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Review Article

Inflammatory Biomarkers in Ischemic Stroke: Mechanisms, Clinical Applications, and Future Directions

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Abstract

Ischemic stroke is a complex cerebrovascular disorder characterized by highly unpredictable outcomes influenced by patient-specific variables, including age, stroke severity, and preventable stroke-related complications such as infections. Analyses of clinical data have indicated a cumulative post-stroke infection rate of approximately 30%, with reported rates ranging from 5% to 65%. Post-stroke infections pose a significant challenge, as they not only increase the financial burden of stroke care but are also associated with adverse clinical outcomes, prolonged hospital stays, and a higher risk of stroke recurrence. The inflammatory response plays a pivotal role in the pathophysiology of ischemic stroke, encompassing the activation of inflammatory cells, the release of inflammatory mediators, and the engagement of inflammatory signaling pathways. Recent advances in molecular biology have facilitated the identification and investigation of numerous inflammation-related biomarkers. This article reviews the roles and mechanisms of key inflammatory biomarkers, including cytokines, chemokines, adhesion molecules, inflammation-related enzymes and mediators, receptors, signaling pathway molecules, and acute-phase proteins in the context of ischemic stroke, highlighting their significance in stroke pathophysiology and prognostic assessment. Additionally, in conjunction with the latest research advances, the article discusses novel biomarkers such as microRNAs and galectin-3, which are emerging as important tools in multiple domains, including diagnosis and treatment. Drawing on clinical diagnostic and therapeutic practices, this review analyzes the diagnostic and therapeutic roles of both novel and traditional biomarkers in the progression of ischemic stroke, following the temporal sequence from disease onset to prognosis. Finally, the article addresses the limitations of current research and offers perspectives on future directions, providing insights that may contribute to the advancement of precision medicine in the management of ischemic stroke.

Introduction

Ischemic stroke is characterized by the interruption of cerebral blood flow, leading to localized ischemia and hypoxia in brain tissue, which results in neurological deficits.[1,2] The pathophysiological processes involved are complex, encompassing not only direct damage to local brain tissue but also extensive remodeling of neural networks and functional impairments. Key mechanisms include disturbances in energy metabolism, excitotoxicity from excessive release of excitatory amino acids such as glutamate, oxidative stress, and inflammatory responses.[3,4] The over-release of excitatory amino acids exacerbates neuronal toxicity, perpetuating a vicious cycle. Additionally, oxidative stress is a critical factor in ischemic stroke; under hypoxic conditions, the generation of reactive oxygen species (ROS) increases, damaging cellular membranes and DNA, and promoting apoptosis.

Following cerebral ischemia, injured neurons and glial cells release a variety of damage-associated molecular patterns (DAMPs), which activate the innate immune system and trigger both local and systemic inflammatory responses.[5] In this context, inflammation plays a dual role: it serves as a protective response to injury while also possessing the potential to cause secondary damage through excessive activation.[6] The infiltration of inflammatory

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cells and the release of cytokines not only exacerbate local damage but may also impair the function of distal brain regions, leading to more widespread neural network dysfunction. Therefore, a comprehensive understanding of the dynamic changes in inflammatory responses during ischemic stroke, as well as their interactions with other pathophysiological processes, is crucial for developing novel intervention strategies and improving patient outcomes.

The utilization of inflammatory biomarkers in the investigation of ischemic stroke holds considerable significance. Firstly, these biomarkers can function as early diagnostic tools, facilitating the identification of high-risk patients and enabling timely intervention. Secondly, they can be employed to assess disease severity and predict prognosis, thereby informing personalized treatment strategies.[7] Furthermore, certain biomarkers may serve as therapeutic targets, guiding the development of novel treatment approaches. In the domain of inflammation-related biomarkers, researchers have identified numerous potential candidate molecules, including cytokines, chemokines, and acute-phase proteins. These biomarkers exhibit substantial promise for application in the diagnosis, prognostic evaluation, and treatment of ischemic stroke.

This literature review aims to synthesize and critically evaluate the current evidence on classical and emerging inflammatory biomarkers implicated across all phases of ischemic stroke (acute, subacute, and chronic). Specifically, it seeks to: (1) elucidate the pathophysiological mechanisms linking inflammatory cascades to cerebral ischemia-reperfusion injury; (2) assess the clinical efficacy of these biomarkers in stroke diagnosis, prognosis, and monitoring of surgical thrombectomy treatment; and (3) identify novel biomarker candidates with translational potential. By integrating preclinical and clinical research, this review establishes a comprehensive framework to guide future biomarker validation studies and precision medicine approaches in cerebrovascular disease.

Search strategy

A computer-based search was performed on the PubMed database to retrieve articles published up to July 20, 2025. To maximize the specificity and sensitivity of the search, a combination of the following terms was used: inflammation, biomarkers, cytokines, ischemic stroke, chemokines, endovascular treatment, and adhesion molecules. Further screening was conducted through titles and abstracts, and only studies analyzing the role of inflammatory biomarkers in the treatment and prognosis of ischemic stroke were included. There were no restrictions on language or study type. The focus was on articles published within the past 10 years.

The inflammatory response following ischemic stroke exhibits a dual nature

Initially, cell death within the infarcted core occurs rapidly due to energy depletion, resulting in the release of DAMPs such as high mobility group protein B1, adenosine triphosphate, and heat shock proteins.[8] These DAMPs engage pattern recognition receptors, including Toll-like receptors (TLR2 and TLR4) and scavenger receptors, thereby initiating innate immune responses.[9] For instance, the interaction of high mobility group protein B1 with TLR4 activates the nuclear factor kappa B (NF-κB) signaling pathway, which subsequently induces the expression of pro-inflammatory cytokines such as interleukin (IL)-1 beta, tumor necrosis factor-alpha (TNF-α), and IL-6.[10] This cascade promotes the infiltration of peripheral immune cells, leading to disruption of the blood-brain barrier (BBB), exacerbation of cerebral edema, and neuronal cell death. Concurrently, ROS generated from mitochondrial damage further amplify inflammatory signaling through oxidative stress, establishing a detrimental feedback loop.[11] Conversely, a moderate inflammatory response is essential for tissue repair and functional recovery. Anti-inflammatory cytokines, including IL-10 and transforming growth factor-beta, play a pivotal role in mitigating excessive inflammation, thereby facilitating nerve regeneration and angiogenesis (Fig. 1).[12]

The significance of inflammatory biomarkers in preoperative evaluation and postoperative treatment of post-stroke mechanical thrombectomy

Inflammatory biomarkers are closely associated with the extent of brain injury, thrombus formation, and mechanisms of secondary injury. Post-stroke sympathetic activation induces neutrophilia and lymphocyte apoptosis,[13] leading to an elevated neutrophil-to-lymphocyte ratio (NLR), which reflects an imbalance in immune homeostasis. A high NLR level (>4.5) is positively correlated with the risk of stroke-associated pneumonia (odds ratio = 1.55). In patients undergoing endovascular thrombectomy (EVT), an elevated NLR predicts a significantly increased risk of poor 90-day functional outcomes (hazard ratio ≈ 2.0).[14]

The platelet-to-lymphocyte ratio serves as an effective indicator of platelet activation and systemic inflammatory response. The systemic immune-inflammation index (calculated as platelet count × neutrophil count / lymphocyte count) integratively reflects thrombogenesis and the inflammatory cascade. Studies confirm that platelet-to-lymphocyte ratio > 145 is an independent predictor of increased hemorrhagic transformation risk after intravenous thrombolysis (area under the curve = 0.81).[15] Notably, the systemic immune-inflammation index has been demonstrated to be the strongest independent predictor of poor prognosis in EVT patients (area under the curve = 0.85).

Furthermore, elevated fibrinogen levels promote thrombosis, while decreased albumin levels exacerbate oxidative stress injury. Consequently, an increased fibrinogen-to-albumin ratio indicates disruption of BBB integrity.[16] Fibrinogen-to-albumin ratio > 0.09 is significantly associated with a higher risk of hemorrhagic transformation (odds ratio = 3.2).

During EVT, neurofilament light chain levels within the ischemic region directly reflect the degree of acute neuronal axonal injury. High neurofilament light chain levels are associated with a 2.4-fold increase in 90-day mortality. Recent research advances, particularly the elucidation of the C-C chemokine receptor type 7 (CCR7) three-dimensional structure,[17] have significantly enhanced understanding of its role in disease and its clinical applications. In the regulation of neuroinflammation post-brain injury, $CCR7^+$ T cells (primarily enriched in the central memory T cell subset) play a complex and critical role. Their mediation of immune cell infiltration into the central nervous system via the C-C motif chemokine ligand 19 (CCL19)/CCR7 ligand-receptor axis directly impacts the risk of secondary injury, timing of surgical intervention, and postoperative neurological recovery. Clinical studies reveal that in cerebral ischemia patients, the frequency of infiltrating $CD8^+GZMK^+CCR7^+$ T cells (often termed T stroke-associated cell cells) shows a significant positive correlation with the National Institutes of Health Stroke Scale score ($r = 0.331$).[17] T stroke-associated cell (TSA) cells promote the release of pro-inflammatory cytokines such as TNF-α and interferon-gamma, activating microglia/macrophages. This activation subsequently enhances the release of matrix metalloproteinases (MMPs) (e.g., MMP-9), leading to BBB disruption and exacerbated cerebral edema.

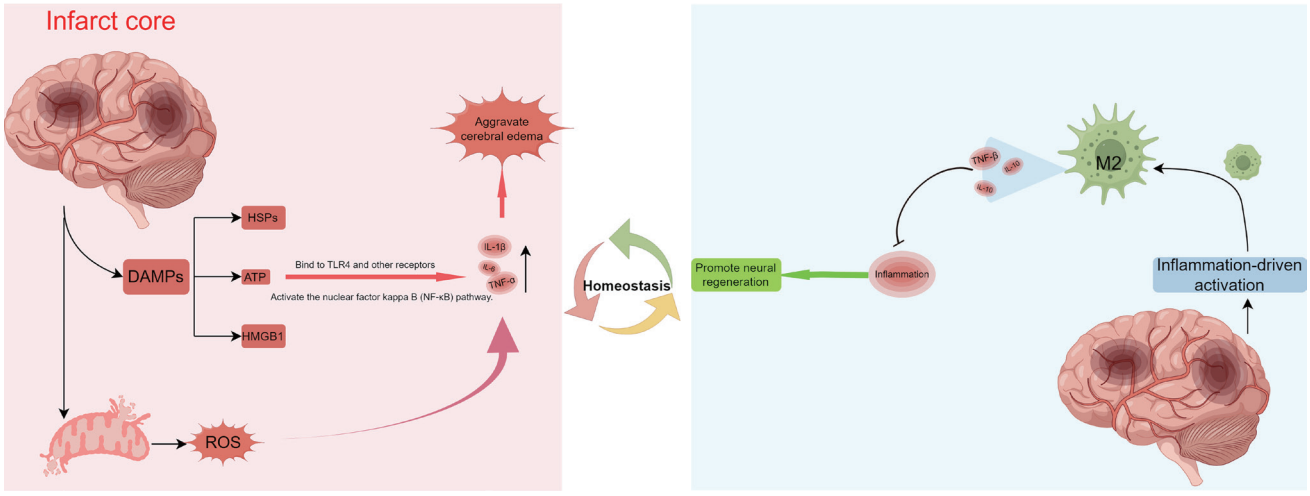

Fig. 1. The dual role of the inflammatory response in ischemic stroke. Cellular death within the infarcted core occurs rapidly due to energy depletion, resulting in the release of DAMPs such as HMGB1, ATP, and HSPs. These DAMPs engage pattern recognition receptors, including Toll-like receptors (TLR2 and TLR4) and scavenger receptors, thereby initiating innate immune responses. For instance, the interaction of HMGB1 with TLR4 activates the NF-κB signaling pathway, which subsequently induces the expression of pro-inflammatory cytokines such as IL-1β, TNF-α, and IL-6. This cascade promotes the infiltration of peripheral immune cells, leading to disruption of the blood-brain barrier, exacerbation of cerebral edema, and neuronal cell death. Concurrently, ROS generated from mitochondrial damage further amplify inflammatory signaling through oxidative stress, establishing a detrimental feedback loop. Conversely, a moderate inflammatory response is essential for tissue repair and functional recovery. Anti-inflammatory cytokines, including IL-10 and TGF-β, play a pivotal role in mitigating excessive inflammation, thereby facilitating nerve regeneration and angiogenesis. The figure was generated using Figdraw (https://www.figdraw.com/). ATP, adenosine triphosphate; DAMPs, damage-associated molecular patterns; HMGB1, high mobility group protein B1; HSPs, heat shock proteins; IL, interleukin; NF-κB, nuclear factor kappa B; ROS, reactive oxygen species; TGF-β, transforming growth factor-beta; TLR2, Toll-like receptor 2; TNF-α, tumor necrosis factor-alpha.

Therefore, elevated levels of circulating or lesion-localized $CCL19^+$ endothelial cells and $CCR7^+$ T cells represent critical biological markers indicating an active phase of neuroinflammation. Surgical interventions (such as recanalization therapy) performed during this active inflammatory phase may increase the risk of reperfusion injury or secondary hemorrhage. Dynamic monitoring of $CCR7^+$ T cell frequency in peripheral blood or cerebrospinal fluid (e.g., using single-cell RNA sequencing technology) provides a powerful tool for assessing neuroinflammatory intensity. This facilitates individualized, delayed surgical decision-making to optimize patient outcomes (Table 1).[18]

Key inflammatory biomarkers and their mechanisms of action in ischemic stroke

Cytokines and chemokines serve as principal modulators of the inflammatory response.[19] In the early stage (within 24 h), activated microglia release IL-1β and TNF-α, which promote neutrophil infiltration through the activation of the NLRP3 inflammasome.[20] During the subacute phase (24 h to seven days), monocytes differentiate into pro-inflammatory M1 macrophages, with MMP-9 contributing to BBB disruption.[21,22] In the chronic phase (beyond seven days), regulatory T cells mediate immune suppression and upregulate reparative cytokines such as IL-10 and transforming growth factor-beta.[23]

Acute phase proteins are synthesized in the liver and are modulated by pro-inflammatory cytokines, serving as key inflammatory biomarkers in ischemic stroke.[24] C-reactive protein (CRP) is the most prominent acute phase protein, playing a pivotal role in activating the complement system, facilitating inflammatory cell infiltration, and exacerbating oxidative stress following a stroke.[25] During the acute phase of stroke (initial hours to 72 h post-onset), CRP levels begin to rise within six to twelve hours after ischemic or hemorrhagic events, peaking within 24 to 48 h, often exceeding 10 mg/L. Mechanistic studies suggest that this elevation is primarily driven by brain tissue injury, which activates microglia and as-

Table 1. The guiding role of selected inflammatory markers before and after EVT surgery

Biomarkers	Testing timing	Judgment value	Clinical prediction application	Clinical impact
NLR	24 h after surgery	>4.5	SAP poor prognosis	OR = 1.55 (SAP)
SII	Preoperative	$>900\times10^9$	EVT has poor prognosis	AUC = 0.85
FAR	24 h before/after surgery	>0.09	Hemorrhagic transformation	OR = 3.29
Local NfL	During EVT surgery (ischemic area)	>9.4 pg/mL	90-day mortality rate	HR = 2.343
$CCR7^+$ T cell	Peripheral blood single-cell sequencing	_	Reperfusion injury	Targeted peptides can reduce damage

AUC, area under the curve; $CCR7^+$ T cell, C-C chemokine receptor type 7 positive T cell; EVT, endovascular thrombectomy; FAR, fibrinogen-to-albumin ratio; HR, hazard ratio; NfL, neurofilament light chain; NLR, neutrophil-to-lymphocyte ratio; OR, odds ratio; SAP, stroke-associated pneumonia; SII, systemic immune-inflammation index.

trocytes, leading to the release of pro-inflammatory mediators such as IL-6 and subsequently stimulating hepatic CRP synthesis.[26]

In the subacute phase (three to seven days), persistent brain injury, exemplified by secondary infections or exacerbated cerebral edema, may result in sustained elevated CRP levels; conversely, in the absence of such complications, CRP concentrations typically decrease. In the chronic phase (weeks to months), CRP levels gradually return to the normal range (<3 mg/L), although chronic inflammatory conditions, such as atherosclerosis or ongoing infections, may sustain or slightly elevate CRP levels. Elevated serum CRP concentrations have been correlated with stroke severity, increased infarct size, and adverse prognostic outcomes.[27]

Differences in CRP levels across stroke subtypes can serve as critical biomarkers for clinical differential diagnosis. For instance, patients with ischemic strokes involving large-area infarctions, such as those resulting from large vessel occlusions, exhibit significantly higher CRP levels than those with lacunar infarctions, indicative of small vessel disease.[28] In thrombotic strokes, atherothrombotic patients often present with elevated CRP levels, reflecting systemic inflammation associated with unstable atherosclerotic plaques.[29] In hemorrhagic strokes, specifically cerebral hemorrhage, a pronounced inflammatory response occurs surrounding the hematoma, and CRP levels may peak more rapidly (within 24 h) and reach higher levels compared to ischemic strokes. CRP levels have also been positively correlated with hematoma expansion and the degree of surrounding edema.

Clinically, CRP has emerged as a valuable biomarker for diagnosing and monitoring stroke across various temporal windows, aiding both acute management and prognostic evaluation due to its rapid, cost-effective, and widely accessible nature, as well as its suitability for dynamic assessment of inflammatory status. Other acute phase proteins, including serum amyloid A and fibrinogen, also play significant roles in the pathophysiology of ischemic stroke.[30] Adhesion molecules such as intercellular adhesion molecule-1 and vascular cell adhesion molecule-1 facilitate leukocyte-endothelial interactions, promoting the migration of inflammatory cells into ischemic cerebral tissue.[31]

The inflammatory response following a stroke involves multiple cytokines, with their dynamic fluctuations closely linked to underlying pathological processes and prognostic outcomes. IL-6 is predominantly produced by microglia, astrocytes, neurons, and peripheral immune cells. Acting as an intracellular signaling pathway activator, IL-6 exerts anti-inflammatory effects slightly earlier than CRP and regulates CRP synthesis. Clinical observations indicate that IL-6 levels rise more rapidly (within 24 h) and reach higher peaks in hemorrhagic stroke compared to ischemic stroke. Studies demonstrate that concurrent assessment of IL-6 and CRP enhances the accuracy of early ischemic stroke diagnosis.[32] Patients with large-area infarctions exhibit significantly elevated IL-6 levels compared to those with smaller infarctions. Elevated IL-6 levels correlate with neurological deficits, as measured by the National Institutes of Health Stroke Scale, and are associated with poorer outcomes, as indicated by a modified Rankin Scale score of ≥3.

TNF-α, another prominent pro-inflammatory cytokine, is primarily secreted by activated microglia, macrophages, neurons, and other cell types. TNF-α levels rise during the acute phase (1–12 h post-stroke), peaking between 12 and 24 h. If inflammation persists, TNF-α concentrations remain elevated. Research indicates that TNF-α levels increase earlier in ischemic stroke than in hemorrhagic stroke.[33] Clinically, TNF-α may transiently elevate following thrombolysis, which is associated with reperfusion injury.[34] Elevated TNF-α levels have been implicated in BBB disruption, cerebral edema, and neuronal apoptosis.

IL-1β is primarily derived from microglia and infiltrating neutrophils.[35] During the acute phase of stroke (1–6 h post-onset), IL-1β levels rise rapidly, peaking at approximately 12 h. In the presence of secondary infections or injuries, IL-1β levels may continue to rise. Laboratory studies have shown that IL-1β concentrations in cerebrospinal fluid are significantly higher than those in serum. Clinical case studies indicate that patients with severe pathologies, such as malignant brain edema, demonstrate higher peak IL-1β levels.

MMPs are a family of zinc-dependent endopeptidases that play a multifaceted and crucial role in the pathological processes of ischemic stroke (acute cerebral ischemia). Their involvement includes disruption of the BBB, regulation of the inflammatory response, and mediation of neuronal damage and repair.[36]

Activation of MMPs in the early stage of ischemia (Acute Phase, 0–24h): Ischemic and hypoxic conditions result in intracellular calcium overload, which activates calcium-dependent proteases such as calpain. This cascade subsequently leads to the activation of pro-MMPs, notably MMP-2 and MMP-9.[37] MMP-9, in particular, has garnered significant attention due to its pronounced post-ischemic activity, which correlates with hemorrhagic transformation and adverse prognostic outcomes. Concurrently, ROS and inflammatory mediators, including TNF-α and IL-1β, further stimulate MMP expression. MMP-9 and MMP-3 facilitate the degradation of extracellular matrix components, including collagen, laminin, and tight junction proteins (such as occludin and claudin), leading to BBB disruption, increased vascular permeability, and the onset of cerebral edema and hemorrhagic transformation (hemorrhagic infarction).[38]

Subacute Phase (24 h–seven Days) – amplification of the inflammatory cascade: MMPs contribute to the infiltration of inflammatory cells, such as neutrophils and macrophages, into ischemic brain tissue. MMP-9 exacerbates neuroinflammation by activating pro-inflammatory cytokines (e.g., IL-1β, IL-6) and chemokines [e.g., C-X-C motif chemokine ligand 12 (CXCL12)].[39] Moreover, neuronal damage and apoptosis are facilitated by MMP-3 and MMP-7, which can directly cleave neuronal membrane proteins (e.g., N-cadherin),[40] thereby disrupting neuronal connectivity. MMP-9 also contributes to the activation of pro-apoptotic pathways, including caspase-3.

Tissue remodeling and repair during the recovery period (weeks to months): MMPs, including MMP-2 and MMP-12, promote angiogenesis and synaptic plasticity through the degradation of scar tissue.[41] However, excessive MMP activation may hinder repair processes. Notably, MMP-9 activates the NF-κB pathway by cleaving the precursor of IL-1β into its active form, thereby amplifying inflammatory signals (Fig. 2).[42–47] Simultaneously, MMP-9 degrades extracellular matrices and may contribute to neuroinflammation by increasing monocyte migration into the CNS or by activating chemokines such as CXCL8, which facilitate leukocyte infiltration.[48] Some MMPs, such as MMP-8, can degrade pro-inflammatory cytokines (e.g., TNF-α), although this effect is often overshadowed in ischemic conditions. MMP-9 levels in the bloodstream rise significantly 2–6 h post-ischemia, peaking at 24 h, and are associated with infarct volume and clinical prognosis. In contrast, MMP-9 concentrations in cerebrospinal fluid may provide a more sensitive measure, although clinical sampling remains limited.

Similarly, miR-874-3p attenuates neuronal apoptosis and oxidative stress by inhibiting microglial activation and the subse-

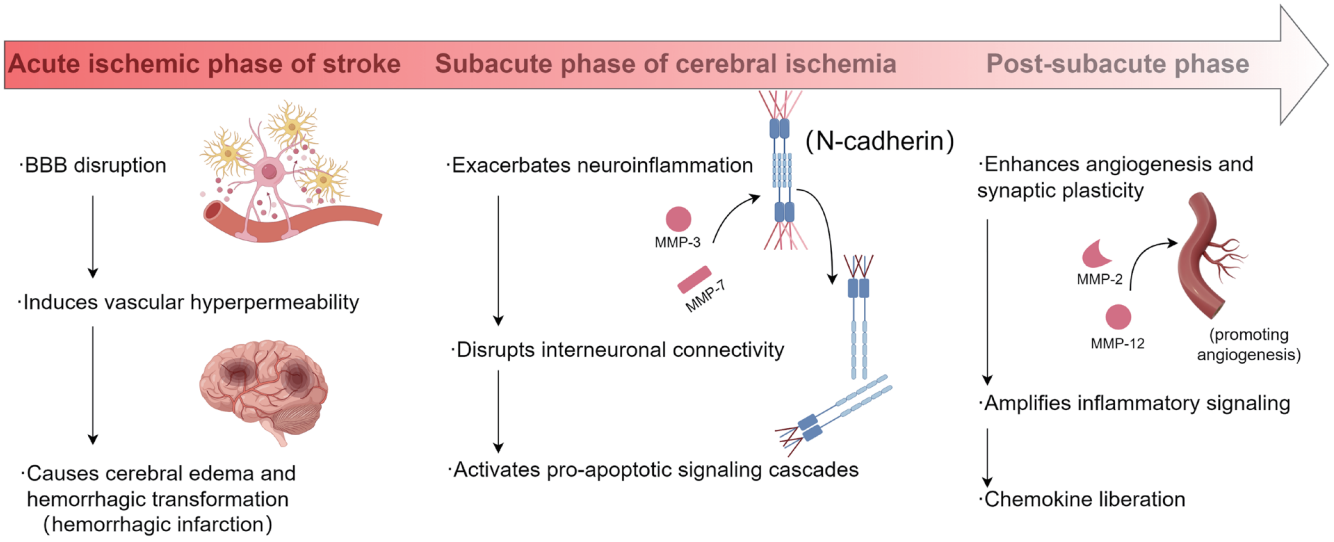

Fig. 2. Temporal dynamics of matrix metalloproteinases (MMPs) in the pathophysiological mechanisms underlying the acute, subacute, and chronic phases of ischemic stroke. The figure was generated using Figdraw (https://www.figdraw.com/). BBB, blood-brain barrier. With the emergence of high-throughput and sensitive technologies, the molecular interaction patterns of long non-coding RNAs in cells have been increasingly elucidated, and they have been continuously linked to disease progression.[44,45] Recent investigations have elucidated the significant roles of novel inflammatory regulatory factors in the pathogenesis and progression of ischemic stroke. MicroRNAs (miRNAs), as small non-coding RNAs, exhibit dual functions in the pathological processes associated with ischemic stroke by targeting genes related to inflammation. Among the miRNA family, miR-126 has been shown to preserve BBB integrity and mitigate brain edema and neuronal injury by inhibiting the expression of vascular cell adhesion molecule-1 and pro-inflammatory cytokines such as TNF-α and IL-6.[46] Studies indicate that overexpression of miR-126 can reduce inflammatory cell infiltration in the ischemic penumbra, promote angiogenesis, and enhance neurological recovery.[47]

quent release of pro-inflammatory cytokines, including IL-1β and TNF-α.[49] In animal models, overexpression of miR-874-3p significantly reduces the extent of cerebral infarction. Conversely, miR-155, recognized as a pro-inflammatory factor, exacerbates BBB disruption, promotes neutrophil infiltration, and amplifies neuroinflammatory responses by downregulating tight junction proteins such as claudin-1 and zonula occludens-1.[50]

In the context of diagnosis and therapeutic intervention for ischemic stroke, miR-124 and miR-9 exhibit significant declines in serum levels within 24 h post-onset, demonstrating negative correlations with cerebral infarction volume and high-sensitivity C-reactive protein (hs-CRP), suggesting their potential as early diagnostic biomarkers. Additionally, miR-151a-3p and miR-384-5p show abnormal expression profiles in the serum of ischemic stroke patients, correlating with disease progression and neurological dysfunction, and thus may serve as indicators for evaluating thrombolytic therapy efficacy and recurrence risk. Evidence suggests that inhibition of miR-15a/16-1 exerts beneficial effects on the prognosis of ischemic stroke. The promising results of miR-15a/16-1 antagomir across diverse demographic groups highlight its potential as a versatile and effective treatment option (Table 2).[51]

Future research may focus on targeted delivery systems, such as specific liposomes or exosomes, to administer miRNA mimetics (e.g., miR-126) or antagonists (e.g., miR-155 inhibitors). This approach aims to precisely regulate target gene expression while minimizing non-specific toxicity, extending potential applications beyond stroke to other cardiovascular and cerebrovascular conditions.

Furthermore, agglutinin family proteins represent another class of novel inflammatory regulatory factors contributing to neuroinflammation and BBB disruption following ischemic stroke. After ischemic stroke, galectin-3 (Gal-3) is released by activated microglia and subsequently activates the NF-κB signaling pathway via interaction with TLR-4, promoting inflammatory cytokines such as IL-1β and TNF-α and exacerbating neuronal injury.[52,53] Notably, Gal-3 levels are negatively correlated with high-density lipoprotein cholesterol, and its elevated expression can exacerbate dyslipidemia and oxidative stress, accelerating atherosclerotic plaque formation and increasing the risk of ischemic stroke recurrence.

Prospective cohort studies have demonstrated that elevated serum Gal-3 levels are independently associated with a heightened risk of 90-day mortality or severe disability in ischemic stroke patients. Dynamic changes in Gal-3 levels may provide a basis for stratified management of high-risk individuals. Current investigations indicate that Gal-3 inhibitors (e.g., TD139) can reduce microglial activation and neutrophil infiltration in animal models,[54] though clinical trials remain preliminary.

Application of inflammatory biomarkers in the diagnosis of ischemic stroke

Inflammatory biomarkers possess significant potential for the early diagnosis of ischemic stroke. Given the acute onset of ischemic stroke, timely diagnosis is critical for effective treatment and improved prognosis. Certain inflammatory markers, including IL-6, CRP, and MMP-9, have been shown to exhibit elevated levels within hours of stroke onset, thereby serving as auxiliary indicators for early diagnosis. Emerging research has also highlighted the potential of novel biomarkers, such as miRNAs and exosome-associated proteins, in facilitating early diagnostic processes.[55]

Furthermore, inflammatory biomarkers may play a pivotal role in identifying stroke subtypes. Ischemic strokes arising from different etiologies exhibit distinct inflammatory profiles. Studies indicate that patients with atherosclerotic strokes frequently present with elevated levels of CRP and IL-6, whereas those with cardi-

Table 2. Pathophysiological regulation mechanism and role of small non-coding RNAs in ischemic stroke

Small molecule non-coding RNA	Regulation mechanism	Pathophysiological effects
miR-126	Inhibit the expression of VCAM-1 and pro-inflammatory cytokines (such as TNF-α, IL-6)	Protecting the integrity of BBB, reducing brain edema, and alleviating neuronal damage
miR-874-3p	Inhibition of microglial activation and subsequent release of pro-inflammatory cytokines (such as IL-1β, TNF-α)	Reduce neuronal apoptosis and oxidative stress damage
miR-155	Downregulate the expression of tight junction proteins such as claudin-1 and ZO-1	Intensify BBB damage, promote neutrophil infiltration and neuroinflammatory response
miR-124	Similar to miR-9, there is a significant negative correlation between infarct volume and hs CRP levels	As an early diagnostic biomarker, it has the potential to evaluate the degree of brain damage and inflammatory status
miR-151a-3p	Similar to miR-384-5p, it is abnormally expressed in the serum of IS patients and is associated with disease progression and the degree of neurological deficit	As a potential biomarker for evaluating the efficacy of thrombolytic therapy and the risk of recurrence
miR-15a/16-1	Inhibition of expression can improve stroke prognosis; Antagonists show therapeutic effects in different populations	Targeting neuroprotection and repair therapy to promote neurovascular repair and functional recovery

BBB, blood-brain barrier; hs CRP, high-sensitivity C-reactive protein; IL, interleukin; TNF-α, tumor necrosis factor-alpha; VCAM-1, vascular cell adhesion molecule-1; ZO-1, zonula occludens-1.

oembolic strokes may exhibit a unique spectrum of inflammatory markers.[56] By analyzing specific combinations of inflammatory markers, it may be possible to differentiate between various stroke subtypes, thereby providing a foundation for personalized treatment strategies.

However, the clinical application of inflammatory biomarkers presents several challenges. First, the sensitivity and specificity of individual biomarkers are often inadequate, necessitating the development of multi-biomarker diagnostic models. Second, the inflammatory response is dynamic, emphasizing the importance of determining optimal sampling time points. Additionally, extrinsic factors that may influence biomarker levels, such as infections and autoimmune diseases, must be considered. Future research should prioritize the development of standardized and reproducible detection methodologies, along with the validation of these biomarkers' diagnostic utility through large-scale clinical trials.

The role of inflammatory biomarkers in prognostic evaluation of ischemic stroke

Inflammatory biomarkers have demonstrated considerable promise in the prognostic assessment of ischemic stroke. Numerous studies have established a close correlation between the levels of specific inflammatory markers and clinical outcomes in stroke patients.[57] For instance, elevated levels of CRP, IL-6, and MMP-9 have been associated with poorer neurological recovery and increased mortality rates.[58] These biomarkers may reflect a persistent inflammatory state following stroke, indicative of more severe tissue damage and impaired repair mechanisms. Recent studies have highlighted the integral role of peroxisome proliferator-activated receptors (PPARs) in modulating the complex pathological network underlying cerebrovascular diseases and their associated risk factors.[59] The activation of PPARγ can reduce the inflammatory response by regulating the production and activation of inflammatory cytokines closely linked to the pathophysiology of intracranial aneurysms.[60] Specifically, PPARγ activation can inhibit mononuclear/macrophage cells from releasing various inflammatory cytokines, including IL-1, IL-6, and monocyte chemoattractant protein-1, thereby reducing the occurrence of inflammatory responses.[61]

Moreover, inflammatory biomarkers may provide critical insights for predicting stroke recurrence. Atherosclerosis, a major contributor to ischemic stroke, is intricately linked to inflammatory processes.[62] Research has shown that sustained elevations in biomarkers such as hs-CRP and IL-6 correlate with an increased risk of stroke recurrence.[63] These findings suggest that monitoring dynamic fluctuations of inflammatory markers could aid in identifying high-risk patients and informing secondary prevention strategies.

Nonetheless, despite recognition of the association between hs-CRP and ischemic stroke incidence and prognosis since approximately 2017, challenges remain in the clinical application of inflammatory biomarkers for prognostic assessment. First, standardized detection methods and reference ranges are essential. Second, integrating multiple biomarkers may enhance predictive accuracy. Furthermore, large-scale, long-term prospective studies are necessary to validate the prognostic significance of these biomarkers. Future research should focus on developing prognostic scoring systems based on inflammatory markers and incorporating them into clinical decision-making processes to achieve more accurate prognostic evaluations and personalized management of ischemic stroke patients.

The potential value of inflammatory biomarkers in the treatment of ischemic stroke

The potential value of inflammatory biomarkers in managing ischemic stroke is primarily reflected in two key areas: as therapeutic targets and as tools for monitoring and adjusting treatment regimens.

Regarding therapeutic targets, numerous inflammation-related molecules and pathways have emerged as focal points for drug development. For instance, monoclonal antibodies targeting IL-1β and IL-1 receptor antagonists have demonstrated neuroprotective

effects in clinical trials.[64] Additionally, MMP inhibitors have been investigated for their capacity to mitigate BBB disruption and reduce the risk of hemorrhagic transformation.[65] Strategies aimed at modulating microglial polarization and enhancing the expression of anti-inflammatory mediators have also garnered significant attention.

In terms of treatment monitoring and adjustment, inflammatory biomarkers have the potential to evaluate therapeutic efficacy and facilitate personalized approaches. Dynamic assessment of biomarkers post-treatment may provide insights into treatment response and serve as a basis for optimizing therapeutic strategies. Emerging studies are exploring decision-making models based on inflammatory markers to achieve more precise and individualized treatment outcomes. However, clinical implementation faces challenges: patient resistance to research sampling, differences in medical histories, and heterogeneity in biomarker levels often limit statistical significance in studies. More research studies are needed to validate the effectiveness and feasibility of these methodologies.

Despite the promising prospects of inflammation-targeted therapies in ischemic stroke, several challenges persist. First, the inflammatory response is inherently complex and dynamic; thus, interventions aimed at a single target may not yield optimal results. Future research should incorporate multifaceted approaches, including investigating the regulatory effects of CRP gene polymorphisms on post-stroke inflammatory responses and exploring the therapeutic potential of targeting the CRP pathway using CRP inhibitors. Second, it is essential to balance anti-inflammatory treatment with the inflammatory responses necessary for tissue repair and regeneration. Additionally, individual variability and the identification of optimal treatment windows must be taken into account. Consequently, future investigations should prioritize multi-target combination therapies and individualized treatment plans guided by biomarker profiles to enhance both efficacy and safety.

Challenges and future directions

Despite the promising potential of inflammation-targeted therapies, significant challenges remain. Firstly, the inflammatory response is complex and dynamic; thus, interventions targeting a single molecule may not yield optimal outcomes. Future research should employ diverse and integrative approaches, including investigating the regulatory effects of CRP gene polymorphisms on post-stroke inflammation and exploring the therapeutic potential of CRP inhibitors.

Secondly, it is imperative to achieve a balance between anti-inflammatory treatments and the essential inflammatory processes for tissue repair and regeneration. Over-suppression of inflammation may inadvertently hinder recovery. Furthermore, individual patient variability and the identification of optimal treatment windows must be carefully considered to maximize therapeutic efficacy.

Consequently, future investigations should prioritize the development of multi-target combination therapies and individualized treatment plans guided by biomarker profiles. Such approaches hold promise for improving both the efficacy and safety of ischemic stroke interventions.

Conclusions

The inflammatory response plays a pivotal role in the pathophysiology of ischemic stroke. Investigating inflammatory biomarkers offers novel insights and opportunities for precision medicine approaches. This review analyzed the diagnostic and therapeutic roles of both novel and traditional biomarkers throughout ischemic stroke progression. These biomarkers are expected to play an increasingly important role in clinical practice, ultimately improving patient outcomes.

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Conflict of interest

The authors declare no conflicts of interest.

Author contributions

Study concept and design (YY), data acquisition (HZ, SL, TX), data analysis and interpretation (YY, HZ, SL, TX), manuscript drafting (YY), manuscript revision (HZ, SL, TX), guarantor of integrity of entire study (SL). All authors reviewed and approved the final version of the manuscript.

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