

Review Article

A Narrative Review of Peripheral Blood Markers for Stroke Prognosis

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Abstract

With stroke becoming the main cause of global morbidity and mortality. The urgent demand for reliable biomarkers to enhance prognostic accuracy and guide individualized clinical decision-making has never been more pronounced. This unmet need is amplified by the disease's heterogeneous etiologies and variable clinical trajectories, which often hinder timely risk stratification and targeted intervention for stroke patients. A growing body of research has delved into diverse categories of candidate biomarkers, encompassing inflammatory mediators, metabolic indicators, and blood cellular parameters and evaluated their potential in predicting short-term and long-term stroke outcomes such as functional independence, recurrence risk, and mortality. Through a narrative review of current literature, we have summarized key biomarkers such as C-reactive protein, interleukins, blood cells, lipid profiles, oxidative stress markers, microparticles and cell-free DNA, clarifying their associations with stroke pathophysiology and clinical endpoints. Simultaneously, we highlighted critical gaps and inconsistencies in existing studies, such as limited validation in multiethnic and underrepresented patient cohorts. Furthermore, we have discussed the practical clinical applications and inherent challenges of translating these biomarkers into real-world settings. Finally, we have proposed future research directions, emphasizing the development of standardized protocols, validation in large-scale prospective cohorts, and exploration of multiple biomarkers to address unmet clinical needs in stroke management.

Keywords

Biomarkers, Prognosis, Clinical Decision-making, Peripheral Blood Markers, Stroke

1. Introduction

Stroke is a critical global health problem and one of the leading causes of death and long-term disability worldwide

[1]. Recent epidemiological data highlight its growing prevalence, and new stroke cases have increased alarmingly in the

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past few decades [2].

The consequences of stroke far exceed mortality, including severe physical, cognitive, and emotional damage, which can significantly reduce the patient's quality of life [3, 4]. A substantial proportion of stroke survivors face lifelong disabilities, including hemiparesis, aphasia, and cognitive deficits, which often necessitate long-term care and rehabilitation. These outcomes impose a profound impact on individuals, families, and caregivers, often leading to emotional distress, reduced independence, and diminished socioeconomic status [5].

In view of the high prevalence and serious consequences of stroke, it is imperative to develop effective prognostic tools. Accurate prognosis assessment is essential for guiding clinical decision-making, optimizing treatment strategies and improving the prognosis of patients. Traditional stroke prognosis evaluation methods often rely on clinical evaluation and conventional risk factors, such as age, blood pressure and complications. However, these methods have limitations in obtaining pathophysiological heterogeneity of stroke and accurately predicting individual prognosis [3, 4]. There is a growing recognition of the need for more objective, reliable and personalized tools to strengthen risk stratification and promote early intervention.

Although a review 16 years ago did not show that blood biomarkers can well predict the prognosis of stroke [6]. In recent years, a large number of new clinical studies have highlighted the potential of peripheral blood biomarkers in improving the prognosis of stroke [7]. These biomarkers

provide a non-invasive and quantifiable means for evaluating disease severity, predicting clinical outcomes and monitoring treatment response. We searched for literature on the correlation between blood cell markers and stroke prognosis on PubMed in the past 10 years. Through evaluation and screening, we have identified C-reactive protein (CRP), interleukins (IL), neutrophil-to-lymphocyte ratio (NLR), lipid profiles, oxidative stress markers, microparticles, cell-free DNA et al as topics for discussion.

2. Pathophysiology of Stroke

Stroke is a serious cerebrovascular event, mainly manifested in ischemic and hemorrhagic forms, each of which is dominated by different but complex biological mechanisms, and significantly affects the prognosis of patients. As shown in Figure 1, ischemic stroke, which accounts for the majority of cases, occurs when cerebral blood flow is blocked, usually due to thrombosis, embolism, or systemic hypoperfusion. This interruption leads to a series of pathophysiological events, including energy failure, excitotoxicity, oxidative stress, inflammation and apoptosis. The lack of oxygen and glucose will rapidly consume adenosine triphosphate (ATP) storage, destroy ion homeostasis and lead to membrane depolarization. The accumulation of glutamate in synaptic space triggers excessive calcium influx, activates protease, lipase and endonuclease, degrades cellular components, and eventually leads to neuronal death [4].

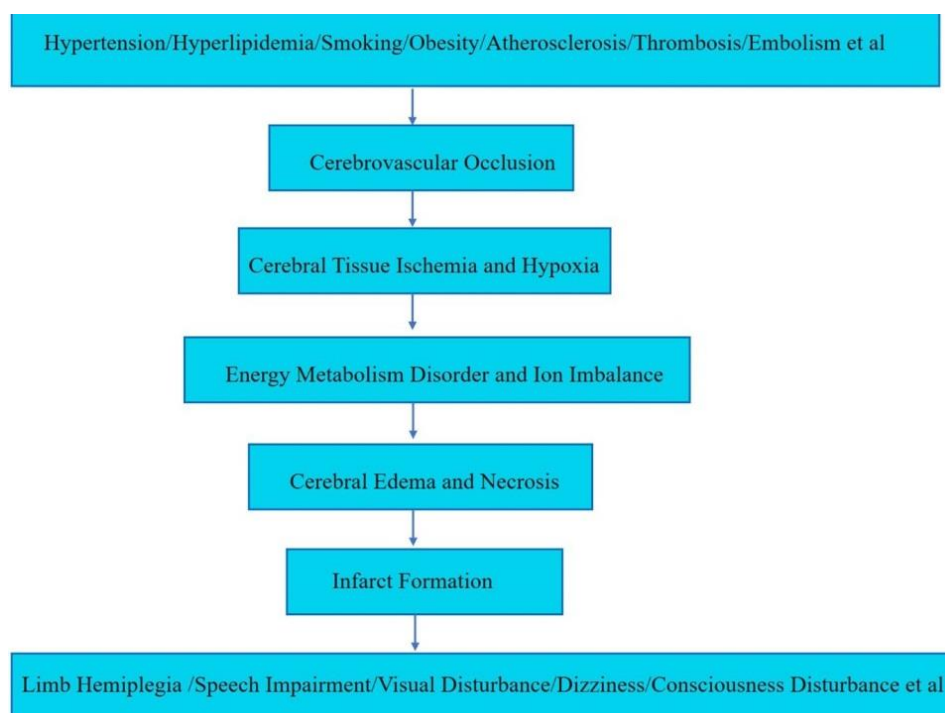


Figure 1. Ischemic Stroke Pathogenesis and Clinical Manifestation.

On the contrary, as shown in Figure 2, hemorrhagic stroke is caused by cerebral vascular rupture, which can lead to intracerebral or subarachnoid hemorrhage. The initial mechanical rupture of brain tissue produces significant mass effect by expanding hematoma, increasing intracranial pressure and damaging cerebral perfusion. In addition, the release

of toxic blood components (such as hemoglobin and iron) initiates secondary injury mechanisms, including oxidative stress, neuroinflammation and blood-brain barrier (BBB) damage. Edema around hematoma further aggravates neuronal injury, leading to deterioration of neurological function and poor recovery [3].

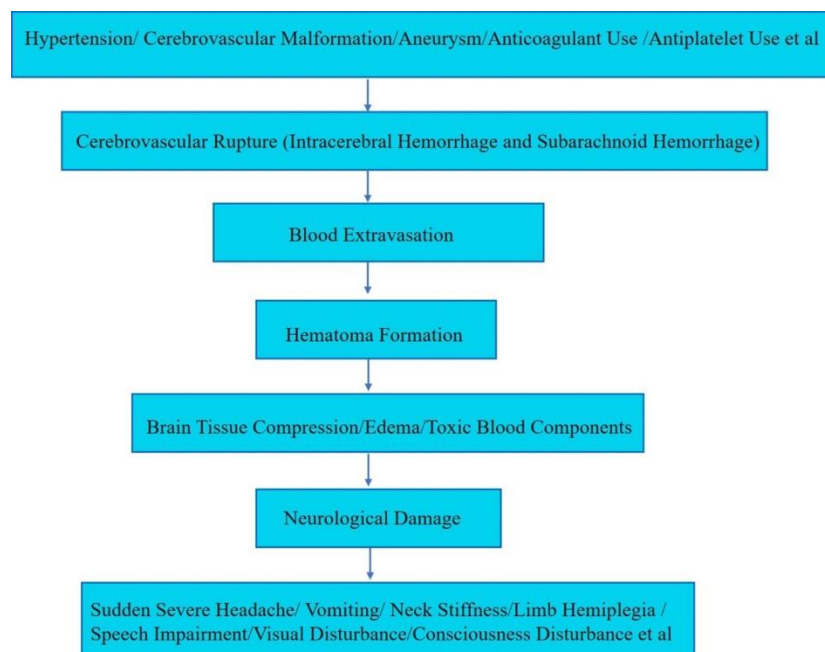


Figure 2. Hemorrhagic Stroke Pathogenesis and Clinical Manifestation.

3. Peripheral Blood Markers

Imaging examinations such as computed tomography (CT) and magnetic resonance imaging (MRI) are still the gold standard for diagnosing stroke and evaluating the degree of brain injury [7]. However, blood based biomarkers, including inflammatory mediators, have shown good prospects in predicting stroke severity, recurrence risk and functional prognosis [8, 9]. These markers provide a minimally invasive and rapid access method to enhance clinical evaluation and inform treatment decisions.

Because of its accessibility and abundant biological information, peripheral blood has become an important resource for clinical diagnosis and biomedical research. As a minimally invasive sample type, peripheral blood provides a practical and informative means for monitoring disease progression and predicting clinical outcomes. Its composition reflects the physiological and pathological changes of the system, which makes it particularly valuable to track dynamic processes under conditions such as stroke. Unlike more invasive sampling methods such as tissue biopsy or cerebrospinal fluid extraction, blood collection is relatively simple, repeatable and well tolerated by patients, allowing longitudinal

assessment of the temporal changes in the captured disease status.

4. Inflammatory Biomarkers

4.1. C-Reactive Protein

CRP is an acute-phase reactant synthesized by the liver during systemic inflammation, infection or tissue injury. Its serum level rises rapidly in the process of inflammatory reaction, making it a widely studied biomarker under various pathological conditions, including cardiovascular and cerebrovascular diseases [10-14]. In the study of stroke, CRP has attracted much attention because of its potential role in reflecting the degree of inflammatory activation after cerebral ischemia or cerebral hemorrhage [11, 12]. The inflammatory cascade caused by stroke will not only lead to the initial brain injury, but also lead to secondary complications, such as edema, neuron death and recovery disorders [15, 16]. Therefore, CRP level has been studied as a potential indicator of stroke severity and a predictor of clinical prognosis.

A large number of clinical studies have shown that the increase of CRP level is related to the severity of neurological

deficit at the onset of stroke. Patients with higher CRP concentrations tend to show more extensive brain injury, the larger the infarct volume on neuroimaging, and the more obvious the clinical injury measured by scales such as the National Institutes of Health Stroke Scale (NIHSS) [10-12, 15, 16]. This association is believed to be due to the pro-inflammatory effect of CRP, which may amplify the

immune response, promote oxidative stress, and aggravate tissue damage. In addition, CRP is also associated with endothelial dysfunction and the instability of atherosclerotic plaque, both of which may lead to the progression of ischemic injury and poor clinical performance [17]. A brief flowchart for CRP is shown in Figure 3.

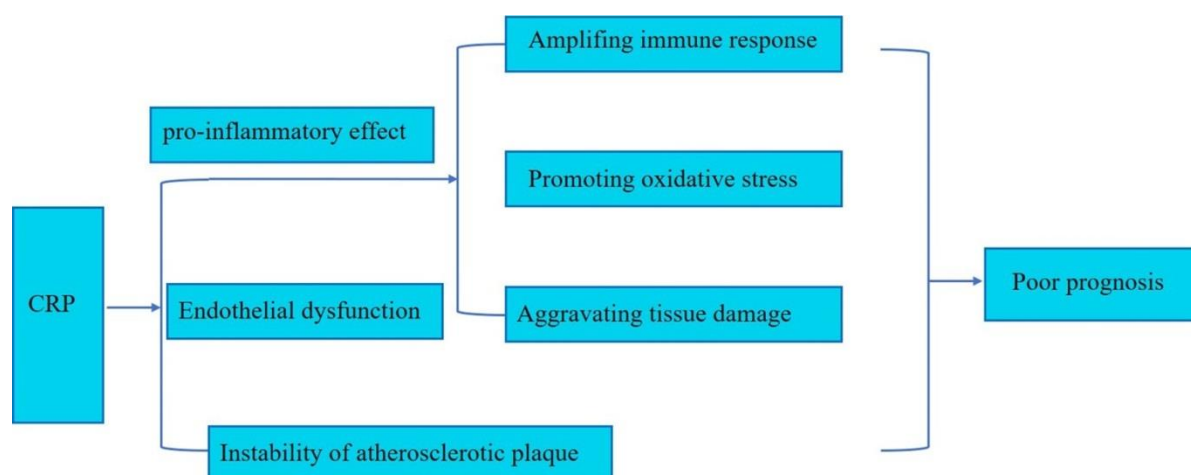


Figure 3. Flowchart for CRP with prognosis.

In addition to the initial stroke severity, CRP was also associated with short-term and long-term functional outcomes. According to the modified Rankin Scale (mRS) and Barthel index, the increase of CRP level in the acute phase of stroke is associated with higher mortality, increased risk of stroke recurrence and poor functional recovery [10-12, 15, 16]. The continuous rise of CRP in the subacute phase is associated with delayed deterioration of neurological function and poor rehabilitation outcomes, emphasizing its dynamic role in monitoring disease progression and predicting complications such as infection or hemorrhagic transformation [18].

Although CRP is a sensitive inflammatory marker, it lacks specificity for stroke related pathology because it may be elevated in other systemic conditions. Current research focus is to explore the combination of CRP and other biomarkers to improve its prediction accuracy. Future studies also need to determine the best time for CRP evaluation and incorporate it into clinical decision-making algorithms to improve the prognosis and management of stroke.

4.2. Interleukins

Interleukins, especially interleukin-6 (IL-6) and interleukin-10 (IL-10), have attracted extensive attention in recent years because of their potential role in regulating the in-

flammatory response after stroke and its impact on the prognosis of patients. These cytokines are part of the immune system, mediate the communication between immune cells, and affect the progress and resolution of inflammation. After acute ischemic or hemorrhagic stroke, the central nervous system undergoes a series of inflammatory processes, which can promote recovery or aggravate neuronal damage. In this process, the systemic release of interleukin from peripheral circulation provides a measurable reflection of the body's immune response, and has been increasingly studied as a prognostic tool for stroke treatment [19-22].

IL-6 is one of the most widely studied interleukins in stroke. It is a pro-inflammatory cytokine that is rapidly upregulated after cerebral ischemia or injury. The level of serum IL-6 in stroke patients continued to rise, especially within 24-48 hours after onset [19]. Clinical studies have proved that there is a correlation between higher IL-6 concentration and increased stroke severity. In addition, according to mRS measurement, elevated IL-6 levels are associated with poor functional prognosis 3-6 months after stroke [19, 23]. This cytokine can further amplify the inflammatory environment by promoting the synthesis of acute phase proteins (such as CRP). Its role in fever and activation of microglia also contributes to secondary brain injury, which has a negative impact on recovery. A brief flowchart for IL-6 is shown in Figure 4.

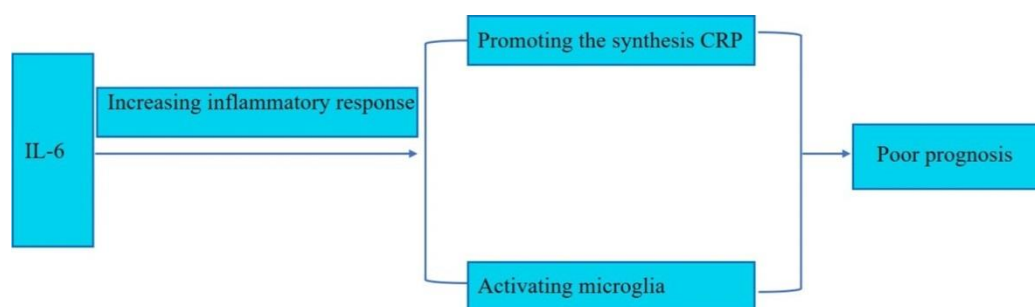


Figure 4. Flowchart for IL-6 with prognosis.

On the contrary, IL-10, as an anti-inflammatory cytokine, plays a protective role in regulating the immune response after stroke. It inhibits the production of pro-inflammatory cytokines such as IL-6, IL-1 β , and TNF- α , thereby reducing the intensity and duration of inflammation. Studies have shown

that higher levels of IL-10 are usually associated with better clinical outcomes, suggesting that it may be used as a compensatory mechanism to counteract excessive inflammation [19, 24]. A brief flowchart for IL-10 is shown in Figure 5.

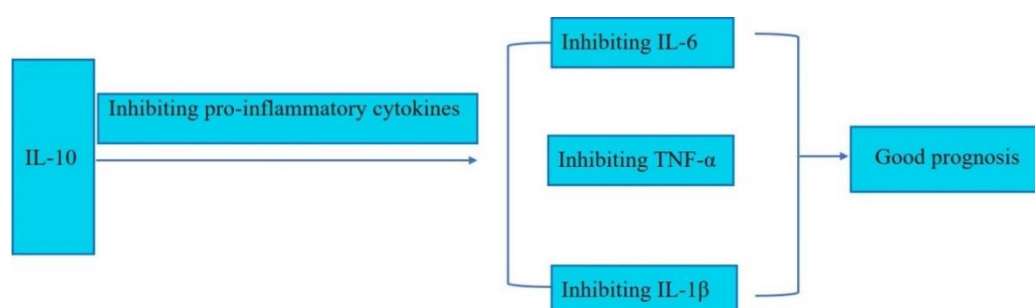


Figure 5. Flowchart for IL-10 with prognosis.

The balance between pro-inflammatory and anti-inflammatory interleukin seems to be a key determinant of the prognosis of stroke. A higher IL-6 to IL-10 ratio has been proposed as a more informative prognostic marker than the absolute levels of either cytokine alone [19]. This ratio reflects the net inflammatory state and has been shown to predict mortality and functional disability more accurately. In addition, the interaction between interleukins and other components of the immune system, such as T regulatory cells and macrophages, further affects the recovery trajectory.

4.3. Neutrophil-to-Lymphocyte Ratio

NLR has become an easily available and potentially prognostic biomarker of inflammation. As systemic inflammation plays an important role in the pathophysiology of stroke, especially in the secondary injury mechanism after ischemic or hemorrhagic events, NLR calculated by conventional whole blood count measurement provides a practical method to evaluate the body's inflammatory response. In a series of acute diseases including cardiovascular and cerebrovascular diseases, the increase of NLR level is related to the increase of disease severity and the deterioration of clinical outcomes [25-27].

In the case of stroke, some studies have shown that there is a significant correlation between high NLR values at admission and poor functional outcomes at follow-up [27]. Our preliminary research involving patients with acute ischemic stroke has shown that those with elevated baseline NLR are more likely to experience unfavorable outcomes, such as higher disability scores on the mRS [27]. This association is particularly evident in patients receiving reperfusion therapy. Excessive inflammatory response may lead to reperfusion injury and hemorrhagic transformation [25, 28].

In addition, NLR is associated with the occurrence of post-stroke complications, including symptomatic intracranial hemorrhage (sICH), cerebral edema, and infections such as pneumonia [11, 28]. These complications seriously affect the recovery and long-term prognosis of patients. The mechanism may involve the imbalance between pro-inflammatory neutrophils and anti-inflammatory lymphocytes, which reflects an aggravating systemic inflammatory state, thereby aggravating neuronal damage and damage recovery. In this case, NLR is not only a marker of the severity of initial stroke, but also a dynamic indicator of the body's response to injury and treatment [26, 29]. A brief flowchart for NLR is shown in Figure 6.

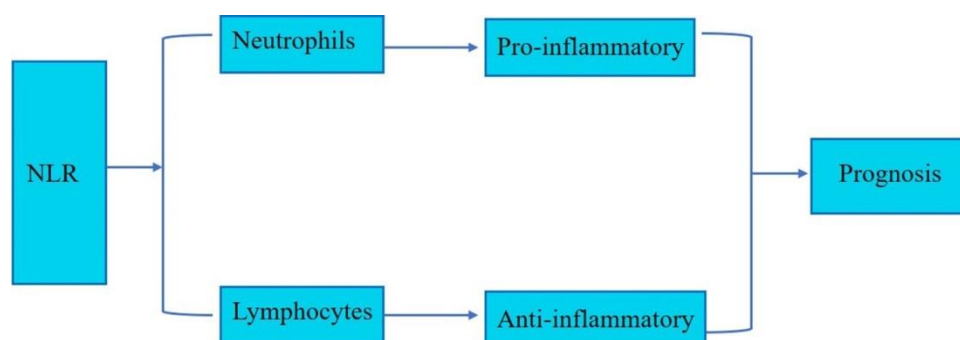


Figure 6. Flowchart for NLR with prognosis.

Although NLR has a good application prospect, its clinical application as a biomarker of stroke prognosis is limited by many factors. The variability of NLR level may be affected by concurrent infection. Although some studies have proposed specific thresholds for NLR to predict poor prognosis, there is still a lack of consensus on the optimal threshold, which limits its applicability in routine clinical practice.

5. Metabolic and Cellular Biomarkers

5.1. Lipid Profiles

With more and more evidence emphasizing its predictive value for the prognosis of ischemic and hemorrhagic stroke, lipid profile has been increasingly considered as a key indicator to evaluate the prognosis of stroke [30]. Dyslipidemia is characterized by abnormal cholesterol and triglyceride levels, which plays an important role in the pathogenesis of atherosclerosis. Atherosclerosis is the main potential cause of ischemic stroke. Recent studies have shown that in addition to the traditional measurement of low-density lipoprotein cholesterol (LDL-C), specific lipid parameters may provide more

detailed insights into the prognosis of stroke. For example, the non-high-density lipoprotein cholesterol to high-density lipoprotein cholesterol ratio (Non-HDL/HDL ratio) has been associated with cerebral atherosclerotic stenosis, suggesting its potential application in risk stratification and treatment decision-making. Elevated Non-HDL/HDL ratio levels reflect the imbalance between atherogenic and anti-atherogenic lipoproteins, which may lead to greater vascular vulnerability and worse clinical outcomes after stroke [31].

Residual cholesterol (RC) refers to the cholesterol content in triglyceride rich lipoproteins excluding LDL-C and HDL-C, which is also an important prognostic factor [30, 32]. Studies have shown that higher RC levels are independently associated with increased risk of stroke, especially in the subtypes of ischemic stroke [30]. This association emphasizes the importance of targeting RC in lipid-lowering therapy for reducing secondary stroke events and improving long-term recovery. In addition, RC may reflect metabolic disorders leading to endothelial dysfunction and plaque instability, which are not conducive to the recovery track after stroke. A brief flowchart for Lipid profiles is shown in Figure 7.

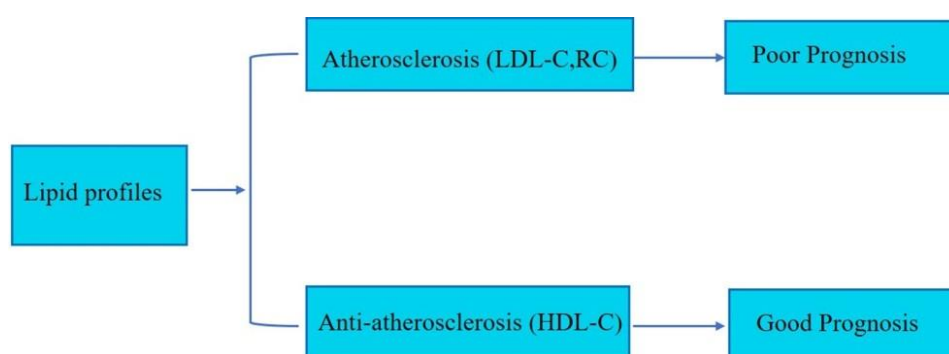


Figure 7. Flowchart for Lipid profiles with prognosis.

The role of lipid-lowering intervention in the prognosis of stroke further emphasizes the clinical relevance of lipid profile. Statins are the cornerstone of lipid-lowering therapy, and have been proved to reduce stroke recurrence and improve

functional prognosis, which may be achieved through lipid-lowering and pleiotropic anti-inflammatory effects [33]. However, the degree of benefit may vary depending on the baseline lipid level and the degree of lipid reduction achieved.

Emerging treatment strategies, including PCSK9 inhibitors and novel lipid-lowering agents, provide a promising way to optimize lipid management in stroke survivors [34].

In addition to pharmacological methods, lifestyle changes, such as personalized dietary intervention, have been proved to be effective in regulating blood lipid levels and improving metabolic health [33]. Studies have shown that customized nutritional strategies can reduce the lipid composition of atherosclerosis and enhance the overall vascular health, which may translate into a better prognosis of stroke. This intervention is particularly important in secondary prevention, where metabolic control plays a key role in long-term recovery.

5.2. Oxidative Stress Markers

Oxidative stress is an important factor in the pathophysiological process of stroke, which affects the progress and recovery potential of neuronal injury. It stems from the imbalance between the production of reactive oxygen species (ROS) and the body's antioxidant defense mechanism [35]. In the case of stroke, especially ischemic stroke, the sudden interruption of blood flow will lead to a series of metabolic disorders, including mitochondrial dysfunction and excessive ROS production. These reactive molecules can damage cellular components, such as lipids, proteins and DNA, thus aggravating neuronal death and helping to expand infarct size [36, 37]. Moreover, oxidative stress is closely related to inflammatory response, which further amplifies tissue damage and weakens the ability of the brain to initiate effective repair process.

In the acute phase of stroke, oxidative stress is closely related to anaerobic glycolysis, which becomes the main source of energy production in ischemic brain. This metabolic change leads to lactic acid accumulation and acidosis, which is a key pathological process that aggravates oxidative stress and promotes neuronal damage. The interaction between oxidative stress and other pathological mechanisms (such as calcium overload and excitotoxicity) causes the self-perpetuating cycle of cell damage [35, 38]. For example, excessive glutamate release after ischemia leads to overactivation of N-methyl-D-aspartic acid (NMDA) receptors, which in turn increases intracellular calcium levels and activates ROS producing enzymes. This synergistic relationship emphasizes the central role of oxidative stress in the pathological progression of stroke [35, 38].

In addition to its contribution to acute injury, oxidative stress also has an important impact on post-stroke recovery. It damages neural plasticity, which is crucial for functional rehabilitation after brain injury [39]. Neuroplasticity includes the ability of the brain to reorganize synaptic networks and form new neural connections, which are crucial for restoring lost function. However, oxidative stress destroys these adaptive mechanisms by changing gene expression, damaging mitochondrial function and interfering with the signaling pathways necessary for synaptic remodeling. Therefore, pa-

tients with long-term or severe oxidative stress are less responsive to rehabilitation treatment, and their long-term prognosis is poor [35, 39].

In view of the harmful effects of oxidative stress, targeted oxidative stress has become a promising therapeutic strategy in the treatment of stroke [35]. Antioxidant interventions, including natural compounds and synthetic agents, have been explored for their neuroprotective potential [40]. Flavonoids, polyphenols and other plant-derived antioxidants have been shown to have the ability to scavenge reactive oxygen species and regulate inflammatory pathways in the preclinical model of stroke [40]. Similarly, pharmaceutical antioxidants such as N-acetylcysteine and vitamin E have shown some efficacy in reducing oxidative damage, although their clinical benefits remain to be fully confirmed [41, 42].

5.3. Microparticles and Cell-Free DNA

Microparticles and cell-free DNA have emerged as promising indicators of stroke severity because they are directly involved in the pathophysiological process after brain injury. Microparticles are membrane-bound vesicles between 0.05 and 1.5 micrometers in size, which are released from different types of cells during activation or apoptosis. These vesicles carry bioactive molecules, including proteins, lipids, and nucleic acids, which reflect the physiological state of their parent cells. In the context of stroke, elevated levels of microparticles have been observed in both animal models and clinical studies, indicating the potential of particulate as a biomarker [43, 44]. These vesicles may contribute to the progression of ischemic injury by promoting inflammation, endothelial dysfunction, and coagulation cascades. Their ability to mediate intercellular communication and regulate vascular responses is related to the dynamic changes in the acute phase of stroke [43, 44]. Moreover, microparticles derived from platelets, leukocytes, and endothelial cells showed distinct expression patterns in stroke patients, indicating that the distribution of microparticles was related to infarct volume or clinical prognosis [43, 44].

Cell-free DNA is another emerging biomarker, which mainly comes from apoptotic or necrotic cells and is released into the blood stream after tissue damage [45, 46]. In stroke, the rapid decomposition of brain tissue leads to the release of DNA fragments into circulation, which can be quantified and analyzed to understand the genetic and epigenetic changes. Studies have shown that the increase of free DNA level in plasma is related to larger infarct size, more severe neurological deficit and worse functional recovery. This association highlights the potential of cell-free DNA as a real-time marker of cell damage and disease progression. In addition, methylation patterns and fragment length profiles of circulating DNA may provide additional insights into the origin and extent of tissue damage [45, 46].

6. Others

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 [47, 48].

7. Limitations of Current Biomarkers

The possible correlation between blood markers and good prognosis of stroke is shown in Table 1. The application of peripheral blood biomarkers in the prognosis of stroke has shown good prospects, but some key challenges hinder its consistency and reliability in the clinical environment. One of the main concerns is the biological heterogeneity across studies. Stroke is a highly heterogeneous disease, whether in etiology, from ischemic to hemorrhagic subtypes, or in patient demographics, comorbidity and baseline health status. This variability affects the expression and predictive value of biomarkers, making it difficult to determine universally applicable indicators.

Table 1. Correlation between peripheral blood markers and good prognosis.

Peripheral blood markers	Good prognosis
C-Reactive Protein (CRP)	Negative
Interleukin-6 (IL-6)	Negative
Interleukin-10 (IL-10)	Positive
Neutrophil-to-Lymphocyte Ratio (NLR)	Negative
Low-density lipoprotein cholesterol (LDL-C)	Negative
Residual cholesterol (RC)	Negative
Reactive oxygen species (ROS)	Negative
Microparticles	Negative
Cell-free DNA	Negative
Fibrinogen	Positive

Another major challenge is the sensitivity and specificity of biomarkers currently used. Many peripheral blood markers, such as inflammatory cytokines or metabolic indicators, are not limited to stroke, but may increase in other systemic diseases, including infection or chronic diseases such as diabetes and hypertension. Lack of specificity can lead to false positive associations and reduce the clinical utility of these markers in predicting the prognosis of stroke. In addition, some biomarkers may not be sensitive enough to detect subtle changes in neurological status or distinguish different prog-

nosis tracks, especially in the early stage after stroke. Dynamic detection of blood markers may be more beneficial for accurately predicting stroke prognosis.

In addition, although there are encouraging findings in exploratory studies, many biomarkers have not been fully verified in large, prospective and multicenter clinical trials. The transformation from discovery to clinical implementation is usually hindered by limited sample size, selection bias and lack of reproducibility in different patient groups. Without strict validation and regulatory approval, the application of these biomarkers in clinical guidelines is still limited.

Finally, more complex analytical methods are needed to integrate multiple biomarkers and clinical variables into the prediction model. Although the prognostic value of a single biomarker is limited, combining it with clinical data, imaging findings and other omics-based biomarkers can improve the prediction accuracy. However, the development and validation of such multimodal models require extensive collaboration, robust statistical methods and larger samples.

8. Emerging Technologies

Recent advancements in biomedical research have increasingly leveraged emerging technologies such as multi-omics and machine learning to enhance the identification and validation of biomarkers, particularly in the context of stroke prognosis. Multi-omics integrates diverse layers of biological data, including genomics, transcriptomics, proteomics, and metabolomics, enabling a comprehensive understanding of the molecular mechanisms underlying stroke progression and recovery. This integrative approach facilitates the discovery of novel biomarkers and integration of multi-marker that may not be detectable through single-omics analyses, thereby improving the accuracy of prognostic models and enabling more precise risk stratification for individual patients.

Machine learning has emerged as a powerful tool for analyzing large-scale, heterogeneous datasets generated through multi-omics approaches. Unlike traditional statistical methods, machine learning algorithms can detect subtle, nonlinear relationships and high-order interactions within complex biological systems. Deep learning models, particularly neural networks, offer the potential to automatically extract features from raw omics data, reducing the need for manual feature selection and enhancing predictive performance.

9. Conclusion

Stroke is still the main cause of disability and death worldwide. It is necessary to identify reliable biomarkers to predict prognosis and guide clinical decision-making. Peripheral blood markers have attracted more and more attention because of their accessibility and potential to reflect the complex pathophysiological process after stroke. Despite the

encouraging findings, the translation of these biomarkers into routine clinical practice remains challenging. Future research should focus on verifying these biomarkers in large-scale, multicenter studies and integrating them into predictive models to help clinicians make timely and accurate prognosis assessment.

Abbreviations

ATP	Adenosine Triphosphate
BBB	Blood-brain Barrier
CRP	C-Reactive Protein
CT	Computed Tomography
IL-6	Interleukin-6
IL-10	Interleukin-10
LDL-C	Low-density Lipoprotein Cholesterol
MRI	Magnetic Resonance Imaging
mRS	modified Rankin Scale
NHHR	High-density LIProtein Cholesterol Ratio
NIHSS	National Institutes of Health Stroke Scale
NLR	Neutrophil-to-Lymphocyte Ratio
NMDA	N-Methyl-D-Aspartic Acid
RC	Residual Cholesterol
ROS	Reactive Oxygen Species
sICH	Symptomatic Intracranial Hemorrhage

Author Contributions

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Shaoliang Zhu: Writing – review & editing

Yi Luo: Writing – review & editing

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Conflicts of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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