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Research article

DWI-FLAIR mismatch guided thrombolysis in patients without large-vessel occlusion: real-world data from a comprehensive stroke centre

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HIGHLIGHTS

- Real-world data on DWI-FLAIR mismatch based thrombolysis.
- Only patients without large vessel occlusion were analysed.
- Thrombolysis was associated with early neurological improvement.
- The rate of intracerebral haemorrhage was not increased.

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ABSTRACT

Introduction: A significant proportion of ischaemic stroke patients present with unknown symptom onset time. DWI-FLAIR mismatch on MRI can help to identify those eligible for thrombolysis. We set out to analyse the short-term efficacy and safety of thrombolysis in a real-world setting.

Methods: A retrospective single-centre observational study was conducted. We collected data between January 2017 and April 2020. Patients with a large vessel occlusion (LVO) were excluded. Outcomes were compared between thrombolysed patients and those who did not receive alteplase due to lack of DWI-FLAIR mismatch or other contraindications. We analysed baseline and discharge NIHSS scores for efficacy and defined good outcome as any neurological improvement (ANI) on the NIHSS. In terms of safety, the presence and severity of intracerebral haemorrhage on follow-up imaging was analysed, and mortality at 90 days assessed.

Results: Seventy-one patients were included in this study, of whom 29 received thrombolysis. Significantly more patients had ANI in the thrombolysed group (OR, 3.16; 95% CI, 1.178–8.479; $p = 0.020$). In a multivariable logistic regression analysis, only thrombolysis correlated with ANI (OR, 3.051; 95% CI, 1.135–8.206; $p = 0.027$). Two thrombolysed patients suffered intracerebral haemorrhage (6.90%), of whom one was symptomatic and eventually fatal. We did not find a significant difference in 90-day mortality between the two groups (OR, 0.81, 95% CI, 0.134–4.856; $p = 1.000$).

Conclusions: Our real-world data demonstrate that thrombolysis based on DWI-FLAIR mismatch in patients without LVO has an early beneficial effect. The rate of intracerebral haemorrhage was similar to this complication reported in large thrombolysis trials with known onset times.

1. Introduction

Determining the exact symptom onset time in acute ischaemic stroke is often difficult. Approximately 14–27% of stroke patients present to the emergency department with unknown symptom onset time [1]. A commonly encountered scenario is a wake-up stroke). Furthermore, agitated or aphasic patients and those with neurocognitive deficits might not be able to tell when their symptoms started, making treatment decisions challenging.

Current guidelines recommend systemic thrombolysis within 4.5 h after symptom onset [2, 3]. If the onset time is unknown and the time last seen well is beyond 4.5 h, then specific imaging modalities can help to establish eligibility for thrombolytic therapy. One option is the MRI based diffusion-weighted imaging (DWI) – fluid-attenuated inversion recovery

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(FLAIR) mismatch concept. DWI detects ischaemia induced changes in cellular water diffusion within minutes [4, 5]. In comparison, T2 weighted imaging and consequently FLAIR imaging have a sensitivity to only detect net water increase and vasogenic oedema that follows cytotoxic oedema [6, 7]. Therefore, it takes at least 1–4 h for the ischaemic stroke to become visible on FLAIR imaging. The PRE-FLAIR (Identification of Stroke Patients $\leq$3 and $\leq$4.5 Hours of Symptom Onset by Fluid Attenuated Inversion Recovery Imaging and Diffusion-Weighted Imaging) study dem onstrated that the DWI-FLAIR mismatch pattern identifies ischaemic lesions within 4.5 h after symptom onset with 78% specificity and 83% positive predictive value [8]. In a multicentre, randomised, double-blind, placebo-controlled trial (Efficacy and Safety of MRI-based Thrombolysis in Wake-up Stroke, i.e. the WAKE-UP trial), alteplase treatment was administered for patients with unknown stroke onset times who were last seen well more than 4.5 h before symptoms were noticed, and had DWI-FLAIR mismatch [9]. Mismatch was defined as a DWI lesion without corresponding marked FLAIR hyperintensity. Patients treated with alteplase had significantly better functional outcomes at 90 days than those who received placebo. However, severe parenchymal haemorrhages were also significantly more common in the treatment arm. Nevertheless, the WAKE-UP trial provided high-quality evidence on the benefit of alteplase treatment in patients with unknown symptom onset times and a DWI-FLAIR mismatch on MRI.

Our study aimed to share our real-world experience and the challenges of selecting patients for thrombolysis based on the DWI-FLAIR mismatch pattern. We set out to analyse the short-term efficacy and safety of alteplase treatment. We also compared the outcome of treated patients to those not eligible for thrombolysis due to no DWI-FLAIR mismatch or other contraindications. Our analysis included patients with unknown symptom onset times as well as cases where MRI was performed because of diagnostic uncertainty within 4.5 h after symptom onset.

2. Methods

2.1. Patients

A retrospective single-centre observational study was conducted between. January 2017 and April 2020. We identified patients with a suspected clinical diagnosis of acute ischaemic stroke, where an MRI showed DWI hyperintensity. Patients with large vessel occlusions (LVO), who were candidates for thrombectomy, were excluded because our main goal was to analyse the effects of thrombolytic therapy alone. Based on the DWI-FLAIR mismatch pattern, the indication for thrombolysis was established by an experienced attending stroke neurologist. All procedures were carried out in accordance with the Hungarian Acute Ischaemic Stroke Diagnostic and Treatment Recommendations [10]. We used a more permissive protocol than the WAKE-UP trial: patients with partial DWI-FLAIR mismatch were also eligible for treatment, and pre-stroke functional dependence or age were not contraindications for thrombolytic therapy. Patients who received alteplase had repeat imaging (CT or MRI) approximately 24 h after thrombolysis. All patients or their legal representatives gave informed consent before treatment. The Ethics Committee of the University of Szeged, Albert Szent-Györgyi Health Centre approved our study (ID: 6/2017-SZTE), which was conducted according to the revised Declaration of Helsinki.

Parameters of patients treated with alteplase were compared to those who did not receive this treatment due to a matched DWI-FLAIR pattern or other contraindications. For each patient, we recorded detailed demographic characteristics and vascular risk profile. Blood glucose was measured from serum samples taken upon arrival to the Emergency Department (ED). Blood pressure readings were recorded upon arrival to ED.

2.2. Imaging protocol

Each patient underwent multimodal brain MRI acutely, performed with a 1.5 T GE Signa Excite MRI scanner. The acute stroke MRI protocol included DWI, FLAIR, and susceptibility-weighted angiography (SWAN). DWI-FLAIR mismatch was defined as an ischaemic DWI lesion with no corresponding signal change on the FLAIR sequences. Partial mismatch was defined as a corresponding FLAIR signal change smaller than the DWI hyperintensity. Figures 1, 2, and 3 show examples for DWI-FLAIR complete mismatch, partial mismatch and matched pattern. The attending radiologist and neurologist rated the mismatch patterns visually.

2.3. Outcome measures

We analysed baseline and discharge National Institutes of Health Stroke Scale (NIHSS) scores as outcome of efficacy. We defined good short term outcomes as any neurological improvement (ANI), as indicated by a lower NIHSS score at discharge compared to baseline.

In terms of safety outcomes, we analysed the occurrence of intracerebral haemorrhage (ICH) on the 24-hour repeat imaging after thrombolysis. The extent of the haemorrhage was graded according to the European Cooperative Acute Stroke Study II (ECASS II) [11]. Symptomatic ICH (sICH) was also defined according to the ECASS II trial criteria (i.e., any haemorrhage leading to death or neurologic deterioration causing at least 4 point increase in the NIHSS score compared to baseline). Hypersensitivity reaction to alteplase, transfer to intensive care unit (ICU), and mortality within 90 days after stroke were recorded. Comparisons of outcomes between genders were also performed.

2.4. Statistical analysis

The outcome measures were categorical variables. For continuous variables, the distribution of data was tested with the Shapiro-Wilk test. Normally distributed variables were expressed as mean $\pm$ SD and non-normally distributed data as median and IQR. Continuous variables were compared with independent samples t-test for normally distributed data or Mann-Whitney U test in the case of non-normal distribution. Pearson's chi-squared test of independence was applied to compare categorical variables, but we used Fisher's exact test where sample sizes were small (i.e. equal to or less than 5). Statistical significance was met when the p-value was <0.05. To compare ANI and mortality between the groups, 95% confidence intervals (CI) and odds ratios (OR) were calculated by standard approaches. We also performed multivariable logistic regression to analyse the correlation between thrombolysis and ANI. We applied a backward likelihood ratio model selection method. Variables included in the analysis were age, gender, admission blood glucose, admission systolic and diastolic blood pressure, baseline NIHSS and thrombolysis. OR and 95% CI were again calculated. Statistical significance was met when the p-value was <0.05. All statistical analyses were performed with IBM SPSS version 22 statistical software (SPSS Inc., Chicago, USA).

3. Results

We identified 121 patients with a clinical diagnosis of acute ischaemic stroke and DWI hyperintensity on their MRI. Patients with known and unknown stroke onset times were both included. MRI images were not available for review in 17 patients due to technical reasons. Twenty-five patients with LVOs were also excluded. Furthermore, eight patients were excluded because their symptom onset was confirmed as beyond the 4.5-hour time window. Eventually, 71 patients were included in our final analysis. Figure 4 shows the flowchart of patient selection.

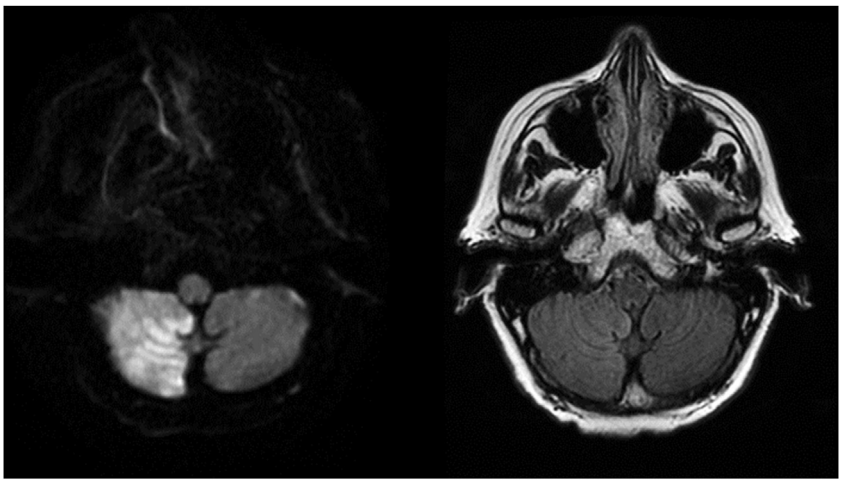

Figure 1. Complete DWI-FLAIR mismatch of a right cerebellar infarct.

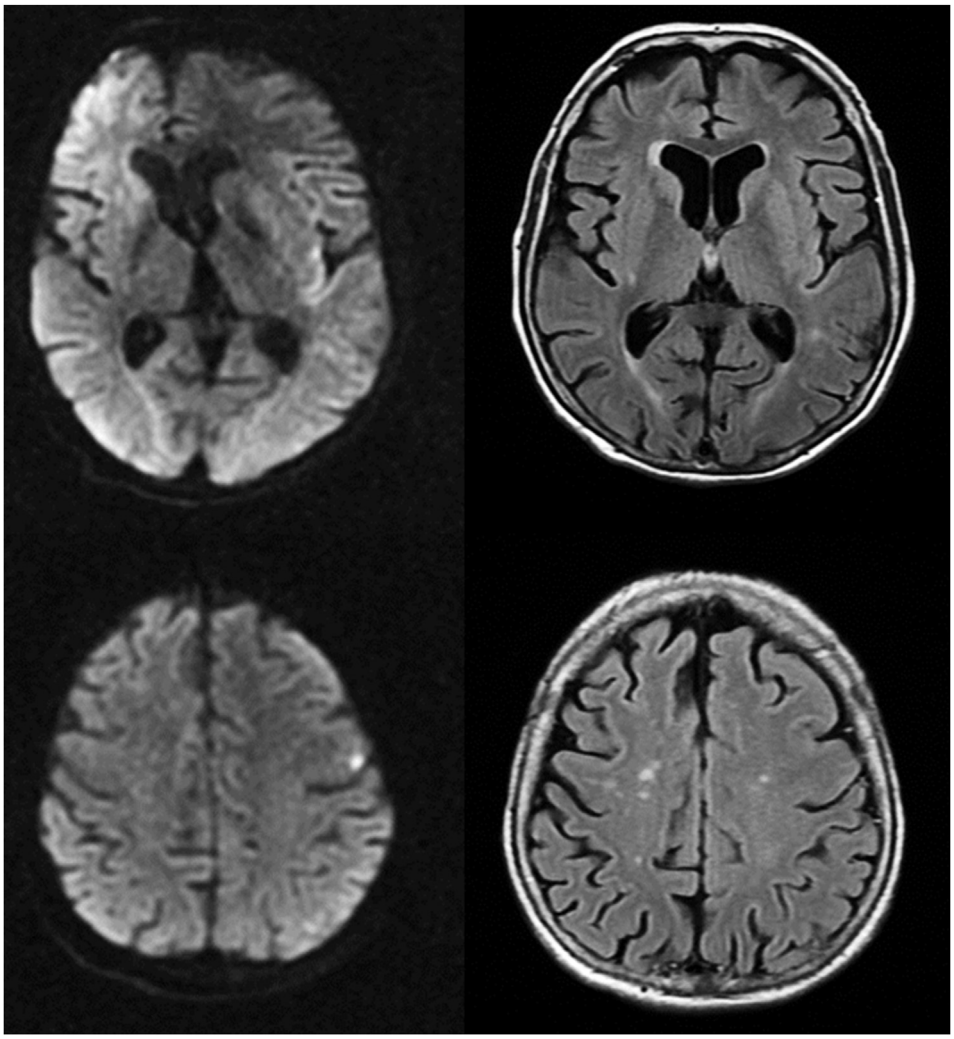

Figure 2. Example for partial mismatch. Superior row: left insular DWI hyperintensity with corresponding FLAIR signal change. Inferior row: the left frontal cortical DWI lesion is not yet visible on FLAIR.

Twenty-nine patients received intravenous thrombolysis. One patient received alteplase despite having a matched DWI-FLAIR pattern because the onset of symptoms was known to be within 4.5 h. In this particular case, MRI was ordered due to diagnostic uncertainty. Six patients had partial DWI-FLAIR mismatch on MRI. Two of these patients were not administered thrombolysis due to sulcal siderosis in one and a previous intracerebral haemorrhage in the other case, as detected on SWAN. Four patients had DWI-FLAIR mismatch but did not receive alteplase due to

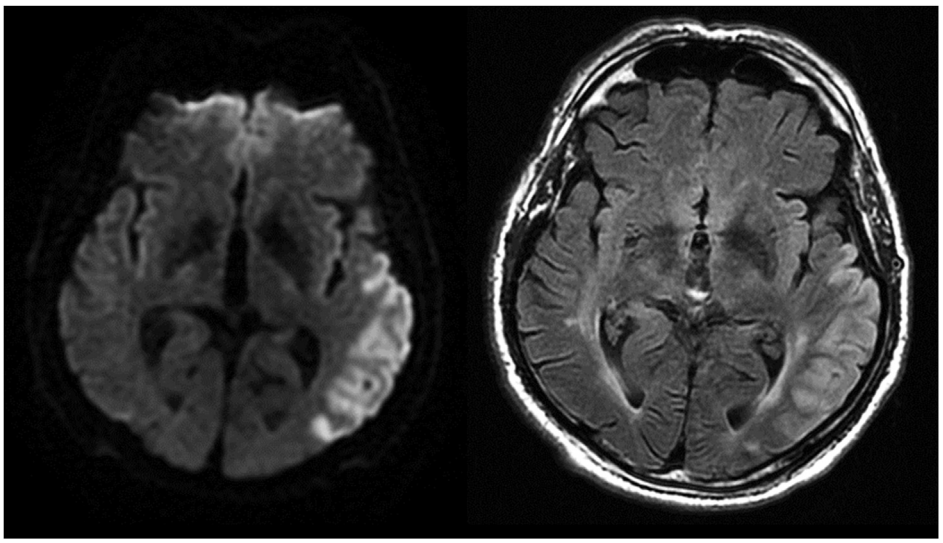

Figure 3. Matched DWI-FLAIR pattern of a left temporal infarct.

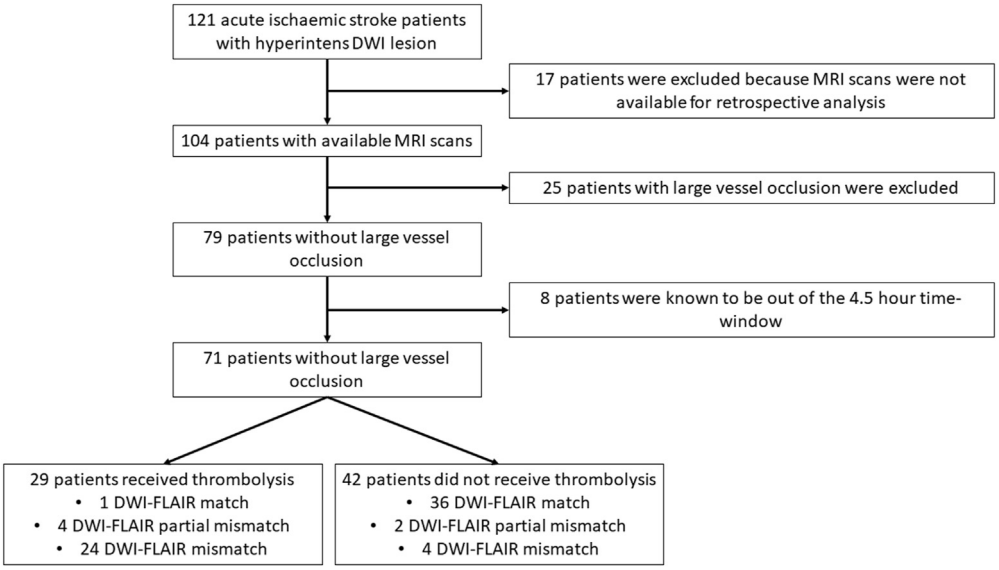

Figure 4. Flowchart demonstrating patient selection in our study.

contraindications: two had signs of previous clinically significant intracerebral haemorrhage on SWAN, one had a haemorrhagic transformation of the culprit infarct, and one had pancreatic cancer and more than ten cortical microbleeds on SWAN. Table 1 presents the demographics and clinical characteristics of our study population. One patient in the non-thrombolysed group suffered a stroke in the emergency department, therefore, a door-to-imaging time is not available for this case. We detected significantly more lacunar infarcts in non-thrombolysed patients ($p = 0.042$). Otherwise, the two groups were well balanced.

3.1. Efficacy and safety outcomes

Significantly more patients had ANI in the thrombolysed group (OR, 3.16; 95% CI, 1.178–8.479; $p = 0.020$). In the multivariable logistic regression analysis, thrombolysis was the only variable that correlated with ANI (OR, 3.051; 95% CI, 1.135–8.206; $p = 0.027$). There were no differences between men and women regarding ANI ($p = 0.451$ among thrombolysed patients and $p = 0.320$ for non-thrombolysed patients).

Only patients in the thrombolysis arm had follow-up imaging. There were no clinical indications for a repeat scan in any of the non-thrombolysed patients. Two thrombolysed patients had intracranial haemorrhage on follow-up imaging (6.90%). One patient had parenchymal haemorrhage type I (PH 1), and another had a remote PH 2. Only the patient with PH 2 had a sICH (3.45%). He died five days after thrombolysis. The initial MRI scan showed a complete DWI-FLAIR mismatch for a right hemispheric lacunar infarct without hypointense signal changes on SWAN. The follow-up CT (Figure 5(A)–(D)) showed a large left parieto-temporo-occipital haemorrhage with perifocal oedema, mass effect, and propagation into the ventricles.

There was no hypersensitivity reaction to alteplase, and there was no need for ICU transfer for ventilation or vasopressor support in either group.

Eighteen patients were lost to long term follow-up. Of the remaining 53 individuals, six died within 90 days after stroke (11.32%): two in the thrombolysed ($n = 20$, 10.00%) and four in the non-thrombolysed group ($n = 33$, 12.12%), with statistically non-significant odds (OR, 0.81, 95%

Table 1. Demographics and clinical characteristics of the study population.

	Thrombolysis (n = 29)	No thrombolysis (n = 42)	p value
Mean age ± SD	73.34 ± 8.66	71.52 ± 9.40	0.404
Male sex – no. (%)	16 (55.17%)	22 (52.38%)	0.817
Medical history – no. (%)			
Hypertension	26 (89.66%)	40 (95.24%)	0.393
Hyperlipidaemia	19 (65.52%)	34 (80.95%)	0.142
Diabetes mellitus	11 (37.93%)	14 (33.33%)	0.690
Smoking	8 (27.59%)	12 (28.57%)	0.928
Excess alcohol consumption	6 (20.69%)	8 (19.05%)	0.864
Atrial fibrillation	8 (27.59%)	12 (28.57%)	0.928
Carotid stenosis > 50%	4 (13.79%)	5 (11.90%)	1.000
Symptomatic carotid stenosis	4 (13.79%)	3 (7.14%)	0.433
Previous carotid endarterectomy or stenting	2 (6.90%)	1 (2.38%)	0.563
Coronary artery disease	3 (10.34%)	5 (11.90%)	1.000
Peripheral artery disease	1 (3.45%)	1 (2.38%)	1.000
Clinical parameters			
Median blood glucose (IQR) – mmol/l	7.70 (6.55–9.75)	6.70 (n = 41, 6.10–9.30)	0.233
Mean systolic blood pressure ± SD – mmHg	167.93 ± 24.09	168.05 ± 30.20	0.986
Mean diastolic blood pressure ± SD – mmHg	90.14 ± 16.33	90.74 ± 18.04	0.885
Median NIHSS score at baseline (IQR)	5.00 (3.00–9.00)	4.50 (3.00–7.00)	0.337
Median NIHSS score at discharge (IQR)	3.00 (2.00–7.50)	4.00 (3.00–6.00)	0.855
Lacunar stroke	5 (17.24%)	17 (40.48%)	**0.042**
Time intervals			
Median door to imaging time (IQR) – min	31.00 (24.50–60.50)	36.00 (n = 41, 22.00–74.50)	0.672
Median imaging to needle time (IQR) – min	34.00 (20.50–42.50)	–	–
Median door to needle time (IQR) – min	70.00 (50.00–109.00)	–	–
Length of hospital stay (IQR) – days	5.00 (4.00–5.50)	5.00 (3.00–6.25)	0.785
Outcome measures			
Any neurological improvement	17 (58.62%)	13 (30.95%)	**0.020**
Haemorrhagic transformation	2 (6.90%)	–	–
sICH	1 (3.45%)	–	–
Transfer to intensive care unit	0 (0.00%)	0 (0.00%)	–
Allergic reaction to alteplase	0 (0.00%)	–	–
Mortality at 90 days	2 (n = 20, 10.00%)	4 (n = 33, 12.12%)	1.000

CI, 0.134–4.856; p = 1.000). Mortality was similar between genders (p = 1.000 for both thrombolysed and non-thrombolysed patients). Autopsies were not performed, and the cause of death was determined on clinical grounds. In the thrombolysed group, one patient died five days after stroke due to the previously mentioned sICH, and one patient died 18 days after stroke due to complications from a sacral pressure sore. In the non-thrombolysed group, one patient died 34 days post-stroke from decompensation of heart failure, and two patients died due to infections at 18 (pneumonia) and 63 (Clostridium difficile) days after stroke, respectively. One patient died at 25 days from complications of a posterior circulation stroke.

4. Discussion

Our real-world data support the use of the DWI-FLAIR mismatch concept for alteplase treatment in acute ischaemic stroke patients without LVO. We analysed ANI to investigate short-term response to alteplase because the actual treatment effect may be better reflected by the NIHSS score rather than the 90-day modified Rankin Scale score (mRS), which is more dependent on a variety of other factors such as comorbidities, polypharmacy, the availability and quality of rehabilitation, support provided by family, and socioeconomic status. It is worth highlighting that the definition of early neurological improvement varies between studies [12]. In the NINDS trial (National Institute of Neurological Disorders and Stroke Recombinant Tissue Plasminogen Activator Stroke Study), it was defined as complete resolution of symptoms or at least a 4-point decrease in the NIHSS score 24 h after treatment [13]. Another study analysed the absolute change between baseline and 24-hour NIHSS scores [14].

As the baseline NIHSS scores were relatively low in our study (a median of 5 and 4.5 points in the thrombolysed and non-thrombolysed arms, respectively), we felt that defining early neurological improvement similar to the NINDS trial was not practical. Furthermore, instead of taking the NIHSS score at 24 h, we measured this outcome at discharge, which in our opinion is reasonable practice considering the median length of hospital stay of only five days in both groups. A number of studies support the use of short-term response to thrombolysis, as an outcome, which has a correlation with functional outcome at 90 days [15, 16]. Jantasri et al. demonstrated that a 2-point difference in the NIHSS score at 24 h after thrombolysis predicts functional outcome at 3 months [15]. In another study, early neurological improvement defined as a reduction in NIHSS score by 10 or an absolute score of 4 or less 2 h after thrombolysis, was an independent predictor of favourable outcome at 3 months [16].

One might argue that ANI could be due to spontaneous recovery and not a consequence of thrombolysis. 16–24% of patients with a disabling stroke reportedly achieve good functional outcome at one week or upon discharge, without thrombolysis [17, 18]. Lacunar syndromes were

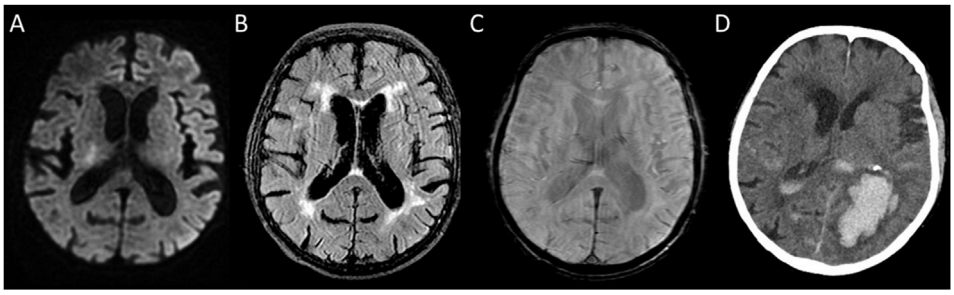

Figure 5. Pre-thrombolysis MRI and 24-hour post-treatment CT of the patient with sICH. (A) DWI demonstrating a right hemispheric lacunar infarct. (B) No corresponding hyperintensity is visible on FLAIR. Periventricular white matter hyperintensities indicate small vessel disease. (C) No microhaemorrhages detected on SWAN. (D) 24-hour repeat CT shows a remote, left parieto-temporo-occipital haemorrhage with perifocal oedema, mass effect, and propagation into the lateral ventricles.

significantly more common in patients with neurological recovery. Lacunar strokes result from lipohyalinosis of small perforating arteries, branch atheromatous disease or microembolisms and they usually have milder clinical presentations compared to large-artery atherosclerosis or cardioembolic strokes [19]. An interesting observation in our study was the significant difference in the proportion of lacunar stroke, which was significantly more common in the non-thrombolysed group. However, ANI was more frequent among thrombolysed patients, which supports the short-term effectiveness of thrombolytic treatment over spontaneous recovery. Our multivariable analysis also demonstrated a significant association between ANI and thrombolysis. Furthermore, the efficacy of thrombolysis in lacunar stroke has been proven in several clinical studies and the post hoc secondary analysis of the WAKE-UP trial [20, 21, 22].

Women differ from men in vascular risk factor profile, stroke subtype and outcome [23, 24, 25]. Women have been found more likely to suffer from stroke-related complications, higher rates of in-hospital death and lesser spontaneous neurological improvement [23]. However, our study did not find differences between genders regarding efficacy and safety outcomes. Kent et al. have also reported no differences in 90-day outcomes [25].

In terms of safety outcomes, we compared our results with those of the WAKE-UP trial. It is worth mentioning that 33.7% of patients in the treated arm of the WAKE-UP trial had occlusion of a large intracranial artery. As discussed earlier, we excluded these patients from our retrospective analysis. Regarding intracerebral haemorrhage, the number of patients with PH1 was not reported in the trial. The percentage of PH2 according to ECASS II was similar: 3.45% in our study compared to 4.0% in the randomised clinical trial. In a pooled analysis of thrombolysis trials, the rate of severe intracranial haemorrhage was 5.2% [26]. In the included studies, symptom onset times were known, and alteplase could be given up to 6 h after symptom onset. The percentage of sICH was also similar: 3.45% in our population vs 2.8% in the WAKE-UP trial. The patient with remote PH2 and consequent sICH had complete mismatch on baseline imaging. No relevant haemorrhagic events occurred in patients with partial FLAIR hyperintensity.

In patients who received alteplase, the 10% mortality at 90 days in our population was higher than the 4.1% in the WAKE-UP study. Potential explanations are that our patients were older with more vascular risk factors present, as well as more disabled at baseline. We did not contraindicate alteplase treatment based on mRS, whereas only patients with mRS 0–1 were included in the WAKE-UP trial.

Our study included only four patients who had thrombolysis with DWI-FLAIR partial mismatch. Therefore, meaningful conclusions about the safety and efficacy of alteplase treatment in patients with such imaging patterns cannot be drawn. Jakubicek et al. reported that 27 thrombolysed patients with partial mismatch did not have higher rates of sICH compared to 37 patients without FLAIR signal change [27]. The beneficial effects of alteplase were similar in the two groups. They implied that the mismatch pattern used in the WAKE-UP trial might be over-selective. Similarly, a report from the Bernese stroke registry found no association between FLAIR hyperintensities and sICH after thrombolysis and thrombectomy [28]. Treatment in that study was indicated based on an "eyeball" assessment of whether the corresponding FLAIR signal change exceeded 50% of the DWI lesion or not. Among 159 patients included, 89 had partial DWI-FLAIR mismatch, in whom the rate of sICH was 6.7%. In our opinion, the concept of alteplase treatment in partial DWI-FLAIR mismatch should be tested in large, prospective, randomised clinical trials to assess whether a broader range of patients could benefit from thrombolysis.

Limitations of our study include the small sample size and the retrospective observational nature of data collection. However, the two groups in our study were similar in terms of vascular risk factor profile and medical management pre-stroke. The non-thrombolysed group comprised of patients with onset times most probably beyond 4.5 h based on their DWI-FLAIR pattern. In addition to comparing the rates of ANI between the two groups, we also performed a logistic regression analysis to investigate the predictors of ANI. This regression analysis identified alteplase treatment as the only variable associated with ANI.

5. Conclusions

In conclusion, our real-world data demonstrate that thrombolysis provides short-term benefit in acute ischaemic stroke patients with a DWI-FLAIR mismatch, in the absence of LVO. The rate of haemorrhagic complications was similar to those published in large clinical thrombolysis trials with known onset times. Randomised studies are warranted to test the efficacy and safety of alteplase treatment in patients with partial DWI-FLAIR mismatch.

Declarations

Author contribution statement

Ádám Annus: Performed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data.

Franciska Zita Gera: Performed the experiments.

László Sztriha: Conceived and designed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data.

Péter Klivényi: Analyzed and interpreted the data.

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Data availability statement

Data will be made available on request.

Declaration of interest's statement

The authors declare no conflict of interest.

Additional information

No additional information is available for this paper.

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