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Fluid-attenuated Inversion Recovery Hyperintense Ischemic Stroke Predicts Less Favorable 90-day Outcome After Intravenous Thrombolysis

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Abstract

Introduction: The absence of an ischemic lesion on magnetic resonance imaging (MRI) fluid-attenuated inversion recovery (FLAIR) is helpful in predicting stroke onset within 4.5 hours. However, some ischemic strokes become visible on FLAIR within 4.5 hours. We hypothesized that the early lesion visibility on FLAIR may predict stroke outcome 90 days after intravenous (IV) thrombolysis, independent of time.

Materials and Methods: We analyzed data from acute ischemic stroke patients presenting over the last 10 years who were screened with MRI and treated with IV thrombolysis within 4.5 hours from onset. Three independent readers assessed whether ischemic lesions seen on diffusion-weighted imaging (DWI) were also FLAIR-positive based on visual inspection. Multivariable regression analyses were used to obtain an adjusted odds ratio of favorable clinical and radiological outcomes based on FLAIR positivity.

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Author Contributions

YK and ML: design and conceptualization of the study, major role in the acquisition, analysis, and interpretation of data, drafted and revised the manuscript for intellectual content. NB: major role in the acquisition of data, revised the manuscript for intellectual content. GN: analysis and interpretation of data. RL, CBW, KCK, AWH, JKL, MMA: revised the manuscript for intellectual content. LLL: design of the study, revised the manuscript for intellectual content.

Conflicts of Interest Statement

The authors have no financial conflicts of interest.

Statements of Ethics

This study is an analysis of the Institutional Review Board approved NIH Natural History of Stroke study (NCT00009243) data; written informed consent was obtained for all patients.

Results: Of 297 ischemic stroke patients, 25% had lesion visibility on initial FLAIR. The interrater agreement for the FLAIR positivity assessment was 84% (κ=0.604, 95% CI 0.557–652). Patients with FLAIR-positive lesions had more right hemispheric strokes (57% vs 41%, p=0.045), were imaged later (129 vs 104 minutes, p=0.036), had less frequent favorable 90-day functional outcome (49% vs 63%, p=0.028), less frequent early neurologic improvement (30% vs 58%, p=0.001), and more frequent contrast extravasation to the cerebrospinal fluid space (44% vs 26%, p=0.008).

Conclusions: Early development of stroke lesion on FLAIR within 4.5 hours of onset is associated with reduced likelihood of favorable 90-day outcome after IV thrombolysis.

Keywords

Therapeutic thrombolysis; Stroke; FLAIR-positive; Functional Outcome; DWI-FLAIR mismatch

INTRODUCTION

The duration of cerebral ischemia prior to reperfusion is one of the strongest predictors of functional outcome.[1, 2] The duration of ischemia and the appearance of the stroke on magnetic resonance imaging (MRI) fluid-attenuated inversion recovery (FLAIR) are related: longer time from onset to imaging increases the likelihood that the lesion will appear on FLAIR.[3–7] However, 23–44% of AIS within 4.5 hours from known onset were found to be FLAIR-positive.[3–6] These data suggest that either the time from onset is imprecise or lesion visibility on FLAIR is mediated by factors other than time that may influence the benefit of thrombolysis.

We hypothesized that in AIS patients treated with intravenous (IV) thrombolysis within 4.5 hours of known onset, those with a visible lesion on pre-treatment FLAIR would be associated with less favorable 90-day outcome. Furthermore, given the apparent dissociation of time and FLAIR positivity of the lesion in some patients, we hypothesized that lesion visibility on FLAIR would predict outcome independent of time.

MATERIALS AND METHODS

Study Population

This is an analysis of patients enrolled in the Institutional Review Board approved NIH Natural History of Stroke study (NCT00009243); written informed consent was obtained for all patients. Patients screened and enrolled by the NIH stroke team at MedStar Washington Hospital Center in Washington, DC and Suburban Hospital in Bethesda, MD between January 1, 2009 through December 13, 2019 were included in this study if: (1) admission diagnosis was AIS; (2) last known normal (LKN) time and symptom discovery time were known; and (3) standard IV thrombolysis within 4.5 hours of LKN was administered. Patients were excluded if: (1) not screened with MRI prior to thrombolysis; (2) thrombectomy, intraarterial thrombolysis, or emergent hemicraniectomy were performed; or (3) enrolled in other clinical trials. Patients were excluded based on their initial MRI if they had imaging evidence of: (1) infra-tentorial stroke;[8, 9] (2) diffusion-weighted imaging (DWI)-negative; or (3) missing FLAIR data. Figure 1 presents the study population profile.

Imaging Protocol

Patients were scanned before and 24 hours after thrombolysis on one of three commercial systems (1.5T Signa, GE Medical Systems, Milwaukee, WI; 3T Skyra, Siemens AG, Munich, Germany; 3T Achieva, Philips Healthcare, Best, the Netherlands). The specific MRI sequences acquired at both time points included DWI, gradient recalled echo (GRE), and pre- and post-contrast FLAIR after a single weight-dependent dosage of gadolinium. The MRI series parameters were comparable across systems. The imaging protocol parameters for the FLAIR varied slightly across the study period, but in general consisted of the following: repetition time/echo time 9,000/120–140 millisecond, inversion time 2,200 millisecond, acquisition matrix of 256 × 128 or 256 × 256, 40 3.5 mm thick contiguous axial oblique slices, and 24 cm field of view.

MRI Review

Pre- and post-thrombolysis MRIs were evaluated for abnormalities on DWI, apparent diffusion coefficient (ADC), GRE, pre- and post-contrast FLAIR sequences. Three readers (YK, ML, NB) performed imaging assessments. Each reader, blinded to the LKN time and outcome, reviewed 2/3 of the MRI studies independently of the other readers, providing two complete sets of imaging reads for each patient. Any discrepancies in imaging reads were determined by consensus of three readers.

Each index ischemic lesion was identified as DWI-bright and ADC-dark on pre-thrombolysis MRI and confirmed to be consistent with the localization provided by the stroke clinician at the time of screening. The patients evaluated as DWI-negative were confirmed by all readers, then were excluded from the analyses.

The DWI lesion volume were calculated by a semi-automated planimetric measurement method, using the Medical Image Processing, Analysis, and Visualization application (v10, Center for Information Technology, NIH).

Lesion visibility on pre-contrast FLAIR was characterized as a parenchymal hyperintensity concordant with the DWI and ADC findings. Visible parenchymal hyperintensity was assessed as FLAIR-positive, or FLAIR-negative if completely absent.

GRE at 24 hours after thrombolysis was assessed for hemorrhagic transformation (HT) by applying the Heidelberg Bleeding Classifications (HBC).[10] The highest grade of HBC was reported when a mixture of grades was present. Symptomatic intracerebral hemorrhage was defined as a local or remote parenchymal hematoma combined with a neurological deterioration by ≥4 points on the 24-hour NIH stroke scale (NIHSS) or death.

Post-contrast FLAIR of the 24-hour post-thrombolysis MRI were assessed for the hyperintense acute reperfusion injury marker (HARM).[11] HARM presented in ≥10 slices was rated as severe. If the severe HARM was restricted to the lesion territory then it was graded as severe-focal, otherwise it was graded as severe-diffuse.

Statistical Analysis

Demographic and clinical data including age, sex, race, ethnicity, lesion laterality, risk factors including hypertension, diabetes mellitus, and tobacco use were reported. Any risk factor data with < 2% prevalence in the study population were excluded from the analyses. Clinical severity assessments included pre-admission modified Rankin Scale (mRS), admission NIHSS, 24-hour NIHSS, 30-day mRS, and 90-day mRS. Time intervals calculated in minutes were LKN-to-MRI, MRI-to-needle, and LKN-to-needle times.

Patients with FLAIR-negative and FLAIR-positive stroke were compared according to outcomes. The primary outcome was a favorable functional outcome at 90 days defined as mRS equal to 0 – 1 or equal to pre-admission mRS. Secondary clinical outcomes were 90-day functional independence defined as 90-day mRS of 0 – 1, return to baseline defined as 90-day mRS equal to pre-admission mRS, all-cause mortality at 90 days, early neurologic improvement (ENI) defined as a reduction of ≥4 points or 24-hour NIHSS equal to 0 – 1,[12] major ENI defined as a reduction of ≥8 points or 24-hour NIHSS equal to 0 – 1,[13] and the rates of discharge to home from the hospital.

Unadjusted analyses were performed on the ordinal or continuous variables using the Mann Whitney U test. As appropriate based on sample size, either the Chi-square test or Fisher's exact test was used for categorical variables. Spearman's Rho test was used to assess the correlation between two continuous variables. Cohen's Kappa test was used to assess interrater agreement. Odds ratios (OR) and 95% confidence intervals (CI) for each outcome were estimated adjusting for the following covariates in a logistic regression model: LKN-toneedle time, DWI lesion volume, age, female sex, admission NIHSS, and unfavorable baseline defined as pre-admission mRS > 1. Descriptive data were reported as median (25th quartile – 75th quartile) or number (percentage) unless otherwise noted. Statistical analyses were performed with IBM SPSS software (version 1.0.0.1406).

RESULTS

From January 1, 2009 through December 13, 2019, 1,003 patients were treated with IV thrombolysis at the two study centers (shown in Fig. 1). A total of 297 patients were eligible and included in this study. Patients were 48% female, 51% White, 44% Black, and 4% Hispanic. Median age was 70 years (59 – 83), admission NIHSS was 6 (3 – 14) and pre-admission mRS was 0 (0 – 1).

In 62% of patients, LKN time equaled symptom discovery time. Median difference of LKN and symptom discovery time for the remaining 38% was 30 minutes (15 – 46). LKN-to-MRI time was 109 minutes (79 – 156), MRI-to-needle time was 32 minutes (22 – 44), and LKNto-needle time was 150 minutes (112 – 190). The MRI-to-needle time was not different between the FLAIR-negative and FLAIR-positive groups. LKN-to-MRI time and LKN-toneedle time were strongly related (ρ=0.939, $p < 0.001$).

The inter-rater agreement across the three readers was 84% for the FLAIR-positive assessment (κ=0.604, 95% CI 0.557–0.652), 96% for the presence of HT (κ=0.889, 95%

CI 0.860–0.917), 91% for HT classification (κ=0.795, 95% CI 0.760–0.829), and 97% for the presence of any HARM (κ=0.932, 95% CI 0.908–0.956).

Seventy-four patients (25%) had visible lesions on pre-thrombolysis FLAIR. Figure 2 compares the clinical presentation, treatment timing, and lesion on the initial MRI for two patients with FLAIR-negative versus FLAIR-positive lesion. Baseline demographic and clinical characteristics are shown in Table 1. FLAIR-positive lesion was associated with right-hemispheric lesion (OR 1.005, 95% CI 1.000–1.010, p=0.045) and longer LKN-to-MRItime (OR 1.786, 95% CI 1.039–3.071, p=0.036) after the regression analysis of the baseline characteristics.

Overall, 48% of patients in the study had a favorable clinical outcome. The median score on the mRS at 90 days was 2 (1 – 4) in the FLAIR-negative group and 3 (1 – 4) in the FLAIR-positive group. After adjustment for the covariates, FLAIR-positive lesion was significantly associated with less favorable 90-day outcome (OR 0.428, 95% CI 0.201–0.912, p=0.028).

Among covariates, older age (OR 0.934, 95% CI 0.908–0.960, p<0.001), greater admission NIHSS (OR 0.907, 95% CI 0.859–0.957, p<0.001), and longer LKN-to-needle time (OR 0.993, 95% CI 0.987–0.999, p=0.018) predicted less favorable 90-day outcome.

Table 2 presents secondary clinical and radiologic outcomes. The FLAIR-positive lesion was associated with less frequent ENIs, and more frequent development of severe HARM at 24 hours after thrombolysis.

DISCUSSION

Our study is the first to report an association between the lesion visibility on pre-thrombolysis FLAIR and less favorable 90-day outcome in AIS patients who receive IV thrombolysis within 4.5 hours of LKN. The difference is clinically meaningful with approximately a 20% greater chance of favorable 90-day outcome when the ischemic lesion is FLAIR-negative versus FLAIR-positive. The association between FLAIR-positive lesion and 90-day outcome in thrombectomy patients was shown in another study.[14]

We found that AIS patients with FLAIR-negative lesion had a 47% greater chance of ENI, compared to the patients with FLAIR-positive lesion. This finding is consistent with a prior study.[12] FLAIR-positive stroke had a stronger association with ENIs than 90-day outcome. The short-term outcomes are less affected by compliance with rehabilitation or social support; thus, they may be better predicted by early imaging features.

Visible stroke on pre-thrombolysis FLAIR was associated with greater odds of severe HARM at 24 hours. HARM is an MRI marker of blood brain barrier (BBB) disruption associated with reperfusion and is associated with worse clinical outcomes.[11, 15] One proposed mechanism for FLAIR lesion hyperintensity is vasogenic edema.[16] As ischemia progresses, the BBB becomes more permeable, and there is influx of water from the vasculature to the parenchyma.[17] An early FLAIR hyperintensity may represent early loss of BBB integrity that may predispose to reperfusion injury, ultimately compromising the clinical outcome. Therefore, the FLAIR-positive stroke patients within 4.5-hour window

may benefit from neuroprotective agents. Many neuroprotective agents have been studied in AIS, but so far none have shown benefit, even in combination with recanalization. [18] Targeting AIS patients with early FLAIR hyperintensity could yield more successful neuroprotection trials. While a prior study reported a higher rate of post-thrombolysis HT in FLAIR-positive group, [19] the rate of HT was not different between groups in our study. The development of HT may require additional factors with BBB disruption, such as hypertension. In our study, patients with severe HT had higher admission mean arterial pressure than patients with mild or no HT (122 mmHg vs. 106 mmHg, p=0.002). FLAIR-positive stroke patients may benefit from a lower post-thrombolysis blood pressure goal than the conventional 185/105 mmHg to prevent severe HT.

Our study has several limitations. It was a retrospective study and is hypothesis-generating, therefore statistical significance particularly in secondary outcomes should be weighed appropriately. Despite approaching all treated AIS patients consecutively, not every patient was enrolled. The proportion of FLAIR-positive patients was small, which is consistent with the early time window but decreases our statistical power. Not everyone in the study population had matched LKN and symptom discovery time, decreasing the predictive power of time on stroke outcome. Across a ten-year period, various imaging protocols were used. However, this adds to the generalizability of our findings, and future studies should determine the optimal FLAIR sequence parameters to select treatment candidates while minimizing scan time. Lastly, most stroke centers in the U.S. screen patients with CT, so our findings are not easily adopted. As more stroke centers adopt acute MRI protocols, predictive early imaging markers will become more valuable.

Conclusion

Even when the LKN was well constrained by the treatment window, patients with FLAIR-positive stroke had less favorable functional outcome. A future clinical trial of thrombolysis combined with neuroprotection or aggressive blood pressure management in patients with FLAIR-positive stroke within 4.5 hours of LKN may be warranted.

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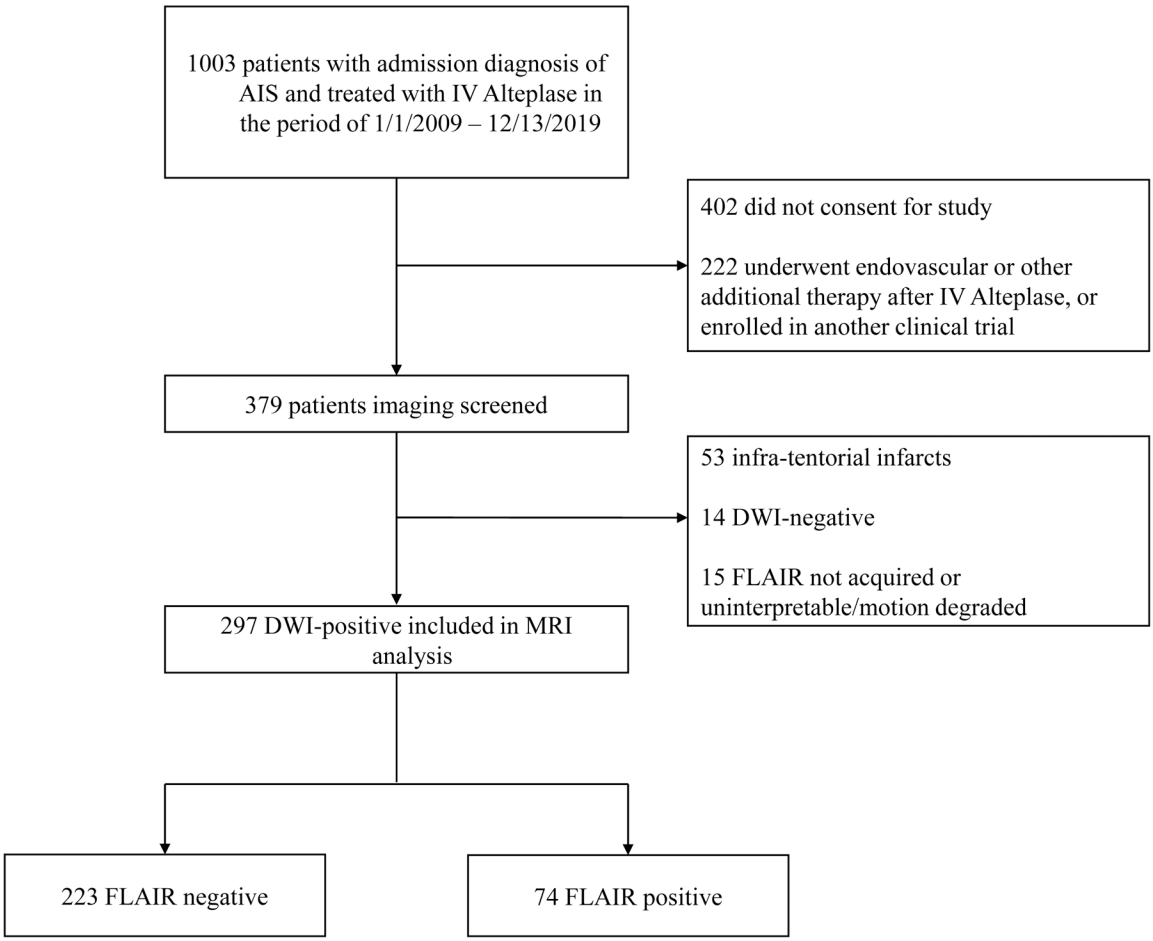

Fig. 1:

Study profile. AIS, acute ischemic stroke; LKN, last know normal time; DWI, diffusion-weighted imaging; IV, intravenous; FLAIR, Fluid-attenuated inversion recovery; MRI, magnetic resonance imaging

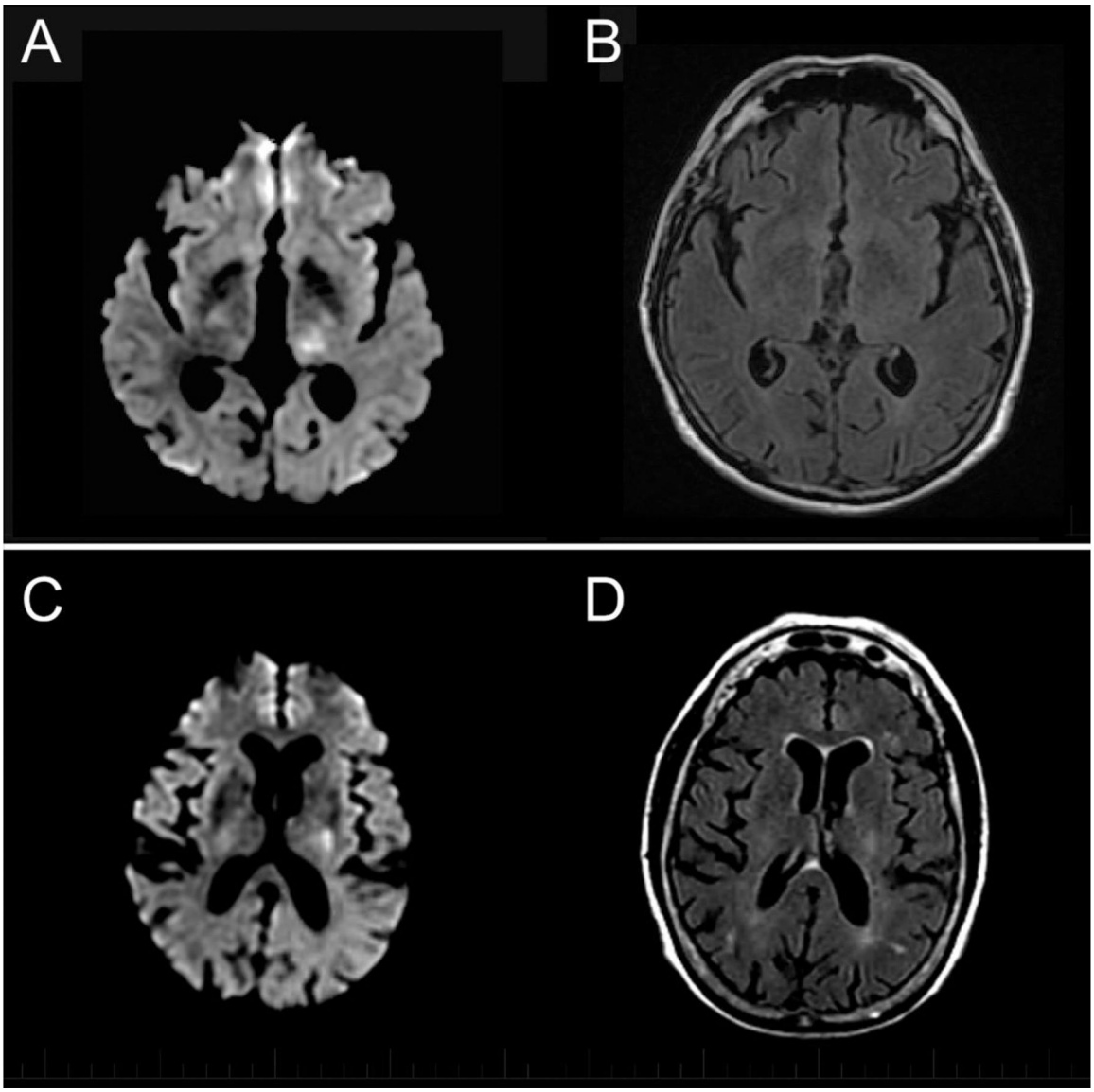

Fig. 2:

Top panel: 69-year-old male presented with acute right-sided weakness at 53 minutes from last known normal (LKN). Admission NIH stroke scale (NIHSS) was 5. Initial MRI showed DWI-positive (A), ADC correlate (not shown), FLAIR-negative (B) lesion. IV thrombolysis was started 77 minutes after arrival. The patient had 24-hour NIHSS of 1 and 90-day modified Rankin Scale (mRS) of 1. Bottom panel: 86-year-old female presented with acute onset right-sided weakness at 80 minutes from LKN. Admission NIHSS was 8. Initial MRI showed DWI-positive (C), ADC correlate (not shown), FLAIR-positive (D) lesion. IV thrombolysis was started 45 minutes after arrival. The patient had 24-hour NIHSS of 7 and 90-day mRS of 3.

Table 1.

Baseline Characteristics

	FLAIR-negative (N = 223, 75%)	FLAIR-positive (N = 74, 25%)	P-value
Age (years) – median (IQR)	73 (60 – 84)	67 (57 – 80)	**0.049**
Female – no. (%)	104 (47%)	39 (53%)	0.366
Race – no. (%)			0.511
White	115 (52%)	35 (47%)	
Black	94 (42%)	37 (50%)	
Asian	4 (2%)	1 (1%)	
Other	10 (4%)	1 (1%)	
Hispanic ethnicity – no. (%)			0.389
Yes	10 (5%)	2 (3%)	
No	213 (95%)	72 (97%)	
LKN-to-MRI time (minutes) – median (IQR)	104 (74 – 149)	129 (95 – 166)	**0.010**
MRI-to-Needle time (minutes) – median (IQR)	32 (22 – 45)	32 (25 – 41)	0.535
LKN-to-Needle time (minutes) – median (IQR)	142 (107 – 188)	169 (120 – 208)	**0.013**
Right hemispheric lesion	92 (41%)	42 (57%)	**0.020**
Admission NIHSS – median (IQR)	6 (3 – 15)	7 (4 – 13)	0.877
Admission MAP (mmHg) – median (IQR)	107 (97 – 119)	107 (95 – 119)	0.661
Admission glucose (mg/dL) – median (IQR)	116 (104 – 139)	116 (102 – 134)	0.597
DWI lesion volume (mL) – median (IQR)	4 (1 – 13)	8 (2 – 27)	0.071
Hypertension – no. (%)	172 (77%)	55 (74%)	0.590
Diabetes Mellitus – no. (%)	42 (19%)	14 (19%)	0.716
Hyperlipidemia – no. (%)	97 (44%)	38 (51%)	0.384
Atrial fibrillation – no. (%)	61 (27%)	17 (23%)	0.527
Congestive heart failure – no. (%)	24 (11%)	12 (16%)	0.340
Previous Stroke / TIA – no. (%)	33 (15%)	15 (20%)	0.400
Coronary artery disease – no. (%)	32 (14%)	10 (14%)	0.701
Cancer – no. (%)	22 (10%)	8 (11%)	0.700
Tobacco use – no. (%)	31 (14%)	18 (24%)	**0.039**
Alcohol use – no. (%)	56 (25%)	25 (34%)	0.159

Abbreviations: DWI, diffusion-weighted imaging; IQR, interquartile range; LKN, last known to be normal; MAP, mean arterial pressure; MRI, magnetic resonance imaging; NIHSS, National Institutes of Health stroke scale; TIA, transient ischemic attack

Table 2.

Primary and Secondary Outcomes

	FLAIR-negative (N = 223,75%)	FLAIR-positive (N = 74,25%)	Adjusted OR (95% CI)	P-value
Primary outcome				
Favorable 90-day outcome†	116 (61%)	27 (49%)	0.428 (0.201 – 0.912)	**0.028**
Secondary clinical outcomes				
90-day independence†	105 (56%)	25 (46%)	0.466 (0.203 – 1.074)	0.073
90-day return-to-baseline†	72 (38%)	17 (31%)	0.702 (0.345 – 1.432)	0.331
90-day all-cause mortality†	21 (11%)	6 (11%)	1.561 (0.482 – 5.057)	0.458
Final modified Rankin Scale†				
0	61 (32%)	16 (29%)		
1	44 (23%)	9 (16%)		
2	11 (6%)	5 (9%)		
3	20 (11%)	6 (11%)		
4	23 (12%)	10 (18%)		
5	11 (6%)	3 (5%)		
6	19 (10%)	6 (11%)		
Early Neurologic Improvement‡	109 (57%)	20 (30%)	0.339 (0.180 – 0.638)	**0.001**
Major Neurologic Improvement‡	87 (46%)	13 (20%)	0.273 (0.134 – 0.558)	< **0.001**
Being Discharged to Home	120 (54%)	35 (48%)	0.681 (0.342 – 1.356)	0.274
Hemorrhagic Transformation				
All type HT§	54 (27%)	23 (35%)	1.735 (0.863 – 3.489)	0.122
Severe HT (HBC 2–3)§	16 (8%)	5 (8%)	1.030 (0.337 – 3.152)	0.958
HBC§				
no HT	150 (74%)	42 (65%)		
HBC 1	38 (19%)	18 (28%)		
HBC 2	13 (6%)	3 (5%)		
HBC 3	3 (1%)	2 (3%)		
Symptomatic ICH‖	6 (3%)	0 (0%)	0.000 (0.000 –)	0.997
Hyperintense Acute Reperfusion injury Marker				
All type HARM¶	85 (44%)	35 (57%)	1.726 (0.908 – 3.281)	0.096
Severe HARM¶	54 (28%)	27 (44%)	2.458 (1.260 – 4.759)	**0.008**
HARM classifications¶				
None	110 (56%)	27 (44%)		
Minor	31 (16%)	8 (13%)		
Severe-focal	27 (14%)	17 (27%)		
Severe-diffuse	27 (14%)	10 (16%)		

Abbreviations: FLAIR, fluid-attenuated inversion recovery; HARM, hyperintense acute reperfusion injury marker; HBC, Heidelberg bleeding classification; HT, hemorrhagic transformation; mRS, modified rankin scale; NIHSS, National Institutes of Health stroke scale;OR, odds ratio

The favorable 90-day outcome was defined as 90-day mRS of 0–1 or as same as pre-admission mRS; 90-day independence was defined as 90-day mRS 0–1; Early neurologic improvement was defined as NIHSS of 0–1 or improved by 4 points or more by 24 hours; Major neurologic improvement was defined as NIHSS of 0–1 or improved by 8 points or more by 24 hours; Severe HARM is defined as an observation of HARM in 10 or more slices on FLAIR imaging.

† 34 in FLAIR-negative and 19 in FLAIR-positive group were missing final mRS data

‡ 33 in FLAIR-negative and 8 in FLAIR-positive group were excluded due to missing 24-hour NIHSS data or admission NIHSS 0–1

§ 19 in FLAIR-negative and 9 in FLAIR-positive group were missing 24-hour MRI data for HT assessment

‖ 30 in FLAIR-negative and 10 in FLAIR-positive group were missing 24-hour MRI or NIHSS for symptomatic ICH assessment

¶ 28 in FLAIR-negative and 12 in FLAIR-positive group were missing 24-hour MRI data for HARM assessment