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Review

Early Parenchymal FLAIR Hyperintensity and Hemorrhagic Transformation After Mechanical Thrombectomy: A Structured Narrative Review

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Abstract

Background: Parenchymal fluid-attenuated inversion recovery (FLAIR) hyperintensity within an acute ischemic lesion marks tissue evolution. Its prognostic value for hemorrhagic transformation after mechanical thrombectomy (MT) is uncertain. **Methods:** We conducted a structured narrative review of cohort studies relating the pretreatment lesion FLAIR signal to hemorrhage after reperfusion therapy. PubMed was the sole bibliographic database searched. Four searches yielded 1051 unique records, and reference-list screening supplemented the search. The full-text assessment stage comprised 79 articles. The studies were classified by treatment, FLAIR construct and hemorrhage endpoint, and synthesized by the direction and precision of effect without pooling. **Results:** Eleven cohort studies (49–412 patients each, 1726 in total) and one meta-analysis were included. Four cohorts enrolled patients treated exclusively or predominantly with MT. In the largest MT cohort ($n = 412$), parenchymal hematoma type 2 (PH2) occurred in 10.7% of FLAIR-positive and 6.8% of FLAIR-negative patients ($p = 0.193$). A separate MT-predominant cohort reported more intracranial hemorrhages of any type (59% vs. 39%) and more hemorrhages meeting a Heidelberg Bleeding Classification class $\geq$ 1c (40% vs. 24%). Across settings, nine cohorts reported point estimates in the direction of more hemorrhages with a greater FLAIR signal or FLAIR positivity. No cohort isolated patients with early-onset M1 occlusion and near-complete reperfusion. **Conclusions:** The evidence from MT and MT-predominant cohorts remains insufficient to establish whether pretreatment FLAIR positivity independently predicts PH2 or symptomatic intracranial hemorrhage. FLAIR positivity alone should not be used to withhold MT. Adequately powered studies with standardized FLAIR readings and separately reported parenchymal hematoma and symptomatic hemorrhage are needed.

Keywords: ischemic stroke; mechanical thrombectomy; FLAIR; DWI–FLAIR mismatch; hemorrhagic transformation; parenchymal hematoma; magnetic resonance imaging; prognostic biomarker

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1. Introduction

Mechanical thrombectomy (MT) is the standard treatment for acute ischemic stroke caused by anterior-circulation large-vessel occlusion. Angiographic restoration of flow

and recovery of injured tissue are, however, not equivalent: reperfusion can coexist with microvascular injury, and hemorrhagic transformation (HT) remains one of the most consequential complications of MT. The clinical significance of HT depends on its type. Petechial hemorrhagic infarction frequently accompanies reperfusion of injured tissue, whereas parenchymal hematoma—particularly space-occupying parenchymal hematoma type 2 (PH2)—and symptomatic intracranial hemorrhage (sICH) are the events of greatest concern; the established classifications therefore report them separately [1,2]. Pretreatment imaging features may help characterize the hemorrhagic risk after reperfusion. Their incremental prognostic value requires evaluation alongside clinical and procedural variables. Under the Heidelberg Bleeding Classification, PH1 occupies less than 30% of the infarct without a substantial mass effect, whereas PH2 occupies at least 30% and produces an obvious mass effect. PH2 carries greater prognostic weight. Symptomatic intracranial hemorrhage additionally requires clinical worsening under the applicable study definition [1,2].

In MRI-based stroke pathways, the parenchymal hyperintensity on fluid-attenuated inversion recovery (FLAIR) imaging within an acute diffusion-weighted imaging (DWI) lesion reflects increasing tissue water content and becomes more frequent with the time from onset. The absence of such a signal—DWI–FLAIR mismatch—identifies, with imperfect sensitivity and specificity, patients likely to be within 4.5 h of onset [3]; it is a probabilistic rather than a deterministic tissue clock. Mismatch was used to select patients with unknown onset for intravenous thrombolysis (IVT) in the WAKE-UP trial [4]. A visible FLAIR lesion may nevertheless appear early in some patients. It has been proposed that early FLAIR positivity marks more severe ischemia and blood–brain barrier injury and therefore a higher risk of bleeding after reperfusion [5–7].

Clinical studies of this hypothesis have reached different conclusions, ranging from strong associations in IVT cohorts [6–8] to null or non-significant findings in MT and other cohorts [9–12]. Part of this divergence arose because several distinct MRI constructs were discussed together: binary lesion FLAIR positivity; quantitative lesion-to-contralateral signal intensity ratios (SIRs); DWI–FLAIR mismatch as an operational classification; FLAIR vascular hyperintensity (FVH), which reflects slow collateral flow [13]; and the hyperintense acute reperfusion marker (HARM), a post-treatment sign of contrast leakage [14]. These differ in anatomy, timing and meaning. A 2025 meta-analysis of IVT cohorts found a non-significant pooled association between FLAIR positivity and HT with substantial heterogeneity [15]; we did not identify a synthesis focused on MT.

The clinical question that motivated this review is narrower than the general literature on FLAIR and hemorrhage. It concerns patients imaged within 3 h of a known onset, with M1 occlusion, pretreatment parenchymal FLAIR hyperintensity concordant with the acute DWI lesion and near-complete reperfusion (mTICI 2c–3), in whom the outcome of interest is a clinically severe hemorrhage (PH2 or sICH) analyzed with a multivariable adjustment. Because this combination of conditions is unlikely to have been studied directly, the review was not designed to estimate a pooled association. Its primary aim was to summarize and critically appraise the cohort studies relating the pretreatment parenchymal FLAIR signal to hemorrhage after reperfusion therapy, with an emphasis on MT, on the distinction between any hemorrhage and clinically important hemorrhage, and on the direction and precision of reported effects. Its secondary aims were to explain why the available findings differ, to map how far they address the target question, and to define the design required to answer it.

2. Materials and Methods

2.1. Review Design

This was a structured narrative review. It was not designed or conducted as a systematic review: the search was limited to PubMed, and title/abstract triage was not performed inde-

pendently in duplicate. To make the process transparent, we report the information sources, eligibility criteria, data items and synthesis methods, and we followed the applicable items of the Synthesis Without Meta-analysis (SWiM) guidelines [16] and of published guidance for reviews of prognostic factors [17,18]. The review protocol was not prospectively registered with PROSPERO or another registry.

2.2. Eligibility Criteria

Population: Adults with acute ischemic stroke who underwent MRI, including DWI and FLAIR, before reperfusion therapy (MT, IVT or both). **Prognostic factor:** Parenchymal FLAIR signal within, or spatially concordant with, the acute DWI lesion, assessed visually (binary) or quantitatively (SIR), or with DWI–FLAIR mismatch status. **Outcomes:** Any HT or intracranial hemorrhage (ICH), parenchymal hematoma (PH) according to the European Cooperative Acute Stroke Study (ECASS) or Heidelberg Bleeding Classification (HBC), or sICH. **Design:** Prospective or retrospective cohort studies reporting group-specific hemorrhage rates or effect estimates; systematic reviews were used for context. **Exclusions:** Studies in which the exposure was FVH, HARM, chronic white matter hyperintensity or a post-treatment imaging marker; case reports; and studies without hemorrhage data.

The included studies were assigned to one of three tiers according to their proximity to the review question. **Tier A:** Cohorts in which all or most (≥80%) patients received MT and the exposure was the lesion-level FLAIR signal. **Tier B:** MT or mixed-reperfusion cohorts with a related exposure (DWI–FLAIR mismatch) or with an unspecified mix of reperfusion treatments. **Tier C:** IVT cohorts and cohorts with mixed or no reperfusion treatment, which provided indirect or mechanistic evidence.

2.3. Information Sources and Search

Four PubMed searches were executed and exported: three FLAIR-focused searches (253, 123 and 46 records) and one broader search combining thrombectomy, hemorrhage and imaging terms (728 records). After deduplication by the PubMed identifier, 1051 unique records remained (99 duplicates). The reference lists of included studies and of the 2025 meta-analysis were screened; this identified one additional eligible MT-predominant cohort.

2.4. Study Selection and Data Extraction

The titles and abstracts were computationally ranked using all terms listed in the keywords section. The ranking determined the screening order. Lower-priority records were also screened, and the ranking alone was never used to exclude a record. The reports judged potentially eligible at title and abstract screening were selected for full-text assessment. At the full-text assessment stage, 79 records were considered using the eligibility criteria in Section 2.2. This stage included records for which a full report could not be obtained. Twelve reports were included (11 cohort studies and 1 meta-analysis), 3 were retained for context, and 64 were excluded. The reasons for exclusion were ineligible exposure (14), no extractable hemorrhage outcome data (8), ineligible study design (12), ineligible population (14), duplicate or overlapping cohorts (5), and conference abstract or unavailable full text (11). The following items were extracted: design and setting; treatment and time window; sample size and number of FLAIR-positive patients; FLAIR definition, reading method and inter-rater agreement; hemorrhage classification, imaging modality and timing; group-specific events; crude and adjusted effect estimates; and covariates. When only percentages were reported, event counts were derived only if they reconciled with the reported totals. Crude odds ratios (ORs) with 95% confidence intervals (Woolf method) were calculated by us from the reported or derived counts and are labeled as such. All numerical findings were checked against the published reports.

2.5. Methodological Appraisal

Each cohort was appraised using the six Quality In Prognosis Studies (QUIPS) domains [17]. We examined the representativeness of the study population, participant loss or incomplete data, the definition and reproducibility of FLAIR measurements, hemorrhage ascertainment, control of confounding, and the adequacy of statistical analysis and reporting. The recurring concerns by domain are summarized in Section 3.6. A single evaluator recorded domain-level concerns, and no overall risk-of-bias grades were assigned. These concerns informed the qualitative interpretation of the results, particularly where severe hemorrhage events were few or estimates were incompletely adjusted.

2.6. Synthesis Methods

The studies were grouped by tier and by endpoint category: (i) any hemorrhage (any HT or ICH, including hemorrhagic infarction) and (ii) more specific hemorrhage outcomes. Within the second category, we retained each study's definition and distinguished the pooled PH, PH1 where separately reported, PH2, symptomatic hemorrhage, and the HBC ≥ 1c threshold. Within each category we tabulated the direction of the point estimate (higher, similar or lower risk with FLAIR positivity), statistical significance and precision. The results were not pooled because the exposure definitions, endpoints, treatments and adjustment sets differed substantially. The certainty of evidence is described qualitatively.

3. Results

3.1. Studies Included

Eleven cohort studies published between 2008 and 2023, including 1726 patients with FLAIR assessment, and one meta-analysis were included (Table 1). Four studies (867 patients) were Tier A [9–11,19], two (336 patients) were Tier B [20,21] and five (523 patients) were Tier C [5–8,12]. Three further studies examined the FLAIR vascular hyperintensity or used the DWI–FLAIR mismatch only as a candidate variable and were used for context only.

Table 1. Cohort studies relating pretreatment parenchymal FLAIR signal to hemorrhage after reperfusion therapy.

Study	Design, Setting	Treatment, Time Window	*n* (FLAIR+)	FLAIR Construct	Hemorrhage Endpoint	Main Result (95% CI)	Tier
Aoki 2021 [19]	Cohort, Japan	EVT; FLAIR+ and FLAIR− groups differed in onset-to-imaging time	227 (87)	Binary lesion FLAIR	Any ICH; HBC ≥ 1c	Any ICH 59% vs. 39% ($p = 0.004$); crude OR 2.26 (1.31–3.89) *. HBC ≥ 1c 40% vs. 24% ($p = 0.011$).	A
Kim 2017 [9]	Prospective registry, Korea	EVT ≤ 8 h; all mTICI ≥ 2b	69 (–)	Continuous SIR (median 1.17)	Symptomatic HT	SIR not associated with sHT ($\beta = 2.75$, $p = 0.63$) or lesion growth.	A
Kimura 2023 [10]	Cohort, Japan	MT for LVO (ICA 30%, M1 44%, M2 23%)	412 (149)	Binary lesion FLAIR	PH2 on CT ≤ 7 days	PH2 10.7% vs. 6.8% ($p = 0.193$); crude OR 1.64 (0.81–3.32) *. Post-MT CT hyperdensity strongly associated with PH2.	A

Table 1. *Cont.*

Study	Design, Setting	Treatment, Time Window	*n* (FLAIR+)	FLAIR Construct	Hemorrhage Endpoint	Main Result (95% CI)	Tier
Meisterernst 2017 [11]	Prospective registry, Switzerland	EVT 63%, bridging 23%, IVT 14%; FLAIR > 50% of DWI lesion usually not treated	159 (89)	Binary focal FLAIR	Any ICH; sICH (PROACT II) on CT/MRI	Any ICH 22.5% vs. 17.1%; crude OR 1.40 (0.63–3.11) *. sICH 6.7% vs. 4.3%; crude OR 1.61 (0.39–6.70) *. Not independent predictors.	A
Sakakibara 2020 [20]	Historical single-center cohort, Japan	MT ≤ 24 h, ICA/MCA	202 (56 FLAIR match)	DWI–FLAIR mismatch	sICH ≤ 72 h	sICH 10% (mismatch) vs. 20% (match), $p = 0.06$; adjusted OR for mismatch 0.36 (0.13–0.97).	B
Ahn 2017 [21]	Retrospective cohort, Korea	Reperfusion therapy ≤ 6 h (modalities as reported)	134 (56)	Qualitative FLAIR change within DWI lesion	Any HT on GRE	Adjusted OR 4.37 (1.72–11.12); HT matched the FLAIR region in 48.2% of FLAIR+ patients.	B
Cho 2008 [8]	Cohort, Korea	Thrombolysis after MRI screening	88 (27)	Focal FLAIR within DWI lesion	sICH ≤ 48 h (any decline; NIHSS ≥ 4)	Adjusted OR 13.64 (1.51–123.28) and 10.44 (1.11–98.35).	C
Hobohm 2014 [6]	Retrospective single-center, Germany	IVT < 3 h	97 (25)	Binary lesion FLAIR	Any ICH on CT ≤ 24 h (ECASS II)	Any ICH 80.0% vs. 16.7%; OR 20.0 (6.3–63.8). PH2 not more frequent ($p = 0.144$).	C
Kufner 2013 [7]	Consecutive cohort, Germany	IVT < 4.5 h	109 (33)	Binary FLAIR, two blinded raters	Any HT on T2* MRI at 24 h (15 HI, 2 PH)	HT 33.3% vs. 9.2% ($p = 0.009$); adjusted OR 18 (2–175).	C
Campbell 2011 [12]	Pooled EPITHET/ DEFUSE trials	MRI 3–6 h; 38/49 received tPA	49 (18 obvious; 30 subtle)	Qualitative and quantitative FLAIR	PH (ECASS)	PH 11% (obvious) vs. 9.7% (none/subtle); crude OR 1.17 (0.18–7.74) *. FLAIR signal present in 98%.	C
Jha 2014 [5]	Prospective two-center cohort, USA	≤12 h; IVT in a subset; no endovascular treatment	180 (continuous)	FLAIR ratio	HT (25 HI, 4 PH); sICH ($n = 3$); ECASS III	Adjusted OR for HT 19.9 per unit (1.92–242.9); stepwise increase from no HT to sICH ($p = 0.012$); ratio correlated with MMP-9.	C

* Crude OR calculated by the review authors from reported counts (Aoki, Meisterernst, and Campbell) or from counts derived from reported percentages that reconcile with the total of 34 PH2 events (Kimura: 16/149 vs. 18/263). All other estimates are as reported. Percentages are FLAIR-positive vs. FLAIR-negative unless stated. CT, computed tomography; EVT, endovascular treatment (the broader category that includes MT); GRE, gradient-recalled echo; HBC, Heidelberg Bleeding Classification (≥1c includes PH1, PH2 and class 3 hemorrhage); HI, hemorrhagic infarction; ICA, internal carotid artery; LVO, large-vessel occlusion; MMP-9, matrix metalloproteinase-9; MT, mechanical thrombectomy; PH, parenchymal hematoma; SIR, signal intensity ratio; tPA, tissue plasminogen activator.

3.2. Mechanical Thrombectomy Cohorts (Tier A)

In the cohort of Aoki et al., 87 of 227 patients treated with endovascular therapy were FLAIR-positive. Any ICH was more frequent in FLAIR-positive patients (59% vs. 39%), as was hemorrhage of HBC class ≥ 1c (40% vs. 24%) [19]. Because the FLAIR-positive and FLAIR-negative groups also differed in onset-to-imaging time and other characteristics, these crude contrasts cannot be attributed to tissue state alone, and HBC ≥ 1c combines PH1, PH2 and extra-parenchymal hemorrhage.

Kimura et al. reported the largest MT cohort ($n = 412$; 36% FLAIR positive; 34 PH2 events). PH2 occurred in 10.7% of FLAIR-positive and 6.8% of FLAIR-negative patients ($p = 0.193$), whereas hyperdensity on CT immediately after MT was strongly associated with PH2 (14.3% vs. 1.1%) irrespective of FLAIR status [10]. The corresponding crude OR of 1.64 (0.81–3.32) is compatible both with no association and with a clinically relevant one; the study was underpowered for an effect of this size rather than evidence against it. The post-MT hyperdensity is a post-treatment marker and may partly represent contrast staining; it cannot substitute for a pretreatment predictor.

Kim et al. examined a continuous FLAIR SIR in 69 patients treated within 8 h who achieved an mTICI ≥ 2b. The SIR was not associated with symptomatic HT ($p = 0.63$) or with lesion growth, which was instead related to the interval between MRI and recanalization [9]. The number of sHT events was small, and the quantitative exposure was not directly comparable with binary visual positivity.

Meisterernst et al. studied a registry in which 86% of patients received endovascular treatment, with or without IVT [11]. Among 159 patients with pretreatment FLAIR, focal hyperintensity was present in 89 (56%). Any ICH (22.5% vs. 17.1%) and sICH (6.7% vs. 4.3%) were numerically higher in the FLAIR-positive patients, but neither difference was significant and the FLAIR hyperintensity was not an independent predictor. Two features limit interpretation: patients with a FLAIR signal in more than half of the DWI lesion were usually not treated, which truncated the exposure; and the inter-rater agreement for FLAIR hyperintensity was only fair.

3.3. Related Exposures and Mixed Reperfusion Cohorts (Tier B)

Sakakibara et al. compared DWI–FLAIR mismatch with match in 202 patients treated with MT within 24 h [20]. An sICH within 72 h was less frequent with mismatch (10% vs. 20%; adjusted OR 0.36, 0.13–0.97). Expressed in the direction used elsewhere in this review, FLAIR-positive (match) lesions carried higher adjusted odds of sICH, although the mismatch status is an operational classification and not the exact inverse of independently rated lesion positivity. The mismatch group, however, had more IVT, more cardioembolism and much shorter onset-to-door times (median 175 vs. 371 min), so the comparison is strongly linked to time from onset.

Ahn et al. analyzed 134 patients who received reperfusion therapy within 6 h [21]. An early FLAIR change within the DWI lesion (41.8%) was independently associated with HT on gradient-echo imaging (adjusted OR 4.37, 1.72–11.12), and in nearly half of FLAIR-positive patients the hemorrhage was located in the region of FLAIR change. The endpoint was any HT, and the mix of reperfusion modalities limits transfer to MT.

3.4. Thrombolysis and Mechanistic Cohorts (Tier C)

In the IVT cohorts, the associations with any hemorrhage were large. Hobohm et al. reported any ICH in 80.0% of FLAIR-positive and 16.7% of FLAIR-negative patients treated within 3 h (OR 20.0, 6.3–63.8) [6]. Importantly, the same study found no excess of PH2 ($p = 0.144$), and hemorrhages were not more often accompanied by clinical deterioration in FLAIR-positive patients (30% vs. 42% of bleeds). Kufner et al. found HT in 33.3% vs. 9.2% of

patients treated within 4.5 h (adjusted OR 18, 2–175); 15 of the 17 events were hemorrhagic infarction and only two were PH [7]. Cho et al. reported adjusted ORs of 13.64 and 10.44 for two definitions of sICH, with confidence intervals spanning two orders of magnitude [8].

Campbell et al., studying patients imaged 3–6 h after onset, found FLAIR hyperintensity in 48 of 49 patients and no difference in PH between obvious and absent/subtle hyperintensity (11% vs. 9.7%) [12]; beyond 3 h, positivity is almost universal and loses discriminatory value. In a mechanistic cohort without endovascular treatment, Jha et al. showed that the FLAIR ratio correlated with plasma matrix metalloproteinase-9 and was independently associated with HT; the stepwise increase towards sICH rested on three sICH cases [5].

The 2025 meta-analysis pooled four IVT cohorts for HT and obtained an OR of 3.47 (0.51–23.57) with $I^2 = 83\%$; the study of Hobohm et al. was identified as an outlier, and in a subgroup with moderate stroke severity the OR was 1.89 (0.51–7.05) [15]. FLAIR positivity was, however, associated with a less favorable 90-day outcome (OR 2.14, 1.01–4.55).

3.5. Direction and Precision of Effects

Table 2 presents the direction of association by outcome definition. All six studies with an estimable contrast for any hemorrhage reported a point estimate in the direction of higher risk, with five statistically significant associations. Among MT or MT-predominant cohorts, Aoki et al. reported a positive association with HBC ≥ 1c, which included PH1 and other hemorrhage types [19]. Kimura et al. reported an imprecise estimate for PH2, and the symptomatic hemorrhage analyses by Kim et al. and Meisterernst et al. did not reach statistical significance [9–11]. Separate PH1 effects were unavailable in the extracted cohort data. The associations for pooled PH, PH2, symptomatic hemorrhage, and HBC ≥ 1c therefore describe distinct outcomes.

Table 2. Direction of the association between FLAIR positivity and hemorrhage, by study-defined hemorrhage outcome.

Study	Tier	Any Hemorrhage (HT/ICH)	Other Reported Endpoints and Associations
Aoki 2021 [19]	A	Higher, significant	HBC ≥ 1c: Higher, statistically significant
Kim 2017 [9]	A	Not reported	sHT: No significant association ($p = 0.63$)
Kimura 2023 [10]	A	Not reported	PH2: Higher, imprecise ($p = 0.193$)
Meisterernst 2017 [11]	A	Higher, not significant	sICH: Higher, not statistically significant (9 events)
Sakakibara 2020 [20]	B	Not reported	sICH: Higher with FLAIR match after adjustment
Ahn 2017 [21]	B	Higher, significant (adjusted)	No separate endpoint reported
Cho 2008 [8]	C	Not reported	sICH: Higher after adjustment, with wide confidence intervals
Hobohm 2014 [6]	C	Higher, significant	PH2: No significant difference ($p = 0.144$)
Kufner 2013 [7]	C	Higher, significant (adjusted)	PH: 2 events, separate association not estimable
Campbell 2011 [12]	C	Not reported	PH: Similar rates (5 events)

Table 2. *Cont.*

Study	Tier	Any Hemorrhage (HT/ICH)	Other Reported Endpoints and Associations
Jha 2014 [5]	C	Higher, significant (adjusted; continuous)	PH: 4 events; sICH: 3 events, with no separate association tested
Summary		6 of 6 higher (5 significant)	Mixed endpoint definitions; see study-specific results above

"Higher" indicates a point estimate favoring more hemorrhage with FLAIR positivity, FLAIR match, or higher FLAIR ratio. PH indicates parenchymal hematoma reported without separate type-specific effects. No standalone PH1 effect was available. HBC ≥ 1c includes PH1, PH2, and class 3 hemorrhages. Symptomatic outcomes retain the original study definitions. FLAIR, fluid-attenuated inversion recovery; HBC, Heidelberg Bleeding Classification; HT, hemorrhagic transformation; ICH, intracranial hemorrhage; PH1, parenchymal hematoma type 1; PH2, parenchymal hematoma type 2; sHT, symptomatic hemorrhagic transformation; sICH, symptomatic intracranial hemorrhage.

3.6. Methodological Concerns

The main concerns are summarized by the QUIPS domains in Table 3. Across studies, the most important were selective inclusion of patients imaged with MRI and exclusion of patients with extensive FLAIR changes; variable definitions and fair-to-good reproducibility of FLAIR readings; heterogeneous hemorrhage classifications and imaging modalities; incomplete adjustment for time from onset, DWI lesion volume, stroke severity and reperfusion grade; and very few severe hemorrhage events.

Table 3. Principal methodological concerns by QUIPS domain.

QUIPS Domain	Main Concerns Observed (Examples)	Likely Consequence
Study participation	MRI-first selection; patients with FLAIR signal > 50% of the DWI lesion usually not treated (Meisterernst); lesions < 5 mL excluded (Jha); 25 of 122 patients excluded for image quality (Hobohm); restriction to successful recanalization (Kim)	Unknown direction; truncation of the exposure may attenuate associations
Study attrition	Missing follow-up imaging and exclusions rarely quantified	Possible differential loss of severe cases
Prognostic factor measurement	Visual vs. quantitative definitions; $\kappa = 0.76$ (Hobohm) vs. Cronbach's $\alpha \approx 0.51$ (Meisterernst); strong dependence on time from onset	Misclassification; confounding by time
Outcome measurement	CT vs. T2*/GRE MRI (more sensitive to petechial hemorrhage); timing from 24 h to 7 days; ECASS II/III, HBC and PROACT II definitions; contrast staining after MT	Inflation of any-HT rates; limited comparability of severe endpoints
Confounding	Onset-to-imaging time, DWI volume, NIHSS, IVT, glucose, blood pressure, collaterals, passes and final reperfusion grade adjusted inconsistently or not at all	Crude associations likely overstated
Statistical analysis	Few severe events (34 PH2 in the largest MT cohort; 2–5 PH or 3 sICH in IVT cohorts); covariate selection by univariable p values; wide CIs	Imprecision; sparse-data bias in adjusted ORs

4. Discussion

4.1. Principal Findings

The four MT or MT-predominant cohorts provide the most direct evidence. Aoki et al. reported more ICH and more HBC ≥ 1c events with FLAIR positivity [19]. The largest MT cohort yielded a higher but imprecise PH2 estimate, and the other two cohorts did not establish an association with symptomatic hemorrhage [9–11]. The confidence interval for PH2 in the largest thrombectomy cohort was compatible with both no association and a clinically relevant increase in risk. In the Kimura cohort, PH2 rates of 10.7% and 6.8% provide a scenario for planning a confirmatory study [10]. A normal-approximation calculation for two independent proportions, with 36% of patients being FLAIR-positive, a two-sided $\alpha = 0.05$, and 80% power, gives approximately 1700 participants for an unadjusted comparison. A multivariable study should also account for the number of PH2 events and the planned covariates.

Across treatment settings, nine cohorts yielded point estimates in the direction of more hemorrhages with higher or positive FLAIR signals. The pattern was clearest for any hemorrhage. For example, Hobohm et al. reported an OR of 20 for any ICH after IVT and no statistically significant difference in PH2 [6]. Differences in treatment, signal definition, and hemorrhage outcome limit the extent to which these results inform prediction of PH2 or symptomatic hemorrhage after MT.

4.2. Sources of Heterogeneity

Several factors explain why the studies differ. The time from onset is the strongest: FLAIR positivity is present in about one quarter of patients imaged within 3 h [6], in 36% of an MT cohort [10], and in 98% of patients imaged at 3–6 h [12]. Early positivity is uncommon and may identify rapidly progressing ischemia, whereas later positivity is nearly universal and uninformative; studies spanning wide windows dilute any early-window effect. The endpoint definition and imaging modality matter: a T2*/gradient-echo MRI detects more petechial hemorrhages than CT [7,21], and after MT, iodinated contrast can mimic or mask a hemorrhage on an early CT [10]. The treatment differs: IVT cohorts [6–8] and MT cohorts [10,19] differ in reperfusion completeness, bridging thrombolysis and the timing of reperfusion. Selection on the exposure, such as withholding treatment when the FLAIR signal exceeds half of the DWI lesion [11], removes the patients in whom an effect would be most expected. Finally, the reading reproducibility ranges from good to only fair [6,11], and non-differential misclassification biases associations towards the null. For MT-specific analyses, the incremental value of FLAIR should be evaluated alongside the baseline NIHSS, pretreatment infarct volume, time from symptom onset to imaging or treatment, and final reperfusion grade. The reperfusion grade is available after the procedure and belongs in analyses that use postprocedural information or that explicitly address outcomes conditional on reperfusion.

4.3. Biological Interpretation

Parenchymal FLAIR hyperintensity reflects net water accumulation, to which vasogenic edema and blood–brain barrier disruption contribute, but its visibility also depends on the acquisition parameters and visual assessment. Early FLAIR positivity is therefore better regarded as a possible correlate of tissue injury than as a direct measure of its severity. The correlation between the FLAIR ratio and plasma matrix metalloproteinase-9 supports a link with barrier injury [5], and the spatial concordance between FLAIR change and subsequent hemorrhage in the study of Ahn et al. is consistent with a local tissue process [21]. Conventional FLAIR does not, however, measure permeability directly. HARM is a postcontrast FLAIR finding in cerebrospinal fluid spaces that reflects gadolinium leakage across a dis-

rupted blood–brain barrier. Its association with HT and PH in WAKE-UP concerns contrast leakage, whereas pretreatment parenchymal FLAIR hyperintensity is an intralesional signal related to tissue water [14]. FVH reflects collateral hemodynamics [13].

4.4. Restriction to Successful Reperfusion

The clinically specific question concerns patients with near-complete reperfusion. Successful reperfusion is a post-baseline event, and restricting analysis to it conditions on a variable that may itself depend on lesion severity, clot characteristics and procedural difficulty. Such a restriction can create spurious associations or hide real ones; the only cohort restricted to successful recanalization reported no all-treated comparison [9]. Studies addressing this question should therefore report an analysis of all treated patients alongside an analysis restricted to mTICI 2c–3, and interpret the restricted estimate cautiously. Causal language should remain cautious even after multivariable adjustment, because residual confounding and conditioning on reperfusion may persist.

4.5. Clinical Implications

The current evidence does not support using FLAIR positivity alone to withhold MT [11,15]. Whether pretreatment FLAIR adds enough prognostic information to guide the frequency or intensity of postprocedural monitoring remains a research question. Its potential contribution should be evaluated alongside the infarct burden, baseline neurological severity, timing, and procedural findings.

4.6. Remaining Questions and Research Agenda

No study isolated the target population (Table 4). Each restriction has a rationale. Imaging within 3 h of a known onset is the window in which FLAIR positivity is uncommon and potentially informative [6,12]. M1 occlusion provides a relatively homogeneous vascular territory and collateral pattern. Near-complete reperfusion (mTICI 2c–3) separates tissue-related risk from that of incomplete reperfusion, subject to the selection issue described above. Because PH2 occurs in fewer than 10% of MT patients [10], a single-center study cannot answer the question. A pooled analysis of existing MRI-first MT registries, or a multicenter prospective cohort, should use blinded FLAIR reading with reported agreement, a quantitative SIR, onset-to-imaging time, DWI volume and final reperfusion grade, and report PH2 and sICH separately according to the HBC [2].

Table 4. Extent to which the included studies address the target question (known onset <3 h, M1 occlusion, lesion-level FLAIR, final mTICI 2c–3, and PH2 and sICH reported separately).

Study	Onset < 3 h	M1 Occlusion	Lesion-Level FLAIR	mTICI 2c–3	Hemorrhage Endpoint
Aoki 2021 [19]	Not isolated	Not isolated	Yes	Not isolated	HBC ≥ 1c; any ICH
Kim 2017 [9]	No (≤8 h)	Not isolated	Quantitative SIR	mTICI ≥ 2b	sHT
Kimura 2023 [10]	Not isolated	M1 44%, with ICA and M2	Yes	Not isolated	PH2
Meisterernst 2017 [11]	No (median 253 min)	Not isolated	Yes; >50% FLAIR excluded	Not reported	Any ICH; sICH
Sakakibara 2020 [20]	No (≤24 h)	ICA and MCA	Mismatch only	Not isolated	sICH
Ahn 2017 [21]	No (≤6 h)	Not isolated	Yes	Mixed reperfusion	Any HT
Hobohm 2014 [6]	Yes (<3 h)	Not M1 only	Yes	IVT; no MT	Any ICH; PH2
Kufner 2013 [7]	No (<4.5 h)	Not M1 only	Yes	IVT; no MT	Any HT

Table 4. *Cont.*

Study	Onset < 3 h	M1 Occlusion	Lesion-Level FLAIR	mTICI 2c–3	Hemorrhage Endpoint
Cho 2008 [8]	Not isolated	Mixed	Yes	Thrombolysis; no mTICI	sICH
Campbell 2011 [12]	No (3–6 h)	Not M1 only	Yes	IVT or placebo	PH
Jha 2014 [5]	No (≤12 h)	Not M1 only	Quantitative ratio	No endovascular	HT; sICH

"Not isolated": A separate analysis of the specified subgroup was not reported.

4.7. Strengths and Limitations

The principal strengths of this review are its explicit focus on a narrow, clinically relevant question and its decision not to pool heterogeneous evidence. It separates FLAIR constructs and hemorrhage endpoints, reports all numerical findings against their sources, recalculates the crude effects in a common metric where possible, and appraises studies across QUIPS domains. It has important limitations. PubMed was the sole bibliographic database searched. Although reference-list screening supplemented the search, reliance on one database and single-evaluator triage may have led to omission of eligible reports. The counts for one study were derived from percentages. The single-evaluator data extraction and QUIPS appraisal may have affected the reproducibility of the extracted items and the interpretation of individual domains, especially where study methods were incompletely described. We retained domain-level observations for qualitative interpretation. Selective publication and selective outcome reporting may have exaggerated the apparent associations; funnel plots and Egger-type tests are not appropriate for so small and heterogeneous an evidence set, and positive IVT studies may be over-represented. Finally, most included cohorts were single-center and retrospective.

5. Conclusions

In MT and MT-predominant cohorts, the pretreatment parenchymal FLAIR hyperintensity shows an association with any hemorrhage in one cohort, while estimates for PH2 and symptomatic hemorrhage remain imprecise. The evidence from IVT and mixed-treatment cohorts provides context for the association with broader hemorrhage outcomes. The available MT evidence does not establish independent prediction of PH2 or symptomatic hemorrhage. FLAIR positivity alone should not be used to withhold mechanical thrombectomy. Multicenter studies should assess its incremental prognostic contribution using standardized FLAIR assessment and report PH1, PH2, and symptomatic hemorrhage separately.

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Abbreviations

CI, confidence interval; CT, computed tomography; DWI, diffusion-weighted imaging; ECASS, European Cooperative Acute Stroke Study; EVT, endovascular treatment; FLAIR, fluid-attenuated inversion recovery; FVH, FLAIR vascular hyperintensity; GRE, gradient-recalled echo; HARM, hyperintense acute reperfusion marker; HBC, Heidelberg Bleeding Classification; HI, hemorrhagic infarction; HT, hemorrhagic transformation; ICA, internal carotid artery; ICH, intracranial hemorrhage; IVT, intravenous thrombolysis; LVO, large-vessel occlusion; M1, first segment of the middle cerebral artery; MCA, middle cerebral artery; MMP-9, matrix metalloproteinase-9; MRI, magnetic resonance imaging; MT, mechanical thrombectomy; mTICI, modified Thrombolysis in Cerebral Infarction; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio; PH, parenchymal hematoma; PH1, parenchymal hematoma type 1; PH2, parenchymal hematoma type 2; PROACT, Prolyse in Acute Cerebral Thromboembolism; QUIPS, Quality In Prognosis Studies; sHT, symptomatic hemorrhagic transformation; sICH, symptomatic intracranial hemorrhage; SIR, signal intensity ratio; SWiM, Synthesis Without Meta-analysis; tPA, tissue plasminogen activator.

References

1. Hacke, W.; Kaste, M.; Fieschi, C.; von Kummer, R.; Davalos, A.; Meier, D.; Larrue, V.; Bluhmki, E.; Davis, S.; Donnan, G.; et al. Randomised double-blind placebo-controlled trial of thrombolytic therapy with intravenous alteplase in acute ischaemic stroke (ECASS II). *Lancet* **1998**, *352*, 1245–1251. [CrossRef]
2. von Kummer, R.; Broderick, J.P.; Campbell, B.C.; Demchuk, A.; Goyal, M.; Hill, M.D.; Treurniet, K.M.; Majoie, C.B.; Marquering, H.A.; Mazya, M.V.; et al. The Heidelberg Bleeding Classification: Classification of bleeding events after ischemic stroke and reperfusion therapy. *Stroke* **2015**, *46*, 2981–2986. [CrossRef]
3. Thomalla, G.; Cheng, B.; Ebinger, M.; Hao, Q.; Tourdias, T.; Wu, O.; Kim, J.S.; Breuer, L.; Singer, O.C.; Warach, S.; et al. DWI-FLAIR mismatch for the identification of patients with acute ischaemic stroke within 4.5 h of symptom onset (PRE-FLAIR): A multicentre observational study. *Lancet Neurol.* **2011**, *10*, 978–986. [CrossRef]
4. Thomalla, G.; Simonsen, C.Z.; Boutitie, F.; Andersen, G.; Berthezene, Y.; Cheng, B.; Cheripelli, B.; Cho, T.-H.; Fazekas, F.; Fiehler, J.; et al. MRI-guided thrombolysis for stroke with unknown time of onset. *N. Engl. J. Med.* **2018**, *379*, 611–622. [CrossRef]
5. Jha, R.; Battey, T.W.K.; Pham, L.; Lorenzano, S.; Furie, K.L.; Sheth, K.N.; Kimberly, W.T. Fluid-attenuated inversion recovery hyperintensity correlates with matrix metalloproteinase-9 level and hemorrhagic transformation in acute ischemic stroke. *Stroke* **2014**, *45*, 1040–1045. [CrossRef]
6. Hobohm, C.; Fritzsch, D.; Budig, S.; Classen, J.; Hoffmann, K.T.; Michalski, D. Predicting intracerebral hemorrhage by baseline magnetic resonance imaging in stroke patients undergoing systemic thrombolysis. *Acta Neurol. Scand.* **2014**, *130*, 338–345. [CrossRef]
7. Kufner, A.; Galinovic, I.; Brunecker, P.; Cheng, B.; Thomalla, G.; Gerloff, C.; Campbell, B.C.V.; Nolte, C.H.; Endres, M.; Fiebach, J.B.; et al. Early infarct FLAIR hyperintensity is associated with increased hemorrhagic transformation after thrombolysis. *Eur. J. Neurol.* **2013**, *20*, 281–285. [CrossRef]
8. Cho, A.-H.; Kim, J.S.; Kim, S.-J.; Yun, S.-C.; Choi, C.-G.; Kim, H.-R.; Kwon, S.U.; Lee, D.-H.; Kim, E.-K.; Suh, D.-C.; et al. Focal fluid-attenuated inversion recovery hyperintensity within acute diffusion-weighted imaging lesions is associated with symptomatic intracerebral hemorrhage after thrombolysis. *Stroke* **2008**, *39*, 3424–3426. [CrossRef]
9. Kim, T.; Chung, J.-W.; Jang, M.S.; Yang, M.H.; Lee, S.-H.; Kim, B.J.; Han, M.-K.; Kim, J.H.; Jung, C.; Lim, J.-S.; et al. The role of the signal intensity ratio on fluid-attenuated inversion recovery in stroke patients achieving successful recanalization with endovascular treatment. *J. Stroke Cerebrovasc. Dis.* **2017**, *26*, 1528–1534. [CrossRef]
10. Kimura, R.; Shoda, S.; Saito, T.; Suzuki, K.; Kutsuna, A.; Kanamaru, T.; Katano, T.; Nakagami, T.; Numao, S.; Suda, S.; et al. Imaging indicators for parenchymal hemorrhage after mechanical thrombectomy in acute stroke. *Stroke Vasc. Interv. Neurol.* **2023**, *3*, e000499. [CrossRef]
11. Meisterernst, J.; Klinger-Gratz, P.P.; Leidolt, L.; Lang, M.F.; Schroth, G.; Mordasini, P.; Heldner, M.R.; Mono, M.-L.; Kurmann, R.; Buehlmann, M.; et al. Focal T2 and FLAIR hyperintensities within the infarcted area: A suitable marker for patient selection for treatment? *PLoS ONE* **2017**, *12*, e0185158. [CrossRef]

12. Campbell, B.C.; Costello, C.; Christensen, S.; Ebinger, M.; Parsons, M.W.; Desmond, P.M.; Barber, P.A.; Butcher, K.S.; Levi, C.R.; De Silva, D.A.; et al. Fluid-attenuated inversion recovery hyperintensity in acute ischemic stroke may not predict hemorrhagic transformation. *Cerebrovasc. Dis.* **2011**, *32*, 401–405. [CrossRef]
13. Chen, N.-H.; Zhang, Y.-M.; Jiang, F.-P.; Liu, S.; Zhao, H.-D.; Hou, J.-K.; Jiang, T.; Shi, J.-Q.; Zhou, J.-S.; Zhang, Y.-D. FLAIR vascular hyperintensity predicts early neurological deterioration in patients with acute ischemic stroke receiving endovascular thrombectomy. *Neurol. Sci.* **2022**, *43*, 3747–3757. [CrossRef]
14. Wouters, A.; Scheldeman, L.; Dupont, P.; Cheng, B.; Ebinger, M.; Jensen, M.; Endres, M.; Gerloff, C.; Muir, K.W.; Nighoghossian, N.; et al. Hyperintense acute reperfusion marker associated with hemorrhagic transformation in the WAKE-UP trial. *Eur. Stroke J.* **2021**, *6*, 128–133. [CrossRef]
15. Zhubi, E.; Bissenov, A.; Lengyel, A.S.; Tóth, R.; Horváth, A.A.; Kéri, S.; Engh, M.A.; Hegyi, P.; Gunda, B. Association of FLAIR positivity and worse outcomes after intravenous thrombolysis in known-onset strokes: A systematic review and meta-analysis. *J. Clin. Med.* **2025**, *14*, 8031. [CrossRef]
16. Campbell, M.; McKenzie, J.E.; Sowden, A.; Katikireddi, S.V.; Brennan, S.E.; Ellis, S.; Hartmann-Boyce, J.; Ryan, R.; Shepperd, S.; Thomas, J.; et al. Synthesis without meta-analysis (SWiM) in systematic reviews: Reporting guideline. *BMJ* **2020**, *368*, l6890. [CrossRef]
17. Hayden, J.A.; van der Windt, D.A.; Cartwright, J.L.; Côté, P.; Bombardier, C. Assessing bias in studies of prognostic factors. *Ann. Intern. Med.* **2013**, *158*, 280–286. [CrossRef]
18. Riley, R.D.; Moons, K.G.M.; Snell, K.I.E.; Ensor, J.; Hooft, L.; Altman, D.G.; Hayden, J.; Collins, G.S.; Debray, T.P.A. A guide to systematic review and meta-analysis of prognostic factor studies. *BMJ* **2019**, *364*, k4597. [CrossRef]
19. Aoki, J.; Sakamoto, Y.; Suzuki, K.; Nishi, Y.; Kutsuna, A.; Takei, Y.; Sawada, K.; Kanamaru, T.; Abe, A.; Katano, T.; et al. Fluid-attenuated inversion recovery may serve as a tissue clock in patients treated with endovascular thrombectomy. *Stroke* **2021**, *52*, 2232–2240. [CrossRef]
20. Sakakibara, F.; Yoshimura, S.; Numa, S.; Uchida, K.; Kinjo, N.; Morimoto, T. Diffusion-weighted imaging–fluid-attenuated inversion recovery mismatch is associated with 90-day functional outcomes in patients undergoing mechanical thrombectomy. *Cerebrovasc. Dis.* **2020**, *49*, 292–300. [CrossRef]
21. Ahn, S.H.; Kim, B.J.; Kim, Y.J.; Kwon, S.U.; Kim, J.S.; Kang, D.W. Fluid-attenuated inversion recovery hyperintensity is associated with hemorrhagic transformation following reperfusion therapy. *J. Stroke Cerebrovasc. Dis.* **2017**, *26*, 327–333. [CrossRef]

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