Original research

Predictors of poor clinical outcome despite complete reperfusion in acute ischemic stroke patients

Noel van Horn,1 Helge Kniep,1 Hannes Leischnner,1 Rosalie McDonough,1 Milani Deb-Chatterji,2 Gabriel Broocks,1,1 Goetz Thomalla,2 Caspar Brekenfeld,1 Jens Fiehler,1 Uta Hanning,1 Fabian Flottmann1

ABSTRACT

Background In patients suffering from acute ischemic stroke from large vessel occlusion (LVO), mechanical thrombectomy (MT) often leads to successful reperfusion. Only approximately half of these patients have a favorable clinical outcome. Our aim was to determine the prognostic factors associated with poor clinical outcome following complete reperfusion.

Methods Patients treated with MT for LVO from a prospective single-center stroke registry between July 2015 and April 2019 were screened. Complete reperfusion was defined as Thrombolysis in Cerebral Infarction (TICI) grade 3. A modified Rankin scale at 90 days (mRS90) of 3–6 was defined as ‘poor outcome’. A logistic regression analysis was performed with poor outcome as a dependent variable, and baseline clinical data, comorbidities, stroke severity, collateral status, and treatment information as independent variables.

Results 123 patients with complete reperfusion (TICI 3) were included in this study. Poor clinical outcome was observed in 67 (54.5%) of these patients. Multivariable logistic regression analysis identified greater age (adjusted OR 1.10, 95% CI 1.04 to 1.17; p=0.001), higher admission National Institutes of Health Stroke Scale (NIHSS) (OR 1.14, 95% CI 1.02 to 1.28; p=0.024), and lower Alberta Stroke Program Early CT Score (ASPECTS) (OR 0.6, 95% CI 0.4 to 0.84; p=0.007) as independent predictors of poor outcome. Poor outcome was independent of collateral score.

Conclusion Poor clinical outcome is observed in a large proportion of acute ischemic stroke patients treated with MT, despite complete reperfusion. In this study, futile recanalization was shown to occur independently of collateral status, but was associated with increasing age and stroke severity.

INTRODUCTION

Recently, several randomized clinical trials have demonstrated the benefit and safety of mechanical thrombectomy (MT) for large vessel occlusion (LVO) stroke within the anterior circulation.1–3 Accordingly, successful recanalization graded by the Thrombolysis In Cerebral Infarction scale (TICI) is presumed to be one of the strongest predictors for favorable clinical outcome.1 In the HERMES (Highly Effective Reperfusion Using Multiple Endovascular Devices) meta-analysis, successful reperfusion was reported in up to 71% of patients.1 Results of the latest trials showed even higher reperfusion rates with up to 95% of patients achieving TICI 2b/3 reperfusion.1–3 However, a substantial proportion of patients experience futile recanalization, defined as poor long-term outcome despite successful reperfusion. Recently, a meta-analysis showed that poor outcome (modified Rankin scale (mRS) at 90 days (mRS90) of 3–6) occurs in 45% of TICI 2b/3 cases.4 Yet another meta-analysis that pooled the results of five randomized clinical trials presented futile reperfusion rates of 54%.5 A clinical explanation for this finding of poor outcome in a considerable number of patients successfully treated with MT is currently missing in the literature. Indeed, the majority of analyses investigating futile reperfusion refer only to TICI 2b/3 reperfusion rates.6–8,9 no studies on poor clinical outcome in patients achieving TICI 3 have been performed, despite known large differences in the outcome and safety profiles between TICI 2b and 3 reperfusion grades.6–10

This study presents the first investigation of the relationship between complete (TICI 3) reperfusion and subsequent long-term poor clinical outcome. We hypothesize that baseline clinical data, stroke severity, comorbidities and treatment circumstances are correlated with poor clinical outcome, despite angiographic results of TICI 3.

METHODS

Study population

In this retrospective single-center study, we evaluated 617 consecutive patients who underwent MT for acute LVO from a prospectively collected database from July 2015 to April 2019. In our clinic, patients with acute LVO routinely undergo MT according to the standard of care. MT is only withheld in patients with large early infarction lesions (Alberta Stroke Program Early CT Score (ASPECTS) <5) or those presenting within the late time window without evidence of perfusion mismatch.

The inclusion criteria of the present study were as follows: (1) acute ischemic stroke due to LVO within the anterior circulation, including the internal carotid artery (ICA) or middle cerebral artery (MCA); (2) complete reperfusion (defined as TICI 3); (3) known admission National Institutes of Health Stroke Scale (NIHSS) and ASPECTS; (4) known mRS90 days after stroke onset; (5) available collateral score on CT angiography (CTA); and (6) pre-mRS ≤2. Figure 1 demonstrates the stepwise patient inclusion process.

Patients underwent MT according to the standard protocol using stent-retrievers and/or aspiration catheters. All patients were under the supervision of
Ischemic Stroke

Figure 1: Flow chart demonstrating the number (n) of patients included in the analysis. Inclusion of n = 123 TICI 3 patients with anterior circulation stroke, known NIHSS, ASPECTS, mRS90, collateral score and pre-stroke mRS ≤2. ASPECTS, Alberta Stroke Program Early CT Score; LVO, large vessel occlusion; mRS, modified Rankin Scale; mRS90, mRS after 90 days; MT, mechanical thrombectomy; NIHSS, National Institutes of Health Stroke Scale; TICI, Thrombolysis in Cerebral Infarction.

Patient inclusion criteria

- Pre-stroke mRS ≤ 2
  - n = 123
- Known NIHSS
  - n = 175
- Known ASPECTS
  - n = 192
- Known collateral score
  - n = 198
- TICI 3 patients
  - n = 250
- Anterior circulation stroke
  - n = 572
- LVO patients treated with MT
  - n = 617
on diffusion-/perfusion-weighted imaging. The diagnosis of ICA
or MCA occlusion was verified on digital subtraction angiography
(DSA) images in all patients. Intracranial collaterals were evaluated
according to the Maas system. All images were analyzed by an
experienced neuroradiologist (> 5 years of experience).

**Procedure and functional outcome**

The following clinical, imaging and procedural data were collected:
use of intravenous thrombolysis, time from onset to admission
and to recanalization (if available), as well as time from puncture
to reperfusion. The angiographic result was assessed on the final
DSA image series and was classified according to the TICI scale;
successful reperfusion was defined as TICI 3.

Experienced neurologists examined all patients, applying
the NIHSS and pre-stroke mRS on admission and at 90 days
follow-up. We defined a binary outcome with mRS90 0–2 as
good and mRS90 3–6 as poor outcome.

**Statistical analysis**

The univariable distribution of metric variables is described
by the median and IQR. Absolute and relative frequencies are
given for categorical data. The association between clinical and
radiological parameters and outcome was assessed by logistic
regression analysis. Multivariable analysis was performed using
a logistic regression model with unfavorable outcome at 3 months
as the dependent variable. The variables included in the multi-
variable analysis as predictor variables included age, sex, baseline
NIHSS, mRS, ASPECTS, time from groin puncture to recanalization,
type of anesthesia, location of vessel occlusion, intrave-
rous thrombolysis, comorbidities, and collateral score.

Statistical analysis of all data, including odds ratios and 95% confidence intervals (OR, 95% CI), were calculated using the
SPSS statistical software (IBM, SPSS Statistics 25.0, Armonk,
New York, USA) and R (R Core Team, 2019, Vienna, Austria).

**RESULTS**

**Baseline characteristics of patients**

Of 617 patients who underwent MT in the designated time
period, the final TICI score was reported in 572 patients; 250/572 patients (43.7%) had complete recanalization (TICI 3).
The inclusion criteria were fulfilled by 123 patients (see patient
selection flow chart, figure 1).

These patients had a median age of 75 years (IQR 67–81),
a median NIHSS on admission of 16 (IQR 12–19), and a median
ASPECTS of 8 (IQR 7–9). Twenty-three out of 123 (19%) patients received general anesthesia. The rate of futile reperfu-
sion (mRS90 of 3–6) was 54.5% (n=67/123), with a median age
of 78 years (IQR 70–83). The remaining 45.5% (n=56) had a median age of 69 years (IQR 62–78) and showed a
favorable outcome 3 months after treatment (mRS90 of 0–2).
Patient characteristics are displayed in table 1; 21% and 9% of
patients with poor and good outcome, respectively, had collat-
eral scores of 1, whereas 16% of patients with poor outcome
and 18% with good outcome had a collateral score of 4. Overall,
according to the scoring system developed by Maas, both
patient groups (ie, those with poor and good outcome) showed
comparable results, as seen in table 2.

**Interventional findings and treatment**

Comorbidities, location of occlusion, intravenous thrombol-
ysis, number of device passages, collateral score, and time from
onset to recanalization did not have a significant impact on clin-
ical prognosis. Data for time from onset to recanalization was
available for 79 patients (64%). Detailed interventional results
are displayed in table 2.

Results of multivariable statistical analysis are shown in
table 3. Poor clinical outcome was significantly associated with
the following parameters after adjusting for confounders: age
(adjusted OR 1.10, 95% CI 1.04 to 1.17; p<0.001), admission
NIHSS (OR 1.14, 95% CI 1.02 to 1.28; p=0.024) and ASPECTS
on admission imaging (OR 0.6, 95% CI 0.4 to 0.84; p=0.007).

**DISCUSSION**

This study was conducted to identify predictors for poor clinical
outcome, despite best possible treatment results after MT. In
our study cohort, approximately half (54.5%) of patients with
complete reperfusion showed poor clinical outcome at 90
days. These findings are in line with those from previous studies
conducted by Kaesmacher et al and Lee et al, who reported futile recanalization rates of 45% and 51.4%, respectively.

Our study, along with several others, identified greater age,
high NIHSS and low ASPECTS as independent predictors
for unfavorable clinical outcome at the 3 month follow-up
timepoint (mRS90 of 3–6). In contrast to previous studies also examining predictors of futile recanalization, we defined
our analysis to completely recanalized patients with a TICI
score of 3, justified by the significant differences in outcome
observed between TICI 2b and TICI 3, as described in a recent
meta-analysis.

Our analysis reveals that patients presenting with greater
age and with advanced focal neurological deficits are more
likely to have developed functional dependency by the 3 month
follow-up (mRS90 of 3–6). Greater age is frequently associ-
ated with poor neurological outcome after stroke, supposedly
due to pre-existing physical and/or cognitive disabilities, higher
frequency of complications during hospitalization, and therefore
overall lower potential for neurological rehabilitation. The
association between greater age and poor clinical outcome has

<table>
<thead>
<tr>
<th>Table 1 Baseline characteristics of TICI 3 patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographics</td>
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<tr>
<td>---------------</td>
</tr>
<tr>
<td>(n=123)</td>
</tr>
<tr>
<td>Age at admission, years (IQR)</td>
</tr>
<tr>
<td>Female, n (%)</td>
</tr>
<tr>
<td>Side of occlusion, left, n (%)</td>
</tr>
<tr>
<td>Vascular risk factors</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
</tr>
<tr>
<td>Diabetes, n (%)</td>
</tr>
<tr>
<td>Dyslipidemia, n (%)</td>
</tr>
<tr>
<td>Atrial fibrillation, n (%)</td>
</tr>
<tr>
<td>Smoking, n (%)</td>
</tr>
<tr>
<td>Clinical presentation</td>
</tr>
<tr>
<td>mRS on admission, median (IQR)</td>
</tr>
<tr>
<td>NIHSS on admission, median (IQR)</td>
</tr>
<tr>
<td>ASPECTS on admission, median (IQR)</td>
</tr>
<tr>
<td>Admission Imaging</td>
</tr>
<tr>
<td>CT, n (%)</td>
</tr>
<tr>
<td>MRI, n (%)</td>
</tr>
</tbody>
</table>

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been previously described by several studies, with noticeably worse clinical outcomes observed for patients between the ages of 60–70 years compared with their younger counterparts, despite similar recanalization and intracranial hemorrhage rates.19 This is in line with our findings, which show that the elderly (>90 years) are more likely to benefit from complete reperfusion than the elderly (figure 2A). This of course does not imply that endovascular therapy is not indicated in older patients. A recent study conducted by Lee et al found that an increase in baseline NIHSS led to increased rates of futile reperfusion, but the clinical benefit of successful reperfusion after MT still outweighed the risks. Nevertheless, it is important to consider the results of the HERMES collaboration, a meta-analysis of five randomized trials, which showed only little therapeutic benefit in patients with initially low NIHSS (≤10).3

In this study cohort, collateral status, as detected on single-phase CTA, was not significantly associated with clinical outcome, contrary to previous findings.21 Bang et al analyzed multiple randomized trials (eg, ESCAPE, SWIFT, PRIME, REVASCAT, BRASIL, DEFUSE, etc) and reported that an evaluation of collateral status may be beneficial to patients within an extended time window (>4.5 hours for intravenous thrombolysis and >6 hours for MT), who would otherwise not be treated.22 However, these studies included patients both with and without successful reperfusion. Because reperfusion success is more likely in patients with a good collateral score,23 the positive effect on clinical outcome is possibly indirect. Nevertheless, no validated scoring system currently exists that sufficiently predicts patient outcome.24 Relatively quick, easy and reproducible CTA-based methods exist for the quantification of collateral status and its influence on ischemic lesion dynamics.25 We conclude that collateral status has a negligible effect in this group of patients, which is in agreement with an MRI-based study that reported collaterals were not a significant predictor of clinical outcome when correcting for reperfusion status. In addition, patients in this study had, on average, rather high ASPECTS, which is known to be correlated with good collateral status.26 Therefore, the majority of patients with poor collateral status may not have been included in this study.

Our analysis also shows that futile recanalization is significantly associated with lower ASPECTS on admission. ASPECTS has been validated for assessment of an early infarct lesion of the anterior circulation and is often employed to select patients who would most likely benefit from MT, thus helping to improve clinical prognosis in such patient collectives. Results from the HERMES meta-analysis provided strong evidence for the efficiency of MT with an ASPECTS ≥6.1 Nevertheless, an ASPECTS <6 is not representative of a definitive treatment threshold. A 2014 study provided evidence for an extension of the cut-off for endovascular treatment to an ASPECTS of ≥5, whereas a very low ASPECTS (0–4) was associated with higher mortality rates (53%) and led to an increased incidence of intracranial hemorrhage after recanalization.28 This study demonstrates that achieving TICI 3 reperfusion with low initial ASPECTS (<5) is much more promising in younger patients (<55 years) than in the elderly (>90 years) (figure 2B).

Other retrospective studies reported an increased risk of poor clinical outcome in patients who underwent general anesthesia. In contrast, a meta-analysis of a recent randomized controlled trial reported no significant differences in clinical outcome between

### Table 2 Imaging and interventional findings

<table>
<thead>
<tr>
<th>Location of occlusion</th>
<th>All</th>
<th>Good outcome (mRS90 0–2)</th>
<th>Poor outcome (mRS90 3–6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(n=123)</td>
<td>(n=56)</td>
<td>(n=67)</td>
<td></td>
</tr>
<tr>
<td>ICA large (with carotid T), n (%)</td>
<td>31 (25%)</td>
<td>6 (11%)</td>
<td>25 (37%)</td>
</tr>
<tr>
<td>MCA M1, n (%)</td>
<td>71 (58%)</td>
<td>41 (73%)</td>
<td>30 (45%)</td>
</tr>
<tr>
<td>MCA M1 proximal, n (%)</td>
<td>47 (38%)</td>
<td>25 (45%)</td>
<td>22 (33%)</td>
</tr>
<tr>
<td>MCA M1 distal, n (%)</td>
<td>24 (20%)</td>
<td>16 (29%)</td>
<td>8 (12%)</td>
</tr>
<tr>
<td>MCA M2, n (%)</td>
<td>17 (14%)</td>
<td>8 (14%)</td>
<td>9 (13%)</td>
</tr>
<tr>
<td>Tandem, n (%)</td>
<td>10 (8%)</td>
<td>6 (11%)</td>
<td>4 (6%)</td>
</tr>
</tbody>
</table>

### Table 3 Logistic regression analysis with odds ratio and p value for analyzed data

<table>
<thead>
<tr>
<th>Data variables</th>
<th>OR</th>
<th>CI 95 %</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>1.10</td>
<td>1.04</td>
<td>1.17</td>
</tr>
<tr>
<td>Sex, male</td>
<td>1.07</td>
<td>0.35</td>
<td>3.38</td>
</tr>
<tr>
<td>Arterial hypertension</td>
<td>0.37</td>
<td>0.10</td>
<td>1.24</td>
</tr>
<tr>
<td>Diabetes</td>
<td>0.98</td>
<td>0.23</td>
<td>4.15</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>0.32</td>
<td>0.07</td>
<td>2.32</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>0.68</td>
<td>0.19</td>
<td>2.32</td>
</tr>
<tr>
<td>Smoking</td>
<td>1.60</td>
<td>0.36</td>
<td>0.34</td>
</tr>
<tr>
<td>mRS on admission</td>
<td>4.93</td>
<td>0.88</td>
<td>85.75</td>
</tr>
<tr>
<td>NIHSS on admission</td>
<td>1.14</td>
<td>1.02</td>
<td>1.28</td>
</tr>
<tr>
<td>ASPECTS on admission</td>
<td>0.60</td>
<td>0.40</td>
<td>0.84</td>
</tr>
<tr>
<td>Maas collateral score</td>
<td>1.06</td>
<td>0.61</td>
<td>1.87</td>
</tr>
<tr>
<td>ICA</td>
<td>1.42</td>
<td>0.02</td>
<td>53.04</td>
</tr>
<tr>
<td>MCA M1 proximal</td>
<td>0.34</td>
<td>0.01</td>
<td>11.07</td>
</tr>
<tr>
<td>MCA M1 distal</td>
<td>0.26</td>
<td>0.00</td>
<td>10.06</td>
</tr>
<tr>
<td>MCA M2</td>
<td>1.64</td>
<td>0.02</td>
<td>70.50</td>
</tr>
<tr>
<td>General anesthesia</td>
<td>15.20</td>
<td>1.13</td>
<td>303.04</td>
</tr>
<tr>
<td>Local anesthesia (including conscious sedation)</td>
<td>3.52</td>
<td>0.37</td>
<td>39.21</td>
</tr>
<tr>
<td>Thrombolysis i.v.</td>
<td>0.54</td>
<td>0.18</td>
<td>1.65</td>
</tr>
<tr>
<td>Groin to recanalization, mins</td>
<td>1.00</td>
<td>0.98</td>
<td>1.02</td>
</tr>
</tbody>
</table>

Calculated OR, CI 2.5%, 97.5%, and p value of all analyzed variables via multivariable regression analysis.

ASPECTS, Alberta Stroke Program Early CT Score; ICA, internal carotid artery; i.v., intravenous; M1, M1 segment of MCA; M2, M2 segment of MCA; MCA, middle cerebral artery; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale.
general anesthesia and conscious sedation.\textsuperscript{33} We also found no significant association between general anesthesia and poor clinical outcome, although the result was borderline (p=0.052). The tendency towards poor outcome after general anesthesia in retrospective studies is most likely caused by a selection bias, as more critically ill patients are more likely to undergo general anesthesia.

The present study confirms the well-known outcome predictors in acute LVO ischemic stroke, where TICI 3 reperfusion has often been proposed as the therapeutic goal.\textsuperscript{32} Understanding why a large subset of these successfully reperfused patients still experience poor outcome could help to identify new targets for therapy and thereby further improve patient outcome. For example, hyperglycemia is a common phenomenon in patients suffering from acute ischemic stroke and is associated with poor clinical outcome.\textsuperscript{33 34} Blood platelet count serves as another potential biomarker that is correlated with poor functional outcome, as well as stroke recurrence and higher mortality rates.\textsuperscript{35} The recently discussed topic of net water uptake in ischemic lesions, calculated in acute multimodal and follow-up CT, is another quantitative imaging parameter that is associated with poor clinical outcome after TICI 2b/3 reperfusion.\textsuperscript{36} More sophisticated imaging analyses of early ischemic signs are also possible on common non-contrast CT scans. For example, automated software applied on non-contrast CT was able to identify future ASPECTS regions (as later verified by CT perfusion) by comparing relative Hounsfield units between the symptomatic and asymptomatic cerebral hemisphere.\textsuperscript{37} The number of device passes could also be included in future studies to investigate possible effects on clinical follow-up.\textsuperscript{38} So far, these findings have not been correlated to TICI 3 reperfusion rates, and comprehensive data as well as more in-depth analyses are needed to better understand the clinical course of these patients.

Our study is subject to some limitations as our dataset represents a retrospective registry observation of prospectively collected data from a single center. It would be interesting to match our findings with those of transregional medical centers with the intent of unmasking similarities and dissimilarities in clinical outcome. Although our standard of care in treating acute ischemic stroke is widely, there are nevertheless differences in the preferences of the dichotomization used in this study for clinical outcome neglects differences between mRS 3, 4, 5 and 6. An extended, more in-depth analysis including a greater number of TICI 3 patients is needed to identify potential minor differences.

\textbf{CONCLUSION}

While the benefit of MT has been repeatedly demonstrated in various trials and meta-analyses, a considerably large number of patients with acute LVO have a poor clinical prognosis despite successful flow restoration. Our findings suggest that advanced age and increased stroke severity are independent predictors for an unfavorable clinical outcome following complete reperfusion, independent of collateral status.

\textbf{Correction notice} Since its online publication, this article has been updated to show that authors ‘Uta Hanning’ and ‘Fabian Flottmann’ are equally contributing.

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\textbf{ORCID iDs} Noel van Horn http://orcid.org/0000-0001-5764-1982
Gabriel Broocks http://orcid.org/0000-0002-7575-980
Fabian Flottmann http://orcid.org/0000-0001-8358-8089

\section*{Ischemic Stroke}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure2.png}
\caption{(A) Three-dimensional surface plot demonstrating the impact of NIHSS at admission (x axis) and age (z axis) on probability for poor clinical outcome after 90 days (mRS 3–6 after 90 days, y axis). A higher NIHSS and greater age lead to an increasing probability of an mRS $\geq 3–6$. (B) Three-dimensional surface plot demonstrating the impact of age (x axis) and ASPECTS (z axis) on probability for poor clinical outcome after 90 days (mRS 3–6 after 90 days, y axis). Greater age and lower ASPECTS lead to an increasing probability of an mRS $\geq 3–6$. ASPECTS, Alberta Stroke Program Early CT Score; mRS, modified Rankin scale; NIHSS, National Institutes of Health Stroke Scale.}
\end{figure}
Ischemic Stroke

REFERENCES


