

Review Article

Prognosis of Acute Ischemic Stroke Based on Peripheral Blood

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Abstract

Acute ischemic stroke remains a leading cause of mortality and long-term disability worldwide, imposing a substantial socioeconomic and clinical burden on global healthcare systems. The heterogeneous nature of stroke pathophysiology, involving complex interactions among vascular occlusion, inflammation, oxidative stress, and neuronal damage, presents major challenges for clinical management and outcome prediction. Accurate and timely prognostic evaluation is therefore critical for guiding clinical decision-making, stratifying patient risk, optimizing therapeutic strategies, and improving long-term functional outcomes. Reliable prognostic models also support the efficient allocation of limited medical resources, especially in acute stroke care settings where early intervention strongly determines prognosis. Peripheral blood biomarkers offer an accessible, minimally invasive, and cost-effective strategy for evaluating stroke severity, predicting complications, and estimating neurological recovery. In this narrative review, we summarize current evidence regarding the role of peripheral blood biomarkers in forecasting clinical outcomes in patients with acute ischemic stroke. We focus on key biomarkers related to inflammatory response, oxidative stress, neuronal injury, and hemostatic dysfunction, emphasizing their diagnostic performance and prognostic significance. This review highlights promising peripheral blood indicators with strong potential for clinical translation and routine practice. Our findings contribute to the rapidly advancing field of stroke prognostication, facilitate evidence-based clinical management, and provide valuable insights for future research toward personalized stroke care and healthcare policy development.

Keywords

Acute Ischemic Stroke, Peripheral Blood Biomarkers, Prognosis Prediction, Clinical Outcomes

1. Introduction

Acute ischemic stroke (AIS) is the main cause of disability and death worldwide, which has brought a huge burden to the global medical system. According to the 2019 global burden

of disease study, stroke is the second most common cause of death in the world, and also the third cause of disability adjusted life years (DALYs). Ischemic stroke accounts for about

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80% of all stroke cases, and its incidence has steadily increased in the past 30 years¹. The World Health Organization (WHO) estimates that about 15 million people suffer from stroke every year, of which nearly 6 million die and another 5 million are disabled. The increasing prevalence of modifiable risk factors such as hypertension, diabetes, dyslipidemia and atrial fibrillation, coupled with the aging population in many countries, has greatly increased the burden of AIS [1].

In China, the trend of AIS is particularly worrying. For many years, stroke has been the main cause of death and disability in China, and ischemic stroke accounts for the majority [2]. The Chinese national stroke screening survey (CNSSS) reported that the prevalence of stroke in adults aged ≥ 40 years reached 2.58% in 2021, equivalent to about 17.04 million stroke survivors nationwide [2]. In addition, compared with the western population, the average age of onset of Chinese patients is significantly younger, and patients under the age of 60 account for a large proportion. This early onset, coupled with the high recurrence rate and long-term disability associated with AIS, has brought a heavy social and economic burden to the family and the medical system [2].

Timely and accurate prognosis prediction is the key to AIS treatment, which directly affects clinical decision-making, treatment intervention and resource allocation. In the acute phase, early detection of high-risk patients with poor prognosis can quickly start active treatment strategies, such as thrombolysis or intravascular therapy, which can significantly improve functional recovery [3-5]. However, despite the progress in neuroimaging and biomarker research, predicting the prognosis of individual patients is still a complex challenge due to the multifactorial nature of AIS pathophysiology and the variability of patients' response to treatment.

In addition, the ability to predict the clinical trajectory is crucial for optimizing the post-stroke care pathway. The prognosis model integrating clinical, radiological and biochemical data can promote risk stratification and enable clinicians to customize rehabilitation plans and secondary prevention strategies according to the specific needs of patients [6-9].

In this article, we summarized the role of peripheral blood biomarkers in predicting the clinical prognosis of AIS patients.

2. Pathophysiology of Acute Ischemic Stroke

AIS is characterized by severe interruption of cerebral blood flow, resulting in neuronal damage and functional defects. Potential pathophysiology involves a series of biochemical and cellular events caused by ischemia and reperfusion [10-12]. The core of AIS is cerebral artery occlusion, usually due to thrombosis or embolism, which causes brain tissue to lose oxygen and glucose. This metabolic crisis leads to an ischemic cascade, a series of events including excitotoxicity, oxidative stress, inflammation and apoptosis. Excitotoxicity results from the excessive release of glutamate, which leads to

overactivation of N-methyl-D-aspartate (NMDA) and α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors, leading to calcium influx and subsequent neuronal damage [13, 14]. Oxygen and glucose deficiency can also damage mitochondrial function, reduce the production of adenosine triphosphate (ATP), lead to the accumulation of reactive oxygen species (ROS), and further aggravate cell damage [10]. The ischemic cascade eventually leads to necrosis and apoptosis, especially in the ischemic core, while the surrounding penumbra may still be saved by timely reperfusion [15]. The inflammatory response after AIS involves the activation of microglia, the infiltration of peripheral immune cells, and the release of pro-inflammatory cytokines such as tumor necrosis factor- α (TNF- α), interleukin-1 beta (IL-1 β), and interleukin-6 (IL-6) [16-21]. These mediators contribute to the destruction of blood-brain barrier (BBB), cerebral edema, and secondary neuronal damage [18, 20]. The integrity of BBB is impaired due to endothelial cell swelling, tight junction degradation and matrix metalloproteinase (MMP) activation, leading to angiogenic edema and hemorrhagic transformation in some cases [18]. Cerebral edema peaks within the first 72 hours after stroke, leading to increased intracranial pressure, brain hernia and mortality [9]. The degree of brain injury is affected by collateral circulation, duration of ischemia and comorbidities such as hypertension, diabetes and atrial fibrillation [22]. Neurological deficits after AIS are highly variable, depending on the location and size of the infarction. The common manifestations include hemiplegia, aphasia, neglect and visual field defect. Infection, deep vein thrombosis, arrhythmia and other systemic complications further complicate the clinical process and seriously affect the prognosis [21, 23]. The prognostic factors of AIS included baseline stroke severity (assessed by the National Institutes of Health Stroke Scale (NIHSS)), early neurological deterioration, infarct volume, and early signs of hemorrhagic transformation on neuroimaging [24, 25]. Timely reperfusion through intravenous thrombolysis or intravascular therapy is still the most effective intervention to limit the expansion of infarction [26, 27].

3. Biomarkers in Neurological Diseases

In the diagnosis and treatment of neurological diseases, the application of biomarkers has become a research hotspot, showing important value in disease diagnosis, prognosis evaluation, curative effect evaluation and so on. Biomarkers are measurable indicators reflecting normal biological process, pathogenic process or treatment intervention response, including molecular markers, imaging characteristics and physiological parameters. In the field of Neurology, the identification and verification of biomarkers can improve the diagnostic accuracy, realize the early detection of disease, and provide the basis for individualized treatment [28]. In neurodegenerative diseases such as Alzheimer's disease (AD) and Parkinson's disease (PD), the study of cerebrospinal fluid biomarkers is relatively mature, including A β 42, total tau protein (t-tau), and

phosphorylated tau protein (p-tau), which can reflect the pathological changes of brain tissue and contribute to early diagnosis and differential diagnosis [29]. However, the invasiveness of cerebrospinal fluid collection limits its wide clinical application. Therefore, in recent years, the research focus has gradually turned to the development of blood-based biomarkers, such as neurofilament light chain (NfL) and glial fibrillary acidic protein (GFAP) in serum, which have shown good diagnostic and prognostic value in various neurological diseases [30, 31].

4. Current Research on Stroke Prognosis

AIS is the main cause of morbidity and mortality in the world. Therefore, it is necessary to develop a robust clinical prognosis prediction model to guide treatment strategies and improve the prognosis of patients [2, 10, 15, 23]. In the past decade, many studies have explored different methods and biomarkers to improve the accuracy of AIS prognosis prediction. Traditional clinical assessment tools, such as NIHSS, have been widely used to assess the severity of initial stroke and related to long-term prognosis. Multiple retrospective cohort studies showed that the higher the NIHSS score at admission, the higher the mortality and the worse the functional recovery [25, 32]. In addition, baseline demographic factors including age, gender and comorbidities such as hypertension, diabetes and atrial fibrillation have been identified as important prognostic indicators. The elderly, especially those over 70 years old, may have poor prognosis due to the reduction of physiological reserve and the increase of the incidence of systemic diseases [2, 3, 10, 23, 33].

Imaging examinations, especially diffusion-weighted magnetic resonance imaging (DWI-MRI) and non-contrast computed tomography (NCCT), play an important role in early prognosis evaluation [34, 35]. The Alberta Stroke Program Early CT Score (ASPECTS) has been widely validated as a reliable tool for quantifying early ischemic changes on CT scans and predicting response to thrombolytic therapy. Multi-center trials showed that the lower ASPECTS score, the larger the infarct volume, and the higher the risk of hemorrhagic transformation [36]. In addition, the presence of large vessel occlusion, especially in the anterior circulation, has been shown to significantly affect clinical outcomes, prompting the combination of angiography and early prognosis assessment [37].

At the same time, peripheral blood biomarkers have become a promising tool for predicting the prognosis of AIS. Inflammatory markers such as C-reactive protein (CRP), IL-6, and MMPs were significantly correlated with infarction progression and clinical deterioration [38-40]. The elevated levels of these biomarkers usually reflect systemic inflammation and BBB destruction, leading to secondary brain injury. Coagulation related biomarkers, including D-dimer, fibrinogen and plasminogen activator inhibitor-1 (PAI-1), have also been

used to predict the risk of hemorrhagic transformation and recurrent stroke [41-44]. In addition, recent studies have explored the role of metabolic biomarkers such as glucose, lactic acid and glycosylated hemoglobin (HbA1c) in the prognosis of AIS [45-47].

5. Peripheral Blood Biomarkers on Acute Ischemic Stroke Prognosis

In recent years, significant progress has been made in the study of predicting the clinical prognosis of AIS patients, especially the application of peripheral blood biomarkers, which provides important practical value for stroke management. In clinical practice, accurate and rapid assessment of the prognosis of patients is very important for optimizing treatment decisions, allocating medical resources reasonably and improving the long-term prognosis. The detection of peripheral blood markers has the characteristics of non-invasive, easy access and strong repeatability, which provides a tool for clinicians to dynamically monitor the progress of disease, so as to achieve personalized treatment.

For example, studies have shown that the plasma fibrinogen level is closely related to the prognosis of patients with acute cerebral infarction, and a lower level often means a higher risk of recurrence and poor functional recovery [48, 49].

In addition, studies have shown that the increase of serum neurofilament light chain protein (snfl) level reflects the severity of brain injury, which provides a reference for the risk assessment of thrombolytic therapy [50, 51].

S100B protein is an important biomarker reflecting brain injury. Many studies have confirmed that its serum level is significantly correlated with cerebral infarction volume and clinical prognosis [52]. The study of Foerch et al found that S100B level in patients with hemorrhagic transformation after thrombolysis was significantly higher than that in patients without hemorrhagic transformation, indicating that this marker can be used to predict thrombolysis related complications [53]. The study of Selçuk et al further confirmed that the dynamic change of S100B in the acute phase was closely related to the infarct volume, especially reached the peak on the third day after the onset, and was weakly correlated with mRS after one month, suggesting its potential predictive value for long-term functional prognosis [54].

In addition to S100B, GFAP has also received considerable attention [51]. Compared with S100B, GFAP showed higher sensitivity in patients with small infarct volumes or mild strokes. Herrmann et al showed that the level of GFAP was significantly correlated with the amount of brain injury and neurological status at discharge, indicating its advantage in assessing the severity of brain injury [55]. Correia et al found that the dynamic change mode of GFAP in the early stage of stroke can effectively predict the clinical prognosis, suggesting its potential application value in early prognosis evaluation [50, 56].

In recent years, researchers have also explored the role of other peripheral blood markers in the prognosis of stroke. Serum inflammatory markers such as CRP, IL-6 and neutrophil-to-lymphocyte ratio (NLR) were also significantly correlated with stroke severity and prognosis [7, 17, 20, 21, 38, 39]. Our preliminary research suggested that NLR can predict poor prognosis in transient ischemic attacks and mild ischemic stroke, highlighting the important role of inflammation in the pathophysiological mechanisms of stroke [57]. The introduction of these indicators not only contributes to the early identification of high-risk patients, but also provides a theoretical basis for the development of anti-inflammatory treatment strategies.

Oxidative stress markers such as superoxide dismutase (SOD) and 8-hydroxydeoxyguanosine (8-OHdG) are also considered to be related to the degree of neuronal injury. Ehrenreich et al.'s study found that erythropoietin (EPO) treatment can significantly reduce the levels of a variety of neural injury markers, including S100B, GFAP, and ubiquitin carboxyl-terminal hydrolase L1 (UCH-L1), indicating its potential neuroprotective effect [58-64].

6. Implications for Clinical Practice

In emergency department and acute care environment, rapid biomarker detection can stratify patients according to risk characteristics, so as to support triage decision. This ability is particularly important in resource limited environments, where care priorities are critical. Point-of-care testing (POCT) devices for biomarkers can provide immediate results, promoting faster diagnosis and risk stratification without delaying the start of treatment. The inclusion of these trials in the stroke early warning program can shorten the time of thrombolysis or intravascular interventional therapy. Thrombolysis or intravascular interventional therapy is time sensitive and very effective when given in time [65].

The inpatient stroke unit can benefit from continuous biomarker monitoring to track disease progression and treatment response. For example, the dynamic changes of biomarkers of oxidative stress or endothelial dysfunction may indicate persistent ischemic injury or reperfusion complications, and guide the adjustment of neuroprotection or antithrombotic therapy. In addition, the discharge plan guided by biomarkers can improve the nursing coordination after acute. Patients with persistent abnormal biomarkers may need long-term monitoring or specialized rehabilitation services.

Biomarker surveillance plays a pivotal role in rehabilitation and secondary prevention strategies, as it offers valuable guidance for tailoring lifestyle modifications and pharmacological interventions to lower the likelihood of disease recurrence. For instance, sustained elevations in lipid-related biomarkers or inflammatory cytokines may necessitate the intensification of statin treatment or more targeted dietary advice. Moreover, longitudinal monitoring of these biomarkers can act as an ef-

fective motivational instrument for patients, furnishing objective evidence regarding how their behavioral adjustments influence disease progression.

To achieve these advantages, healthcare systems need to allocate resources to develop infrastructure for biomarker testing, provide staff training, and integrate relevant data. It is also essential to standardize biomarker thresholds, validate these indicators across diverse populations, and ensure their effective incorporation into clinical practice.

7. Limitations

Although the use of peripheral blood biomarkers to predict clinical outcomes in AIS shows considerable promise, current research is constrained by several notable limitations and unresolved issues. A major obstacle is the substantial heterogeneity across study populations and methodological approaches, which compromises the generalizability and cross-study comparability of results. Many investigations are limited by small, single-center cohorts that fail to reflect the full spectrum of stroke patients, thus restricting the external validity of their conclusions. In addition, the absence of standardized protocols for biomarker selection, quantification, and analytical methods introduces significant variability, hindering the reliable replication of results across different research settings and clinical practice.

Another notable constraint is the inadequate adoption of multi-omics strategies in both the discovery and validation phases of biomarker research. Although several peripheral blood indicators—including inflammatory cytokines, coagulation factors, and metabolic markers—have demonstrated prognostic value, the majority of investigations concentrate on a restricted panel of biomarkers, neglecting the intricate cross-talk among genomic, proteomic, and metabolomic signatures. This overly focused approach risks missing critical biological pathways that underpin stroke outcomes, thereby diminishing the precision and reliability of predictive models.

Furthermore, a substantial number of current investigations are plagued by methodological flaws, such as insufficient control for confounding factors including age, comorbid conditions, and initial stroke severity. Given that these variables can exert a profound impact on clinical prognosis, they require stringent adjustment to accurately delineate the independent prognostic utility of the biomarkers under evaluation.

Evidence is derived from retrospective analyses or case-control studies, which are inherently susceptible to selection bias and cannot definitively establish causal associations. Furthermore, the scarcity of large-scale, multicenter clinical trials substantially impedes the translation of these promising biomarkers into standardized clinical applications.

8. Future Research Directions

To further explore the utility of peripheral blood biomarkers

in predicting the prognosis of AIS patients, it is essential to broaden the research scope across multiple dimensions. Current studies predominantly focus on the predictive value of individual biomarkers, yet the complexity of AIS typically involves the interplay of multiple biological pathways. Therefore, future investigations should prioritize the integration of multi-omics data—encompassing genomics, epigenomics, proteomics, and metabolomics—to develop comprehensive predictive models. Such multimodal marker integration may not only substantially improve the model's predictive accuracy but also help elucidate the underlying pathophysiological mechanisms of the disease [66].

Along with the continuous advancement of machine learning and artificial intelligence (AI) technologies, the use of multi-indicator combined models for predicting stroke prognosis has increasingly emerged as a focus of academic research [67]. Through the integration of various peripheral blood parameters, clinical features, and imaging data, the establishment of efficient predictive models can facilitate improvements in prediction accuracy, which in turn guides the formulation of personalized rehabilitation programs and secondary prevention strategies. These research progresses not only boost the scientificity and accuracy of stroke management but also drive the shift from empirical medicine to evidence-based and precision medicine, laying a solid theoretical and technical foundation for enhancing patient prognosis and decreasing recurrence rates.

Current research on biomarkers frequently relies on specific population cohorts, and the generalizability of their predictive capacity across distinct racial, gender, and age subgroups remains to be further verified. For future investigations, it is necessary to expand sample sources to encompass patients with more diverse geographical origins and racial backgrounds, thereby assessing the applicability of biomarkers in different population groups. Additionally, attention should be paid to the impacts of environmental factors and lifestyle on biomarker expression—including dietary patterns, physical activity intensity, and comorbidities—since these elements may compromise the stability of biomarkers and weaken their predictive utility.

Research focusing on specific subgroups also holds considerable significance. Elderly people, diabetic patients, hypertensive patients, and those with recurrent strokes show notable disparities in disease progression and prognostic outcomes, while the performance of current biomarkers in these populations remains insufficiently clarified. Future studies may adopt stratified analysis or subgroup modeling approaches to identify combinations of markers that possess high predictive value for specific groups, and further explore how these markers interact with clinical features.

The significance of dynamic changes in biomarkers throughout the disease progression warrants in-depth investigation. Currently, the majority of studies rely on blood samples collected at hospital admission or during the acute phase, failing to take into account the dynamic evolution of these

markers over the entire disease course. For future research, longitudinal observation protocols can be designed to collect peripheral blood samples at multiple time points, enabling the analysis of temporal trends in biomarkers and their associations with clinical outcomes. Such dynamic monitoring is expected to provide more accurate temporal insights for prognostic evaluation.

It is imperative to enhance the standardization of biomarker research and its translation into clinical practice. The establishment of unified protocols for sample collection, processing, and analysis is essential to guarantee the comparability and reproducibility of research data. Meanwhile, promoting multicenter clinical trials to verify the application effectiveness of marker models in real-world clinical scenarios can provide solid evidence-based support for their practical clinical application.

The incorporation of AI into clinical prognosis prediction—especially for AIS—has brought about a transformative advancement in both medical research and clinical practice [68]. AI-powered technologies, encompassing machine learning and deep learning algorithms, have become progressively proficient at processing large-scale, complex datasets obtained from peripheral blood biomarkers, clinical documentation, and imaging techniques. These systems are able to detect subtle patterns and correlations that often escape conventional statistical approaches, in turn improving the accuracy and promptness of prognostic prediction. By utilizing multivariate analytical methods to assess the relative contributions of diverse biomarkers—such as inflammatory indicators, coagulation factors, and metabolic markers—these models provide a more sophisticated comprehension of disease progression [69].

Concurrently, the development of advanced computational tools has facilitated the integration of multimodal data, merging peripheral blood biomarkers with neuroimaging characteristics and clinical variables to build robust predictive frameworks. Specifically, deep learning approaches—most notably convolutional neural networks—have demonstrated considerable potential in extracting predictive features from brain imaging data; when integrated with blood-derived biomarkers, these features can further enhance the refinement of prognostic models. This complementary interaction between imaging and biochemical data is especially valuable in AIS, as the early identification of infarct core and penumbra dynamics can provide critical guidance for treatment selection and prognostic stratification of patients. Additionally, natural language processing tools powered by AI are being applied to extract relevant clinical information from unstructured electronic health records, thereby expanding the breadth and depth of datasets available for predictive model construction [70].

Another promising research frontier involves the use of AI for real-time monitoring and dynamic prognostic prediction. When combined with AI analytical tools, wearable biosensors and point-of-care diagnostic instruments can deliver continuous streams of physiological and biochemical data, allowing

for timely adjustments to prognostic assessments. This capability holds particular value in critical care environments, where rapid shifts in a patient's condition demand immediate clinical intervention. Through the analysis of temporal trends in biomarker concentrations and physiological parameters, AI systems can identify early warning signals of patient deterioration, facilitating proactive adjustments to therapeutic strategies. Additionally, decision support systems powered by AI are currently under development to assist clinicians in interpreting complex prognostic data, which in turn enhances the quality of clinical decision-making and optimizes approaches to patient management.

In spite of these technological advances, a number of hurdles persist in the widespread implementation of AI for prognostic prediction. To ensure the reliability and generalizability of AI-based prognostic outcomes, it is imperative to address key issues related to data quality, model interpretability, and clinical validation. Beyond these technical concerns, careful attention must also be paid to ethical considerations, including data privacy protection, algorithmic bias mitigation, and adherence to regulatory requirements. That said, as AI technologies continue to advance and mature, their incorporation into routine clinical workflows is poised to transform the field of stroke prognosis—delivering more precise, personalized, and proactive approaches to patient care.

9. Conclusion

The current review presents a narrative overview of studies focusing on predicting the clinical prognosis of AIS using peripheral blood indicators. A range of peripheral blood markers—including plasma fibrinogen, serum neurofilament light chain protein, S100B protein, GFAP, CRP, IL-6, NRL, SOD, 8-OHdG, glucose, and glycated hemoglobin—exert significant indicative effects on the clinical prognosis of AIS patients. Conducting timely evaluations of the clinical prognosis in AIS patients helps clinicians implement appropriate interventions promptly, which in turn improves patients' clinical outcomes, enhances their quality of life, and alleviates the burden imposed on individuals, families, and society.

Abbreviations

AD	Alzheimer's Disease
AI	Artificial Intelligence
AIS	Acute Ischemic Stroke
AMPA	Alpha -Amino-3-Hydroxy-5-Methyl-4-Isoxazolepropionic Acid
ASPECTS	Alberta Stroke Program Early CT Score
ATP	Adenosine Triphosphate
BBB	Blood-Brain Barrier
CNSSS	Chinese National Stroke Screening Survey
CRP	C-Reactive Protein
DALY s	Disability Adjusted Life Years

DWI-MRI	Diffusion-Weighted Magnetic Resonance Imaging
EPO	Erythropoietin
GFAP	Glial Fibrillary Acidic Protein
HbA1c	Glycosylated Hemoglobin
IL-1 β	Interleukin-1 beta
IL-6	Interleukin-6
MMP	Matrix Metalloproteinase
NCCT	Non-Contrast Computed Tomography
NfL	Neurofilament Light Chain
NIHSS	National Institutes of Health Stroke Scale
NLR	Neutrophil-to-Lymphocyte Ratio
NMDA	N-methyl-D-aspartate
p-tau	Phosphorylated Tau Protein
PAI-1	Plasminogen Activator Inhibitor-1
PD	Parkinson's Disease
POCT	Point-of-Care Testing
ROS	Reactive Oxygen Species
snfl	Serum Neurofilament Light Chain Protein
SOD	Superoxide Dismutase
t-tau	Total Tau Protein
TNF- α	Tumor Necrosis Factor-Alpha
UCH-L1	Ubiquitin Carboxyl-Terminal Hydrolase L1
WHO	World Health Organization
8-OHdG	8-hydroxydeoxyguanosine

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Shun Liu: Writing – original draft

Yi Luo: Writing – original draft, Writing – review & editing

Jinglian Zhou: Writing – review & editing

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Conflicts of Interest

The authors declare no conflicts of interest.

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