
Good clinical outcome (mRS ≤2) at 3-month follow-up	47 (40.2)

Data are presented as the mean ± SD, *n* (%), or median (IQR). ACA, anterior cerebral artery; ASPECTS, Alberta Stroke Program Early CT Score; eTICI, extended treatment in cerebral ischemia; IAT, intra-arterial thrombectomy; ICA, internal carotid artery; IVT, intravenous thrombolysis; MCA, middle cerebral artery; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale.

Table 3. Univariate association between dichotomous predictors and poor clinical outcome

Variable	OR	95% CI	*p* value
Age >80 years	4.000	1.089–14.698	0.037
NIHSS at presentation >15	7.092	3.015–16.680	<0.001
ASPECTS <8	2.220	1.039–4.744	0.040
Tan collateral score <2	2.006	0.762–5.282	0.159
Treatment IVT	0.580	0.257–1.312	0.191
Time from onset to end of IAT <360 min	2.203	0.915–5.302	0.078
eTICI score <2B	10.443	3.380–32.264	<0.001
eTICI score <2C	11.431	4.639–28.167	<0.001

ORs (for poor clinical outcome) were computed using univariate logistic regression with a forced entry autoregressive covariance matrix. ASPECTS, Alberta Stroke Program Early CT Score; eTICI, extended treatment in cerebral ischemia; IAT, intra-arterial thrombectomy; IVT, intravenous thrombolysis; mRS, modified Rankin scale; NIHSS, National Institutes of Health Stroke Scale.

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Table 4. Multivariate association between dichotomous predictors and poor clinical outcome

Variable	OR	95% CI	*p* value
Age >80 years	6.798	1.160–39.829	0.034
NIHSS at presentation >15	7.316	2.276–23.524	0.001
ASPECTS <8	0.901	0.291–2.787	0.856
TAN score <2	2.093	0.462–9.468	0.338
Treatment IVT	0.516	0.167–1.596	0.251
Time from onset to end of IAT <360 min	0.172	0.699–7.420	0.172
eTICI score <2C	10.324	3.483–30.597	<0.001

ORs were computed using multivariate logistic regression with a forced entry autoregressive covariance matrix. ASPECTS, Alberta Stroke Program Early CT Score; eTICI, extended treatment in cerebral ischemia; IAT, intra-arterial thrombectomy; IVT, intravenous thrombolysis; mRS, modified Rankin scale; NIHSS, National Institutes of Health Stroke Scale.

Table 5. mRS score per eTICI score

eTICI score	Good functional outcome (mRS 0–2), *n*	Poor functional outcome (mRS 3–6), *n*
0	1	11
1	2	6
2A	1	17
2B	12	25
2C	18	5
3	13	5

eTICI, extended treatment in cerebral ischemia; mRS, modified Rankin scale.

1.2–39.8), NIHSS at presentation (OR 7.3, 95% CI 2.3–23.5), and eTICI score cutoff <2C (OR 10.3, 95% CI 3.5–30.6) were significantly associated with a poor clinical outcome at 3 months (see Table 4). The ASPECT score, Tan collateral score, additional treatment with IVT, and time from symptom onset to the end of IAT procedure were not significantly associated with clinical outcome.

ROC analyses showed an AUC of a model without reperfusion status of 0.81 (95% CI 0.75–0.89), including the variables age, NIHSS at presentation, ASPECTS, Tan collateral score, time of symptom onset to the end of IAT procedure, and additional IVT at admission. A model incorporating eTICI (cutoff ≥2C) led to an AUC of 0.88 (95% CI 0.81–0.94). The likelihood ratio test for a model with an eTICI cutoff ≥2C versus a model without reperfusion status was 20.9 ($p < 0.001$).

Reperfusion Status

Eighteen out of 23 (78.3%) patients with an eTICI of 2C had a good clinical outcome, whilst only 12 out of 37 (32.4%) patients with an eTICI 2B score had a good clinical outcome. The positive predictive value (PPV) of eTICI 2C was 0.78; whilst the PPV of eTICI 2B was 0.32. The distribution of functional outcome versus reperfusion status is displayed in Figure 2 and Table 5.

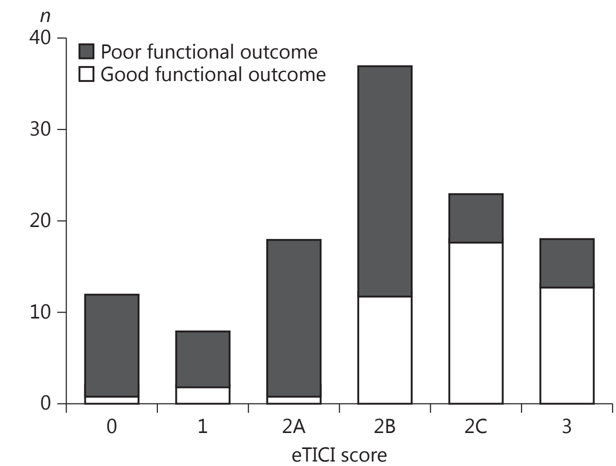

Fig. 2. Distribution of functional outcome per eTICI score. Good functional outcome/poor functional outcome: eTICI 0, *n* = 1/11; eTICI 1, *n* = 2/6; eTICI 2A, *n* = 1/17; eTICI 2B, *n* = 12/25; eTICI 2C, *n* = 18/5; eTICI 3, *n* = 13/5.

Discussion

Our study showed that reperfusion status after IAT has an additional prognostic value over baseline clinical and radiological characteristics, which has utility to provide patients and their families with a more accurate prognosis of functional dependence. Moreover, we found a substantial difference in clinical outcome between patients with a reperfusion status of eTICI 2B versus eTICI 2C, demonstrated by a large difference in PPV for good clinical outcome, favoring a cutoff at ≥2C. It has been previously suggested that TICI scores incorporating 2C would better correlate with patient outcome and may positively influence an IAT procedure [25]. A previous study stated that using eTICI ≥2C as opposed to ≥2B as the definition of successful reperfusion was a better predictor of outcome, especially of mRS 0–1 [26]. Our study results seem in line with those findings. Another recent study suggested that the outcome of patients with eTICI 2C is not clearly worse than patients with eTICI 3, whilst outcomes of both groups are significantly better than with eTICI 2B [32].

Older prediction score models include the Houston Intra-Arterial Therapy 2 (HIAT2) score, Totaled Health Risks in Vascular Events (THRIVE) score, Stroke Prognostication using Age and NIHSS (SPAN-100) index, iScore, and Pittsburgh Response to Endovascular therapy (PRE) score [19–23]. These models incorporate age and the severity of symptoms at presentation (NIHSS or Canadian Neurological Society score) and various variables such as prestroke mRS, ASPECTS, glucose at presentation, etiology of stroke, and medical history. However, previous studies have shown mTICI to be an important independent predictor of outcome [9–11] and this is not included in those models.

The patient characteristics of our study population, i.e., NIHSS at presentation, ASPECTS, rate of successful reperfusion status, and functional outcome, were in accordance with previous studies [2–4]. Most of the identified predictors were similar to those found in previous studies, i.e., advanced age, NIHSS at presentation, and successful revascularization [9, 11]. Previous studies already demonstrate the importance of revascularization and highlight aiming for swift and complete revascularization when performing IAT [9–11, 24, 33]. In contrast to previous studies [2, 3], ours did not show a significant influence of time from symptom onset to the end of IAT. However, this variable was dichotomized at 360 min, which is the accepted time window for IAT. Patients treated outside this time window may have had favorable baseline parameters, thus possibly introducing selection bias. However, our findings suggest that patients may still benefit from IAT when performed more than 6 h after symptom onset and should not be excluded solely due to this time window, as previously demonstrated [34].

Recent results from the ESCAPE investigators showed that a neurological improvement in the first 2 days following a stroke predicted functional outcome with greater accuracy than other common variables [35]. Also, follow-up imaging was demonstrated to be a good predictor and possibly superior to mTICI scores [36, 37]. However, it would be beneficial for both patient and caregiver to have an early indication of prognosis to improve patient-caregiver communication and manage expectations.

With regards to radiological predictors, baseline CT ASPECTS was a significant predictor of outcome in univariate analysis, as demonstrated before [8, 9, 12–14, 17, 29]. However, in multivariate analysis, CT ASPECTS was not an independent predictor of outcome. A possible explanation could be the limited sample size in combination with the strong association between clinical stroke severity (NIHSS) and the extent of ischemic changes (ASPECTS) [38], which resulted in an insignificant predictive value of ASPECTS when clinical characteristics were also included. Moreover, recent studies have shown that CT ASPECTS and CT perfusion findings were not independent predictors when reperfusion status was included [11, 38]. CT ASPECTS has limited inter- and intrarater reliability [39] and is less predictive than diffusion-weighted imaging (DWI)-ASPECTS or CT perfusion [40–42]. However, recent studies using MRI DWI-ASPECTS also highlighted the importance of reperfusion status for the prediction of outcome [33, 43].

The limited prognostic value of the Tan collateral status in our cohort could be related to the use of single-phase CT instead of multiphase CTA. Single-phase CTA may underestimate the extent of the collateral status [18]. Some studies found that collateral status was not an independent predictor of outcome when other variables were taken into account [14, 38]. Our results suggest that CT/CTA findings at presentation are of limited value for predicting clinical outcome and should be interpreted with caution [8, 42].

One of the strengths of this study is that all patients with a proximal occlusion in the anterior circulation in whom IAT was performed were included without using any additional imaging inclusion criteria, which increases the generalizability of our results. Other strengths include a near-complete follow-up and no other clinical selection criteria being used besides the exclusion of patients with a prestroke dependent functional status (mRS >2).

A limitation of our work is that it is a single-center study with a limited number of patients. Also, no independent core facility for imaging analysis scored the reperfusion status. However, the imaging analyses were performed by 2 independent experienced stroke researchers who were blinded for functional outcome. Our findings should be verified on a larger scale, preferably in a multicenter setting. This could ultimately lead to a scoring system to predict outcome after IAT, preferably incorporating reperfusion status.

In conclusion, advanced age, higher NIHSS at presentation, and poor reperfusion status after IAT were the strongest predictors of a poor clinical outcome. These findings provide useful and early information on prognosis for both the patient and caregiver, and could ultimately lead to the development of a prediction algorithm designed for prognosis after IAT. Moreover, the introduction of an extension of the mTICI scoring system, i.e., eTICI, seems to improve diagnostic accuracy given the large difference in clinical outcome between eTICI 2B and 2C.

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Disclosure Statement

The authors declare that they have no competing interests. No funding of any kind was received for the conduction of this study.

Author Contributions

I.R.v.d.W. conceptualized the study. L.D. and V.J.G. collected cases and drafted the manuscript. V.J.G. carried out the statistical analyses. H.H. and I.R.v.d.W. performed the imaging analysis. R.G.N., S.C.C., M.G., and I.R.v.d.W. contributed to critical revision of the manuscript. All authors helped in the revision of the manuscript and approved the final version.

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