REVIEWS
ОБЗОРИ

HEMORRHAGIC RISK AFTER ACUTE ISCHEMIC STROKE: BLOOD BIOMARKERS FOR HEMORRHAGIC TRANSFORMATION AND SYMPTOMATIC INTRACEREBRAL HEMORRHAGE

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КРЪВНИ НЕВРОБИОМАРКЕРИ ЗА ОЦЕНКА НА РИСКА ОТ ХЕМОРАГИЧНА ТРАНСФОРМАЦИЯ И СПОНТАНЕН ИНТРАЦЕРЕБРАЛЕН КРЪВОИЗЛИВ СЛЕД ОСТЪР ИСХЕМИЧЕН ИНСУЛТ

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Abstract:

Hemorrhagic transformation after acute ischemic stroke is clinically uneven: it may remain a small petechial finding, but it may also become a parenchymal hematoma with neurological deterioration. This review discusses blood biomarkers that have been examined in relation to hemorrhagic transformation and symptomatic intracerebral hemorrhage, especially in patients treated with intravenous thrombolysis, mechanical thrombectomy, or bridging therapy. The evidence is arranged by biological signal rather than by test name alone. Matrix metalloproteinase-9 and cellular fibronectin are closest to blood-brain barrier and extracellular-matrix failure. Glial fibrillary acidic protein, neurofilament light chain, and S100B mainly describe astroglial or axonal injury burden. Neutrophil-to-lymphocyte ratio, D-dimer, fibrinogen, and von Willebrand factor add inflammatory, fibrinolytic, hemostatic, and endothelial information. At present, none of these markers is sufficiently standardized for isolated treatment selection. Their more credible role is within multimodal risk profiles combined with imaging, clinical severity, and reperfusion data.

Key words:

acute ischemic stroke, blood biomarkers, hemorrhagic transformation, reperfusion therapy, risk stratification, symptomatic intracerebral hemorrhage

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Резюме:

Хеморагичната трансформация, позната в българската литература и като „вторично хеморагично инфарциране", варира от ограничени петехиални кръвоизливи в исхемичната зона до паренхимен хематом с възможно неврологично влошаване. В настоящия обзор се разглеждат кръвни биомаркери, изследвани във връзка с хеморагичната трансформация и спонтанен интрацеребрален кръвоизлив, особено при пациенти след интравенозна тромболиза, механична тромбектомия или комбинирано реперфузионно лечение. Два от невробиомаркерите – матриксната металопротеиназа-9 и клетъчният фибронектин, са най-близо до увреждането на кръвно-мозъчната бариера и извънклетъчния матрикс.

Глиалният фибриларен кисел белтък (glial fibrillary acidic protein (GFAP), невро-филаментната лека верига (neurofilament light chain (NfL) и S100B отразяват предимно астро-глиално и невроаксонално увреждане. Съотношението не-утрофили/лимфоцити, D-димерът, фибриногенът и факторът на Von Willebrand допълват оценката чрез възпалителна, фибринолитична, хемостатична и ен-дотелна дисфункция. Не е намерен универсален предиктор за хеморагична трансформация, но е реалистично включването на кръвните невробиомаркери в мултимодални модели за оценка на риска от хеморагична трансформация и интрацеребрален хематом.

Ключови думи: остър исхемичен инсулт, кръвни невробиомаркери, хеморагична трансфор-мация, реперфузионна терапия, спонтанен интрацеребрален кръвоизлив

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Introduction

Hemorrhagic transformation is one of the complications that gives acute ischemic stroke its clinical uncertainty. The term is simple, but the event is not. On follow-up imaging, the finding may be a narrow petechial blush inside a completed infarct. In another patient, it may be a parenchymal hematoma, with edema, mass effect, worsening consciousness, or death. The biological background is also mixed. Experimental and clinical work has described microvascular injury, inflammatory cell entry, oxidative stress, endothelial dysfunction and loss of extracellular matrix support as parts of the same process [1, 2].

The radiological language introduced in the European Cooperative Acute Stroke Study remains useful because it separates hemorrhagic infarction from parenchymal hematoma and makes the extent of bleeding visible in a reproducible way [3]. At the bedside, however, the more difficult question is not only whether blood is seen on follow-up imaging. The question is whether the bleeding is clinically relevant. Symptomatic intracerebral hemorrhage is therefore usually defined by both imaging and neurological deterioration, although the exact definitions used in trials and registries have not always been identical [4, 5].

The issue became more important, not less, after the success of reperfusion treatment. Alteplase remains time-dependent, and endovascular thrombectomy changed the prognosis of large-vessel occlusion stroke in selected early and late windows [7-12]. Yet the decision to restore flow is made in a vessel bed that may already be injured. Infarct size, early ischemic signs, baseline neurological deficit, glucose, blood pressure, collateral pattern and time from onset are helpful, but they are still indirect descriptors of the vascular wall [6].

Blood biomarkers are attractive for this reason. They can carry information about processes that are not fully visible at the moment of the treatment decision: basement membrane breakdown, astroglial damage, axonal injury, neutrophil-driven inflammation, fibrinolysis and endothelial activation. Earlier reviews of stroke biomarkers have shown that this field is promising, but also uneven, because many studies used different assays, different sampling windows and different hemorrhage definitions [13-15]. The present review summarizes the main biomarker groups relevant to hemorrhagic transformation and symptomatic intracerebral hemorrhage after acute ischemic stroke, with attention to clinical usefulness rather than to statistical association alone.

Search Approach and Limitations of the Review

A narrative review was prepared from peer-reviewed literature on circulating biomarkers, hemorrhagic transformation, symptomatic intracerebral hemorrhage, blood-brain barrier injury, reperfusion-related vascular damage and acute ischemic stroke outcome. PubMed, Scopus and Web of Science were considered the primary biomedical sources. Searches combined terms for acute ischemic stroke, thrombolysis, thrombectomy, hemorrhagic transformation, symptomatic intracerebral hemorrhage, matrix metalloproteinase-9 (MMP-9), cellular fibronectin, glial fibrillary acidic protein (GFAP), neurofilament light chain (NfL), S100B, neutrophil-to-lymphocyte ratio (NLR), D-dimer, fibrinogen and endothelial dysfunction.

Preference was given to systematic reviews, meta-analyses, prospective cohorts, multicenter observational studies and pivotal reperfusion trials. Mechanistic papers were also retained when they

clarified why a particular marker might be linked to bleeding. A formal meta-analysis was not attempted. The literature is too heterogeneous for a single pooled conclusion: samples may be drawn before treatment, after treatment or at 24-72 hours; hemorrhagic transformation may include petechial bleeding or only parenchymal hematoma; and some cohorts are thrombolysis-based, whereas others include contemporary thrombectomy populations.

For that reason, the text is organized by biological domain. A marker of extracellular matrix degradation should not be read in the same way as a leukocyte-derived index or an axonal protein. This organization also reflects the practical clinical question. The value of a blood test depends not only on whether it is associated with hemorrhage, but on when it can be obtained, how stable the assay is, how easily confounders alter the result and whether the information arrives early enough to change monitoring or management.

How Biomarker Signals Should Be Read

The neurovascular unit is the starting point for interpretation. Acute ischemia causes endothelial swelling, tight-junction failure, pericyte and astrocyte dysfunction, leukocyte recruitment and progressive permeability of the blood-brain barrier. Reperfusion may rescue threatened tissue, but it can also expose weakened microvessels to pressure shifts, reactive oxygen species and inflammatory amplification [1, 2, 6]. Bleeding becomes possible when the supporting architecture of the vessel wall is no longer sufficient.

Timing is not a minor detail. A value measured before thrombolysis reflects the pretreatment condition of the infarcted vascular bed. A value obtained after recanalization may include reperfusion injury, evolving necrosis, post-procedural inflammation or delayed axonal damage. Glial proteins may rise earlier when astrocytic and barrier structures are damaged, while NfL may continue to increase as axonal injury unfolds [25-27]. The same number therefore has different meanings on admission, after thrombolysis or on the third day.

Matrix metalloproteinases provide one of the clearest mechanistic links. MMP-9 can digest collagen IV, laminin, fibronectin and other basement membrane components. Its activity is promoted by neutrophils, inflammatory cytokines, oxidative stress and endothelial injury. This explains why it has been studied repeatedly in thrombolysis-treated stroke and why elevated levels have been connected with hemorrhagic conversion [16-18].

Other markers describe adjacent, not identical, processes. Cellular fibronectin points toward endothelial and basement membrane damage. GFAP and S100B suggest astroglial disruption and blood-brain barrier stress. NfL reflects axonal injury burden, which is important but not hemorrhage-specific. Inflammatory and coagulation markers describe the systemic environment in which vascular leakage may occur [28-37]. In practice, a biomarker panel is more biologically reasonable than a single test.

Vascular Matrix and Barrier Markers

Among the available markers, MMP-9 has the most direct biological relation to hemorrhagic transformation. Early studies described its expression after cardioembolic stroke and linked higher concentrations with later hemorrhagic conversion [16, 17]. In thrombolysis-treated patients, serum cellular fibronectin and MMP-9 were evaluated as screening markers for parenchymal hematoma, giving this pathway a stronger translational position than many other candidate markers [18]. Systematic reviews and meta-analytic work have supported an association with hemorrhagic transformation, although the magnitude of risk varies between studies [19, 20].

This does not make MMP-9 ready for independent clinical use. Published thresholds differ because studies used different matrices, laboratory platforms, sampling times and outcome definitions. Infection, systemic inflammation, malignancy and vascular comorbidity may also raise circulating levels. The marker is useful because it is close to the mechanism; it is unsafe if treated as a simple yes-or-no rule.

Cellular fibronectin is less familiar in routine laboratories, but it is conceptually important. It reflects injury of endothelial and basement membrane structures. Higher plasma concentrations have predicted hemorrhagic transformation after thrombolysis, and the combination with MMP-9 is appealing because both markers point toward vascular structural failure [18, 21]. The problem is mainly implementation. Many emergency laboratories cannot measure it rapidly, and commonly accepted clinical thresholds are lacking.

Blood-brain barrier imaging may eventually help interpret these markers. Permeability changes can precede visible hemorrhage, and a biomarker signal is more credible when it matches imaging evidence of barrier failure [39]. This combined approach is more realistic than expecting a single blood value to capture the full vascular state of the infarct.

Glial, Axonal and Inflammatory Markers

GFAP has been examined mainly in the early distinction between intracerebral hemorrhage and ischemic stroke [22-24]. For hemorrhagic transformation, it should be read more cautiously. It does not measure bleeding directly. Rather, it indicates astroglial disruption and, indirectly, injury of the neurovascular unit. A high concentration may therefore identify a patient with a larger or biologically unstable infarct, especially when clinical severity and imaging are concordant.

NfL adds another layer. It is a marker of neuroaxonal injury, and higher concentrations in acute ischemic stroke have been associated with infarct burden, secondary injury and functional outcome [25-27]. Its relation to hemorrhagic transformation is indirect. A large infarct with substantial axonal damage is more likely to coexist with damaged microvessels, but NfL does not demonstrate barrier rupture. Its most useful role is to quantify tissue injury burden within a broader vascular and inflammatory profile.

S100B occupies a middle position. Older work linked it with infarct severity and malignant middle cerebral artery infarction [28, 29]. More recent multicenter data showed that serum S100B measured within the first 24 hours added information for the prediction of symptomatic intracranial hemorrhage and brain edema [30]. Its specificity is imperfect, but its clinical interest is clear: it reflects astroglial injury and barrier dysfunction in a form that is more accessible than many experimental proteins.

Inflammation is both important and difficult to interpret. Interleukin-6, tumor necrosis factor-alpha, C-reactive protein and leukocyte indices have all been linked with stroke severity or outcome [31, 32]. The NLR is attractive because it comes from the complete blood count and can be calculated immediately. Meta-analysis supports its prognostic value in stroke, and revascularization cohorts have linked higher values with symptomatic hemorrhagic transformation [33, 34]. Still, this ratio is easily disturbed by pneumonia, urinary infection, chronic inflammatory disease, malignancy, stress response or corticosteroid exposure. It is a readily available warning signal, not a diagnostic test.

Hemostasis, Endothelium and the Reperfusion Window

D-dimer and fibrinogen are clinically familiar, which makes them easier to implement than many neurobiomarkers. After intravenous thrombolysis, D-dimer elevation has been associated with symptomatic intracranial hemorrhage and poor functional outcome [35]. A decrease in fibrinogen after alteplase may indicate reduced hemostatic reserve and a higher risk of intracerebral bleeding [36]. These findings are plausible, but they depend on timing. A pretreatment value, an early post-treatment change and a later follow-up value do not describe the same state.

Von Willebrand factor represents endothelial activation and vascular risk. High levels have been associated with stroke risk in population data, but direct evidence for predicting hemorrhagic transformation is weaker than for MMP-9 or cellular fibronectin [37]. It may be useful as part of an endothelial-risk layer, particularly when combined with imaging and other markers of microvascular injury.

The reperfusion setting matters. In intravenous thrombolysis, hemorrhage may arise when ischemic endothelial injury, fibrinolysis, inflammation and matrix degradation converge. In thrombectomy, additional variables enter the picture: infarct core, collateral flow, number of device passes, procedural time, final reperfusion grade and post-procedural blood pressure. In bridging therapy, several mechanisms accumulate in the same patient. A multimarker profile is therefore easier to defend than a single analyte: MMP-9 or cellular fibronectin for matrix failure, NLR for inflammation, D-dimer and fibrinogen for fibrinolysis and hemostasis, and GFAP or NfL for tissue injury burden [16-21, 33-36].

No biomarker should delay reperfusion. Tests available only by delayed batch analysis may still help prognosis, surveillance or trial enrichment. They cannot guide acute treatment in the same way as glucose, platelet count, coagulation tests or imaging. After reperfusion, slower markers may become more useful. They may support closer observation, earlier follow-up imaging, repeat coagulation assessment or a lower threshold for investigating neurological worsening.

Table 1. Practical interpretation of selected blood biomarkers for hemorrhagic risk after acute ischemic stroke

Biomarker	Main signal	Potential clinical reading	Main caveat
MMP-9	Basement membrane and extracellular matrix degradation	Closest blood signal to barrier failure; it is associated with parenchymal hematoma and symptomatic hemorrhage [16-20]	Thresholds and assays differ across studies
Cellular fibronectin	Endothelial and basement membrane injury	It supports the interpretation of severe vascular structural damage, especially with MMP-9 [18, 21]	Limited emergency availability
GFAP	Astroglial and neurovascular unit injury	It may identify extensive tissue disruption and complement imaging [22-24]	Not a direct hemorrhage marker
NfL	Neuroaxonal injury	It adds information on infarct and axonal injury burden [25-27]	Indirect relation to bleeding
S100B	Astroglial injury and barrier dysfunction	It is associated with edema and symptomatic intracranial hemorrhage in recent cohort data [28-30]	Limited specificity
NLR	Inflammatory activation	Rapid, inexpensive warning signal for poorer outcome and hemorrhagic complications [33, 34]	It is strongly confounded by systemic inflammation
D-dimer	Fibrinolysis and coagulation activation	Post-thrombolytic increase may indicate bleeding risk [35]	It is nonspecific and timing-dependent
Fibrinogen	Hemostatic reserve	Early fall after alteplase may suggest vulnerability to bleeding [36]	It requires dynamic interpretation
vWF	Endothelial activation	Supportive marker of endothelial dysfunction and vascular risk [37]	Direct evidence for hemorrhagic transformation is limited

Note: The table supports interpretation and does not imply that any biomarker should be used as an isolated treatment-selection criterion.

Acronyms: GFAP – glial fibrillary acidic protein; MMP-9 – matrix metalloproteinase-9; NfL – neurofilament light chain; NLR – neutrophil-to-lymphocyte ratio; vWF – Von Willebrand factor

From Single Tests to Risk Profiles

Clinical readiness is not the same as statistical significance. A marker must be reproducible between laboratories, add information beyond clinical and imaging predictors, and be available at the time when a decision is actually made. It must also be robust enough for stroke populations, where atrial fibrillation, infection, diabetes, renal dysfunction, malignancy and polypharmacy are common.

The present evidence does not support using any circulating biomarker as an isolated exclusion criterion for alteplase or thrombectomy. That use would be dangerous. It could withhold effective treatment from patients who might benefit. A more defensible role is risk enrichment: closer observation, stricter physiological control, earlier follow-up imaging, coagulation surveillance or enrollment in trials of neurovascular protection.

Multimarker models are the logical next step. One development and validation study showed that routine circulating markers can improve risk reclassification for hemorrhagic transformation, parenchymal hematoma and symptomatic hemorrhagic transformation [38]. The study illustrates the direction of the field: risk should be treated as a combination of pathways, not as a one-marker diagnosis. Future models should integrate matrix degradation, endothelial activation, inflammation, fibrinolysis, astroglial injury and axonal injury, together with infarct volume, collateral status, reperfusion grade and early neurological course [39, 40].

Point-of-care technology will determine how much of this can reach clinical practice. A rapid biomarker panel might be relevant during the acute pathway if it returns results within the same practical window as imaging and routine coagulation testing. A slower panel may still be useful after reperfusion. Machine learning may help combine heterogeneous variables, but opaque scores are unlikely to be accepted in acute stroke unless calibration, external validation and biological interpretability are clear.

For research, the most informative design would combine baseline imaging, early blood sampling, standardized post-treatment sampling and blinded adjudication of hemorrhage subtype. The endpoint should distinguish hemorrhagic infarction, parenchymal hematoma and symptomatic intracerebral hemorrhage. It should also record whether the patient received alteplase, tenecteplase, thrombectomy or bridging therapy. Only then can the same biomarker be tested in the clinical situation in which it is intended to be used. This is especially important because late-window thrombectomy and advanced imaging selection have changed the risk profile of many treated patients [11, 12, 38-40].

The preferred clinical output should probably be categorical rather than absolute. A report stating that a patient has a vascular-matrix dominant profile, an

inflammatory-fibrinolytic profile, or a high tissue-injury profile would be easier to discuss than an opaque probability score. Such categories would also protect against overinterpretation of a single abnormal test. For example, an elevated NLR may be driven by pneumonia rather than by the infarct; high D-dimer may reflect atrial fibrillation, malignancy or venous thrombosis; and increased NfL may reflect total axonal injury rather than bleeding risk. A useful model must keep these alternative explanations visible.

A separate practical issue concerns sampling time. Many papers report biomarker values as if the sampling moment were a background detail, but in stroke it is part of the result. A day-0 sample and a day-3 sample should not be mixed in the same interpretation. Matrix degradation may be most informative in the early period of barrier failure; fibrinogen change is meaningful only in relation to thrombolytic exposure; NfL is often delayed compared with astroglial markers. Future reports should therefore provide time from symptom onset, time from reperfusion, sample matrix, centrifugation delay, storage conditions and assay platform. Without these details, a numerical threshold is difficult to reproduce across hospitals [25-27, 35, 36].

After treatment, the question changes. The first hours after alteplase or thrombectomy are less about eligibility and more about surveillance. A patient with severe baseline deficit, large infarct core, incomplete reperfusion and elevated markers of vascular injury would deserve a lower threshold for control imaging and careful blood pressure management. Conversely, a patient with technically successful thrombectomy but high early glial markers may still require caution, because reperfusion success does not necessarily mean that the injured microvascular bed is stable. In this phase, GFAP, S100B, MMP-9, D-dimer and fibrinogen may be more useful as monitoring signals than as selection tools [18, 21-24, 30, 35, 36].

The practical use of biomarkers differs before and after reperfusion. Before treatment, the clinician needs information that can be obtained immediately and interpreted without delaying a proven therapy. In this narrow window, routine markers such as platelet count, coagulation tests, glucose, C-reactive protein, NLR, D-dimer or fibrinogen are more realistic than specialized neuroprotein assays. Even then, the result should be read as a modifier of risk, not as a substitute for imaging or neurological assessment. A high inflammatory or fibrinolytic signal may justify closer surveillance, but it should not automatically cancel a reperfusion option that otherwise meets accepted criteria [7-12, 33-36].

Practical Interpretation in Reperfusion-Treated Patients

A final practical point is communication. If biomarkers are introduced into stroke pathways, the result should be reported in language that can be used by neurologists, emergency physicians, neuroradiologists and intensive-care teams. A laboratory comment such as ‘increased MMP-9’ is not enough. The report should state whether the sample was drawn before or after reperfusion, whether preanalytical quality was acceptable, and whether the result is being used for research, surveillance or formal risk prediction. Clear reporting would reduce the risk that a probabilistic biomarker is misread as a treatment prohibition.

This pragmatic framing is important because biomarker research often moves faster than clinical implementation. A test may be scientifically persuasive but still unsuitable for the first treatment decision if the result is late, unstable between platforms, or difficult to explain during emergency care.

Limitations

This article is a narrative review rather than a systematic review. No pooled effect estimates were calculated, and the weight of evidence was judged through interpretive synthesis. The underlying literature varies in patient selection, treatment exposure, timing of sampling, biomarker platform, imaging protocol and definition of hemorrhagic transformation. Positive associations are also more likely to reach publication.

Therapeutic context is another limitation. Evidence from alteplase-treated cohorts should not be transferred uncritically to modern thrombectomy populations, and thresholds derived from one assay may not apply to another. Serum and plasma values are not interchangeable. A further practical limitation is availability: several promising markers require specialized laboratory platforms and are not yet compatible with emergency treatment workflows.

Finally, association is not action. A biomarker becomes clinically useful only if it changes care in a way that improves outcome. For hemorrhagic transformation, this means better surveillance, safer supportive management or better selection for trials, without postponing reperfusion therapy.

Conclusions

Blood biomarkers can make hemorrhagic risk after acute ischemic stroke biologically more legible. MMP-9 and cellular fibronectin are closest to blood-

brain barrier and extracellular matrix injury. GFAP, NfL and S100B add information about astroglial and neuronal injury burden. NLR, D-dimer, fibrinogen and vWF are more accessible, but less specific.

At present, no single marker is sufficiently validated for independent treatment selection. The realistic future is a multimodal risk profile that combines biomarkers with clinical severity, infarct size, vascular imaging, barrier permeability, reperfusion status and conventional risk factors. Such models should be introduced only after prospective validation shows that they improve patient care without delaying effective reperfusion.

Declarations

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