Recent Advances in Prognostic Biomarkers After Cerebral Infarction: Mechanisms and Clinical Applications (Postprint)

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Abstract

Ischemic stroke, as one of the leading causes of global disability and mortality, has witnessed significant advances in research on prognostic biomarkers in recent years. This study reviews the mechanisms of action and research progress in prognostic assessment of various biomarkers in ischemic stroke, including blood cell analysis indices (such as red cell distribution width), omega-3 polyunsaturated fatty acids, cytokines (such as interleukin-6, tumor necrosis factor-alpha), microRNAs (miRNAs, such as miR-21, miR-155, miR-126), and exosomes. Research findings indicate that concentrations of blood cell analysis-related indices, omega-3 polyunsaturated fatty acids, interleukin-6, and tumor necrosis factor-alpha are closely associated with the severity and prognosis of ischemic stroke. Specifically, higher baseline red cell distribution width is associated with an increased risk of recurrent ischemic stroke and is negatively correlated with the time to recurrence of ischemic stroke. Specific miRNAs such as miR-21 improve neurological functional recovery by inhibiting apoptosis and promoting neuronal survival; whereas miR-155 exacerbates brain injury by regulating inflammatory responses, and its expression level can predict the recurrence of ischemic stroke; furthermore, miR-126 plays a critical role in angiogenesis and neuroprotection. Exosomes significantly attenuate inflammation and injury induced by ischemia-reperfusion by carrying anti-inflammatory factors, neurotrophic factors, antioxidant enzymes, and heat shock proteins, thereby influencing the prognosis of ischemic stroke. Although these biomarkers demonstrate substantial potential in prognostic evaluation of ischemic stroke, their clinical application still faces numerous challenges, including inter-individual variability, insufficient research on long-term effects and safety, and issues of technical standardization. Future research should further investigate the mechanisms of action of these markers, develop standardized detection methods, and conduct large-scale clinical validation, with the aim of applying them in clinical practice to improve the prognosis

and quality of life of patients with ischemic stroke.

Full Text

Review and Monograph

Recent Advances in Prognostic Biomarkers After Cerebral Infarction: Mechanisms and Clinical Applications

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Abstract Ischemic stroke (IS) is one of the leading causes of disability and mortality worldwide. In recent years, significant progress has been made in research on prognostic biomarkers for ischemic stroke. This review examines the mechanisms and prognostic value of various biomarkers, including hematological indices (such as red cell distribution width), ω-3 polyunsaturated fatty acids, cytokines (e.g., interleukin-6, tumor necrosis factor-α), microRNAs (miRNAs such as miR-21, miR-155, miR-126), and exosomes. Studies demonstrate that hematological indices, ω-3 polyunsaturated fatty acids, and concentrations of IL-6 and TNF-α are closely associated with stroke severity and prognosis. Specifically, elevated baseline red cell distribution width correlates with increased risk of recurrent ischemic stroke and is inversely associated with time to stroke recurrence. Particular miRNAs, such as miR-21, improve neurological recovery by inhibiting apoptosis and promoting neuronal survival, while miR-155 exacerbates brain injury by regulating inflammatory responses, with its expression level predicting stroke recurrence. Additionally, miR-126 plays a crucial role in angiogenesis and neuroprotection. Exosomes significantly mitigate ischemia-reperfusion-induced inflammation and injury by carrying anti-inflammatory factors, neurotrophic factors, antioxidant enzymes, and heat shock proteins, thereby influencing ischemic stroke prognosis. Despite the tremendous potential of these biomarkers in prognostic assessment, clinical application faces numerous challenges, including interindividual variability, insufficient research on long-term effects and safety, and issues with technical standardization. Future research should further investigate the mechanisms of these markers, develop standardized de-

tection methods, and conduct large-scale clinical validation to facilitate their clinical application and improve outcomes and quality of life for ischemic stroke patients.

[**Keywords**] Brain Infarction; Prognosis; Biomarkers; Cytokines; MicroRNAs; Exosomes; Review

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Stroke, or cerebrovascular accident, is classified into ischemic and hemorrhagic types, both of which can cause various neurological deficits that severely impact patients' language, motor function, and daily living activities [1]. Ischemic stroke, also known as cerebral infarction, accounts for approximately 85% of all stroke cases [2]. According to the 2019 Global Burden of Disease (GBD) report, there were 12.2 million incident cases, 101 million prevalent cases, and 6.55 million deaths from stroke globally [3]. In China, the situation is particularly severe, with 3.94 million incident cases, 28.76 million prevalent cases, and 2.19 million deaths [4]. Stroke has become the second leading cause of death and the third leading cause of disability worldwide, representing a major public health challenge [3]. It is estimated that 33-42% of stroke patients require assistance with daily living activities within six years of onset, while 36% remain disabled five years after onset [5], imposing a heavy burden on families and society.

Current treatments for ischemic stroke primarily include intravenous thrombolysis, mechanical thrombectomy, and antiplatelet therapy. Intravenous thrombolysis using recombinant tissue plasminogen activator (rt-PA) is limited by a 4.5-hour time window and carries hemorrhage risk. Although mechanical thrombectomy can extend the treatment window to 6-24 hours, it is only suitable for patients with large vessel occlusion and carries risks of vascular injury and re-thrombosis. Antiplatelet therapy is mainly used for secondary prevention rather than acute treatment. Despite significant advances in secondary prevention and treatment over recent decades, the disability and mortality rates of ischemic stroke remain high due to treatment time window limitations and ischemia-reperfusion injury risks. Therefore, early diagnosis and timely treatment are crucial for improving prognosis.

Good prognosis can alleviate patients' physical and psychological suffering, improve quality of life, and reduce economic burden on families and society. In recent years, research on prognostic biomarkers for ischemic stroke has become a focus for scholars worldwide. These markers have important clinical reference value for predicting stroke progression and prognosis. Blood cell analysis, a rapid and convenient clinical test, provides valuable information. Inflammatory responses play an indispensable role in the pathogenesis of ischemic stroke, with inflammatory cytokines being key mediators. Additionally, recent studies have found that ω-3 polyunsaturated fatty acids (ω-3 PUFA), microRNAs (miRNA), and exosomes are closely associated with ischemic stroke prognosis.

Given the broad scope of biomarkers, this review focuses on recent advances in prognostic markers including hematological indices [such as red cell distribution

width (RDW)], ω-3 PUFA, miRNA, and exosomes, aiming to provide reference for their application in prognostic assessment. These biomarkers were selected because they play important roles in pathogenesis and prognosis assessment, and have been extensively studied. The review first discusses well-validated biomarkers with strong evidence that have been applied clinically or validated in large cohort studies, then explores findings from smaller studies, to provide new insights for prognostic assessment and clinical treatment of ischemic stroke.

Literature Search Strategy: Computer searches were conducted in CNKI, VIP, Wanfang Data, Web of Science, and PubMed for studies on prognostic biomarkers after cerebral infarction, from database inception to March 2024. Search terms included subject headings and free text. Chinese search terms: "cerebral infarction AND blood cell analysis," "cerebral infarction AND inflammatory factors," "cerebral infarction AND polyunsaturated fatty acids," "cerebral infarction AND microRNA," "cerebral infarction AND exosomes." English search terms: "(cerebral infarction OR ischemic stroke) AND red cell distribution width," "(cerebral infarction OR ischemic stroke) AND neutrophil to lymphocyte ratio," "(cerebral infarction OR ischemic stroke) AND platelet to lymphocyte ratio," "(cerebral infarction OR ischemic stroke) AND inflammatory factors," "(cerebral infarction OR ischemic stroke) AND PUFA," "(cerebral infarction OR ischemic stroke) AND miRNA," "(cerebral infarction OR ischemic stroke) AND exosomes." Inclusion criteria: (1) Chinese or English literature only; (2) studies on prognostic biomarkers after cerebral infarction; (3) research including mechanisms and clinical applications. Exclusion criterion: inability to obtain full text.

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1. Hematological Indices and Their Potential Mechanisms in Cerebral Infarction

1.1 Red Cell Distribution Width (RDW) RDW is an index measuring the variability in red blood cell volume in peripheral blood, with increased values indicating greater heterogeneity in red cell size [6]. Elevated pro-inflammatory cytokine levels in plasma may inhibit erythropoietin (EPO)-induced red cell maturation and proliferation while reducing EPO receptor expression, thereby increasing RDW [6-7]. Traditionally used for anemia classification and differential diagnosis [8], recent research has revealed its important role in stroke prognosis assessment [7]. Although the exact mechanisms remain unclear, they may be related to hemodynamic changes. Elevated RDW leads to anisocytosis, affecting peripheral circulation function and potentially serving as an independent or synergistic factor for increased circulatory resistance and vascular occlusion [9].

Xue et al. [10] conducted a retrospective analysis of 629 acute ischemic stroke patients and found through multivariate analysis that higher RDW was significantly associated with moderate to severe stroke (OR=2.21, 95%CI=1.30-

3.75, P=0.003), modified Rankin Scale scores of 3-6 at 3 months (OR=1.86, 95%CI=1.02-3.41, P=0.044), and Barthel Index scores <85 (OR=2.27, 95%CI=1.25-4.12, P=0.007). Multiple logistic regression analysis further confirmed the association between RDW and stroke severity as well as poor functional outcomes. Li et al. [11] performed a retrospective analysis of 606 acute ischemic stroke patients aged $ $80 years and found that higher RDW was significantly positively correlated with in-hospital mortality (HR=3.31, 95%CI=2.47-4.45, P<0.001). Additional studies have reported that elevated baseline RDW is not only associated with increased risk of recurrent ischemic stroke but also inversely correlated with time to stroke recurrence [12-13]. Therefore, RDW shows promise as a reliable and economical indicator for assessing prognosis and recurrence risk in ischemic stroke patients, providing important evidence for clinical management and prognostic evaluation.

1.2 Neutrophil-to-Lymphocyte Ratio (NLR) Neutrophils, derived from granulocyte-monocyte progenitors in bone marrow, are terminally differentiated, short-lived phagocytic cells that play important roles in various diseases including trauma, infectious diseases, metabolic disorders, and autoimmune conditions [14]. Inflammatory responses are key factors causing cerebral ischemic injury [15], with neutrophils directly damaging neurons through release of proteolytic enzymes (such as neutrophil elastase) and causing microvascular mechanical obstruction through aggregation [16]. Cai et al. [17] conducted a case-control study of 225 Chinese Han patients with acute ischemic stroke and found that in patients with infarct area >1.5 cm, both neutrophil count (R^2=0.07, P=0.0208) and NLR (R^2=0.07, P=0.0447) were positively correlated with infarct size, revealing that elevated peripheral blood neutrophil levels in the early stage of stroke predict poor prognosis.

As a composite parameter, NLR more accurately reflects immune cell activity and offers higher stability, sensitivity, and specificity [18]. NLR has been validated as a prognostic marker for cardiovascular diseases, immune disorders, tumors, and infections [19-20]. Kocaturk et al. [21] found that in acute ischemic stroke, NLR was significantly correlated with infarct volume in anterior circulation stroke (ACS) and served as an independent predictor of 3-month mortality. In ACS patients, infarct volume showed significant correlation with NLR (r=0.482, P$ 0.001).$Multivariateanalysisrevealed NLRastheonlyindependentpredictorof3-monthmortality(OR = 1.186, 95$4.7. Another case-control study showed NLR was an independent predictor of in-hospital gastrointestinal bleeding in acute ischemic stroke patients receiving dual antiplatelet therapy, with predictive sensitivity of 87.8% and specificity of 85.7% [22]. Similarly, Xu et al. [23] conducted a prospective study of 341 ischemic stroke patients and demonstrated that NLR was closely associated with stroke progression (SP) and poor outcomes, with an area under the ROC curve (AUC) of 0.6117 (95%CI=0.5341-0.6893, P=0.0032) for predicting poor functional outcomes, an optimal cutoff value of 4.2139, and predictive sensitivity and specificity of 52.7% and 72.0%, respectively. As a low-cost, easily accessible biomarker, NLR holds significant value in stroke

diagnosis and prognostic evaluation.

1.3 Platelet-to-Lymphocyte Ratio (PLR) Platelets, derived from mature megakaryocytes in bone marrow, are essential for maintaining vascular integrity and hemostasis. In cerebral ischemia, inflammatory responses damage endothelial cells, activating and aggregating platelets to form thrombi that obstruct vessels and cause cerebral tissue ischemia and infarction [24]. PLR, as a novel inflammatory index reflecting both thrombotic and inflammatory responses, is closely associated with the occurrence, severity, and prognosis of acute ischemic stroke.

Tsalta-Mladenov et al. [25] conducted a prospective study of 141 acute ischemic stroke patients and found PLR was significantly associated with poor functional outcomes ($P<0.001$) and could predict hemorrhagic transformation (HT) in young acute ischemic stroke patients. ROC curve analysis showed that when the optimal cutoff value for predicting 3-month poor outcomes was 122.6, sensitivity was 77.8% and specificity was 61.5% (AUC=0.613, P=0.031). Another prospective observational study indicated PLR was associated with stroke severity and may serve as a prognostic marker for ischemic stroke, helping prevent potential complications [26]. Wen et al. [27] performed a retrospective study of 157 young patients with first-ever acute ischemic stroke and found PLR was associated with independent risk factors for hemorrhagic transformation. ROC analysis revealed that when the cutoff value for predicting hemorrhagic transformation was 109.073, sensitivity and specificity were 80.6% and 67.4%, respectively. Li et al. [28] conducted a retrospective study of 158 acute ischemic stroke patients and found PLR was significantly associated with recurrent ischemic stroke ($P<0.001$). ROC analysis showed PLR>115.9 provided optimal prediction of recurrent stroke with sensitivity of 78.9% and specificity of 57.2% (AUC=0.72, P=0.021). Additionally, Sun et al. [29] found that PLR at 24 hours after rtPA thrombolysis was significantly increased in patients with poor outcomes and mortality, independently associated with increased risk of poor prognosis and death. Therefore, PLR may serve as a simple yet effective indicator for ischemic stroke prognosis, offering high predictive value for disease outcomes.

[**Figure 1: see original paper**] shows the potential mechanisms of hematological indices and PUFA in predicting disease progression and outcomes during cerebral infarction.

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2. Inflammatory Factors and Their Correlation with Ischemic Stroke Prognosis

Inflammatory responses are crucial in the pathogenesis of ischemic stroke [30], with microglia (MG) playing a key role. The M1 phenotype of MG produces various pro-inflammatory and cytotoxic factors, including IL-1β, IL-6, IL-23,

and TNF-α [32]. M1 polarization exacerbates brain injury by releasing inflammatory mediators, reactive oxygen species (ROS), and proteases, upregulating C-reactive protein (CRP) expression, inducing neuronal excitotoxicity, and damaging the blood-brain barrier (BBB) [33]. Additionally, matrix metalloproteinases (MMPs) further compromise BBB integrity by degrading extracellular matrix (ECM) and tight junction proteins (TJs) [34]. Given the importance of inflammatory responses in ischemic stroke pathology, inflammatory factor concentrations may be key determinants of disease progression and thus have potential as prognostic biomarkers. [**Figure 2: see original paper**] illustrates the key mechanisms of inflammatory factors in predicting disease outcomes after cerebral ischemia.

2.1 C-Reactive Protein (CRP) CRP is a non-glycosylated protein synthesized by hepatocytes that significantly increases during various inflammatory processes, serving as a sensitive marker of inflammation [35]. However, due to limited sensitivity of CRP, detection of high-sensitivity CRP (hs-CRP) is particularly important in clinical practice and has become a key tool for predicting disease progression and prognosis. Pu et al. [36] measured pre-admission serum hs-CRP levels in 119 acute ischemic stroke patients and found that patients with good prognosis had significantly lower median hs-CRP and NIHSS scores than those with poor prognosis ($P<0.001$), indicating that serum hs-CRP levels are closely associated with prognosis in acute ischemic stroke, with higher levels predicting worse outcomes. When the hs-CRP cutoff was set at 11.835 mg/L, sensitivity for predicting 90-day outcomes was 95% and specificity was 92.5% (AUC=0.986), demonstrating the efficacy of hs-CRP in predicting acute ischemic stroke prognosis. Chen et al. [37] further confirmed that admission hs-CRP levels were significantly positively correlated with mortality, recurrence risk, and poor prognosis in ischemic stroke patients. High hs-CRP levels indicate poor prognosis and may increase stroke recurrence and mortality rates. Cheng et al. [38] conducted a retrospective study of 212 acute ischemic stroke patients and found through logistic regression analysis that hs-CRP>1.60 mg/L was negatively correlated with good thrombolytic response (OR=0.496, 95%CI=0.266-0.927, P=0.028). Therefore, hs-CRP>1.6 mg/L can serve as a predictor of poor prognosis in acute ischemic stroke patients receiving intravenous thrombolysis. This finding provides important reference for evaluating thrombolytic efficacy and predicting prognosis. In summary, hs-CRP, as a sensitive inflammatory marker, demonstrates significant value in predicting prognosis in acute ischemic stroke patients and may become an important tool for prognostic assessment and clinical decision-making.

2.2 Matrix Metalloproteinase-9 (MMP-9) MMPs are key regulators of vascular injury after stroke, primarily derived from activated macrophages, astrocytes, and extravasated neutrophils, with the ability to degrade various protein components in the extracellular matrix including collagen, elastin, and fibronectin [34]. Among them, MMP-2, MMP-9, MMP-3, and MMP-12 have been

implicated in BBB damage after stroke [39]. Regarding the role of MMP-9 in ischemic stroke prognosis prediction, Yuan et al. [40] conducted a case-control study including 168 ischemic stroke patients and 40 healthy controls, using enzyme-linked immunosorbent assay (ELISA) to measure plasma MMP-9 concentrations and brain CT or MRI at 3-14 days after stroke onset to diagnose spontaneous hemorrhagic transformation (sHT). The results showed that when MMP-9 concentration >181.7 ng/mL, it demonstrated high sensitivity (82.9%) and specificity (81.3%) for predicting hemorrhagic transformation, with positive predictive value of 48% and negative predictive value of 95.8%. Additional studies have reported that MMP-9 expression levels are significantly positively correlated with stroke severity [41]. Li et al. [42] further found that MMP-9 and brain-derived neurotrophic factor (BDNF) show time-dependent associations in predicting prognosis in acute ischemic stroke patients. Specifically, gradual decrease in MMP-9 levels combined with increasing BDNF levels often predicts better prognosis. Notably, dynamic changes in MMP-9 and BDNF are superior to baseline measurements for predicting outcomes in acute ischemic stroke. In summary, MMP-9 shows significant potential in ischemic stroke prognosis prediction, with its level changes associated with post-stroke BBB damage, hemorrhagic transformation risk, and stroke severity, making it a promising biomarker for acute ischemic stroke prognosis assessment.

2.3 Interleukin-6 (IL-6) IL-6 is an immunomodulatory and chemotactic inflammatory cytokine that plays an important role in post-stroke inflammatory responses [43]. Elevated serum IL-6 concentration after stroke causes neuronal death and BBB disruption, exacerbating brain injury [44]. Multiple studies have shown close associations between IL-6 concentration and stroke severity and prognosis. Shaafi et al. [45] conducted a cross-sectional study of 45 acute ischemic stroke patients, assessing NIHSS and modified Rankin Scale scores on days 1, 5, 90, and 365, and measuring serum IL-6 levels on days 1 and 5 by ELISA. The results showed IL-6 was significantly positively correlated with NIHSS and modified Rankin Scale scores, with higher levels in deceased patients, indicating that higher IL-6 levels predict worse outcomes. Li et al. [46] conducted a prospective study of 180 patients with first-ever acute ischemic stroke and found that IL-6 levels were significantly elevated in the poor prognosis group, identifying IL-6 as an independent risk factor for functional outcome, with higher levels indicating worse prognosis. Additionally, IL-6 can serve as a marker for futile reperfusion after mechanical thrombectomy. Mechtouff et al. [47] performed a cohort study of 164 acute ischemic stroke patients undergoing mechanical thrombectomy (MT), collecting peripheral blood samples before IV thrombolysis, and at 6h, 24h, 48h, and 3 months after admission. Using ELISA kits to detect IL-6, CT scans on day 1, and follow-up MRI on day 6, multivariate analysis showed that high IL-6 levels within 24h of admission (OR=6.15, 95%CI=1.71-22.10) were associated with futile reperfusion. In conclusion, IL-6 has important value in predicting ischemic stroke prognosis, with serum IL-6 levels useful for predicting stroke severity, functional outcomes, and

futile reperfusion after MT.

2.4 Other Inflammatory Factors TNF-α plays a key role in neurotoxic substance generation and local inflammatory responses, and is considered an important indicator for predicting stroke prognosis [48]. Studies have shown that TNF-α levels within 24h of ischemic stroke onset are closely related to infarct size [49]. In patients with lacunar infarction, blood TNF-α levels are independently associated with poor outcomes at 3 months [50]. Additionally, lipoprotein-associated phospholipase A2 (Lp-PLA2), as a vascular-specific inflammatory marker, is considered an independent predictor of ischemic stroke [51]. Research shows that elevated Lp-PLA2 levels are significantly associated with poor functional outcomes at 3 months and 1 year after ischemic stroke [52]. Li et al. [53] further demonstrated that elevated serum Lp-PLA2 levels are significantly correlated with incidence, severity, and recurrence rate of acute ischemic stroke. In summary, TNF-α and Lp-PLA2 have important value in predicting ischemic stroke prognosis and may serve as key biomarkers for clinical diagnosis and assessment, providing new perspectives for prognostic prediction and clinical treatment.

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3. Correlation Between PUFA and Ischemic Stroke Prognosis

Fatty acids are classified as saturated and unsaturated, with unsaturated fatty acids further divided into monounsaturated and polyunsaturated fatty acids (PUFA), including ω-3 and ω-6 types. ω-3 PUFA includes α-linolenic acid (ALA), docosahexaenoic acid (DHA), and eicosapentaenoic acid (EPA). Studies indicate that ω-3 PUFA plays an important role in reducing neurological damage caused by ischemic stroke, providing neuroprotective effects [54], and effectively reducing the risk of ischemic stroke [55]. Lin et al. [56] revealed that ω-3 PUFA inhibits microglial release of TNF-α by suppressing a disintegrin and metalloproteinase 17 (ADAM17) activity, and promotes microglial release of exosomal nerve growth factor while activating the neuroprotective TNF-α/nuclear factor B (NF- B) pathway. These two mechanisms work synergistically to achieve neuronal protection.

Recent advances further confirm the value of ω-3 PUFA in predicting and improving prognosis in ischemic stroke patients. Suda et al. [57] conducted a retrospective study of 281 Japanese patients diagnosed with acute ischemic stroke within 24h of onset and found that early neurological deterioration (END) was negatively correlated with EPA/AA ratio (OR=0.18, P=0.003), DHA/AA ratio (OR=0.045, P=0.001), and (EPA+DHA)/AA ratio (OR=0.45, P=0.002), revealing that low serum ω-3 PUFA/ω-6 PUFA ratio at admission may predict neurological deterioration in acute ischemic stroke. Song et al. [58] performed a prospective study showing that ω-3 PUFA was negatively correlated with admission stroke severity and 3-month poor outcomes, suggesting ω-3 PUFA as a potential blood biomarker for prognosis in acute non-cardiogenic ischemic

stroke patients. Another cross-sectional study also showed EPA was negatively correlated with ischemic stroke prevalence [59]. Shojima et al. [60] further confirmed that low EPA/AA ratio at admission was associated with poor long-term prognosis and increased mortality in ischemic stroke patients. In summary, ω-3 PUFA, as a potential blood biomarker for ischemic stroke prognosis, has important roles in prognosis assessment and treatment, with its concentrations and ratios offering valuable predictive information.

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4. Correlation Between miRNA and Ischemic Stroke Prognosis

miRNAs are non-coding RNAs that play critical roles in gene expression regulation and exhibit important regulatory functions in multiple aspects of acute ischemic stroke pathology, including energy failure, inflammatory responses, and apoptosis [61]. Consequently, miRNAs hold promise as reliable blood biomarkers for risk prediction, precise diagnosis, and prognosis assessment in acute ischemic stroke. Numerous studies have confirmed that many miRNAs are closely associated with the development and clinical course of acute ischemic stroke [62].

4.1 miR-21 miR-21 has been clearly identified as a key factor that effectively inhibits apoptosis and strongly promotes neuronal survival during the initiation and progression of ischemic stroke [63]. Zhou et al. [64] revealed in an oxygen-glucose deprivation (OGD) model that miR-21 significantly inhibited apoptosis in mouse neuroblastoma (N2A) cells after oxygen-glucose deprivation/reperfusion (OGD/R) treatment. Additionally, Yan et al. [65] showed in a middle cerebral artery occlusion (MCAO) mouse model that downregulating miR-21 expression significantly upregulated p53 and Bax expression while downregulating Bcl-2, exacerbating ischemic neuronal injury, demonstrating the central role of the miR-21/p53/Bcl-2/Bax signaling pathway in regulating ischemic injury. Notably, miR-21 expression levels are closely related to prognosis in ischemic stroke patients. Specifically, high miR-21 expression often predicts better prognosis, likely due to its ability to inhibit apoptosis, reduce brain injury, and promote neural tissue repair and regeneration, thereby effectively improving patient outcomes [66]. Yuan et al. [67] further noted that post-stroke cognitive impairment (PSCI) patients had significantly higher miR-21 expression than cognitively normal (PSCN) patients, suggesting that higher serum miR-21 levels at admission correlate with higher risk of post-stroke cognitive impairment. Therefore, miR-21 alone or combined with specific indicators (such as FA values) may serve as an important diagnostic biomarker for distinguishing PSCI from PSCN.

4.2 miR-155 miR-155 is an immune regulatory miRNA that plays a pivotal role in ischemic brain injury by precisely regulating downstream signaling pathways [68]. Studies show that upregulated miR-155 expression can activate inflammatory signaling pathways in macrophages and T lymphocytes (TC), pro-

moting release of inflammatory cytokines such as TNF-α and IL-1β and exacerbating inflammatory responses and brain tissue damage [62,69]. Additionally, miR-155 can regulate NF- B and MAPK signaling pathway activity, profoundly affecting inflammatory mediator release and regulation [70,71]. Notably, knocking down miR-155 expression significantly alleviates inflammatory responses and brain injury after cerebral ischemia [68]. Therefore, miR-155 plays an important role in regulating inflammatory responses and ischemic brain injury, holding promise as a potential prognostic biomarker and novel therapeutic target for ischemic stroke.

Yang et al. [72] found in a transient middle cerebral artery occlusion (tMCAO) mouse model that miR-155-5p expression in choroid plexus epithelium (CPE) was significantly increased after OGD/R treatment, while inhibiting miR-155-5p markedly reduced autophagy levels in mouse brain tissue. Zhang et al. [73] conducted a case-control study of 93 ischemic stroke patients and 70 non-stroke controls, revealing that plasma endothelial microparticles (EMV) and EMVs-miR-155 levels were significantly elevated in acute and subacute phases of ischemic stroke and positively correlated with infarct volume and NIHSS scores. Multivariate logistic regression analysis further identified plasma EMVs and EMVs-miR-155 as important independent risk factors for ischemic stroke. The study also noted that EMVs-miR-155 could serve as a predictor of ischemic stroke occurrence in non-stroke individuals. Chen et al. [74] found that miR-155 expression was elevated in acute ischemic stroke patients and decreased after treatment. ROC curve analysis showed that when miR-155>2.665, sensitivity and specificity for predicting acute ischemic stroke were 77.05% and 65.75%, respectively. Follow-up results showed that recurrent patients had higher miR-155 expression than non-recurrent patients, and when miR-155>2.630, sensitivity and specificity for predicting recurrence were 88.89% and 69.77%, respectively. Therefore, serum miR-155 has good predictive value for both onset and prognosis of acute ischemic stroke.

4.3 miR-126 miR-126 is an endothelial cell-specific miRNA involved in regulating angiogenesis. Under cerebral hypoxic conditions, miR-126 effectively inhibits ischemia-hypoxia-induced oxidative stress and inflammatory responses by regulating endothelial cell function [61,63]. miR-126 reduces BBB disruption by inhibiting MMPs expression and preventing degradation of junction proteins (such as zonula occludens-1, claudin-5, and occludin) [75]. Additionally, upregulating miR-126 expression can stimulate vascular endothelial growth factor (VEGF) and PI3K/Akt signaling pathways, promoting angiogenesis and neural repair [75,76].

miR-126 expression levels in ischemic stroke are closely related to infarct size, disease severity, and prognosis. Specifically, upregulated miR-126 expression promotes neurovascular repair and regeneration, making it a positive prognostic factor for ischemic stroke. Pan et al. [77] established a cerebral ischemia-reperfusion (MCAO) mouse model and confirmed that miR-126-3p/miR-126-5p

significantly reduced ischemic stroke volume, alleviated brain edema, decreased tight junction protein degradation and IgG leakage, and markedly improved prognosis in mice with ischemic stroke. Furthermore, upregulated miR-126-3p and miR-126-5p expression inhibited pro-inflammatory cytokine expression such as IL-1β, TNF-α, and adhesion molecules [74]. These results suggest miR-126 may play roles in angiogenesis and neuroprotection, thereby reducing brain injury and improving prognosis. Other studies have shown that plasma miR-126 levels are lower in acute ischemic stroke patients than in controls and negatively correlated with NIHSS scores and TNF-α, IL-1β, and IL-6 levels, suggesting that higher plasma miR-126 levels indicate lower disease risk, less severity, and better prognosis [78]. Additionally, Qi et al. [79] found that miR-126 expression levels correlate with neurological function, self-care ability, and prognosis in ACI patients, holding important value for predicting patient outcomes.

miRNAs play key regulatory roles in cell differentiation, biological development, and disease processes. Currently, more than 2,000 human miRNAs have been annotated in databases [80]. In addition to miR-21, miR-155, and miR-126, many other miRNAs are closely associated with ischemic stroke prognosis [60,62,66]. For example, the neuroprotective role of miR-124 in cerebral ischemia injury has been extensively studied and recognized. Research shows miR-124 can effectively promote neuronal survival and regeneration by regulating inflammatory responses and apoptosis, playing important neuroprotective roles after stroke. Additionally, studies have found miR-223 has significant effects in regulating inflammatory responses and reducing brain injury, with high expression levels closely associated with better functional outcomes. Furthermore, miR-181 family members play important roles in cell death and inflammatory responses after cerebral ischemia. Specifically, inhibiting miR-181a expression significantly reduces brain injury and improves neurological function, demonstrating its great potential in post-stroke neuroprotection. Similarly, miR-30d exerts protective effects after cerebral ischemia by regulating autophagy-related gene expression, with high expression levels closely associated with better prognosis. In conclusion, multiple miRNAs play vital roles in the pathophysiological processes of ischemic stroke and are closely related to patient prognosis. In-depth investigation of these miRNAs' mechanisms and regulatory networks may provide novel biomarkers and therapeutic targets for precise diagnosis, effective treatment, and prognostic assessment of stroke.

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5. Correlation Between Exosomes and Ischemic Stroke Prognosis

Exosomes are membrane-bound vesicles 30-150 nm in diameter secreted by various cells through exocytosis, carrying bioactive molecules including proteins, lipids, RNA, and DNA. Exosomes enter target cells by binding to receptors on the target cell membrane or through endocytosis, thereby playing central roles in intercellular signal transduction and material exchange, profoundly influencing numerous physiological and pathological processes including immune

regulation, apoptosis, angiogenesis, and neural repair [81]. In the pathological process of ischemic stroke, exosomes exhibit multiple mechanisms: carrying anti-inflammatory factors to alleviate inflammation induced by ischemic stroke, promoting neural protection and repair in damaged areas; transporting neurotrophic factors (such as BDNF and nerve growth factor) to assist neuronal survival and axonal regeneration; delivering antioxidant enzymes and heat shock proteins to effectively relieve oxidative stress induced by ischemia-reperfusion; and strengthening BBB integrity to reduce brain edema and secondary injury after ischemic stroke [82-83].

In recent years, research on exosomes in ischemic stroke prognosis assessment has attracted increasing attention [84]. Multiple studies have revealed that specific miRNAs in exosomes (such as miR-124, miR-21) are closely associated with prognosis in ischemic stroke patients [85]. These miRNAs significantly influence neurological recovery by finely regulating inflammatory responses and apoptosis. Specifically, miR-21 improves post-stroke neurological function by inhibiting apoptosis and promoting neuronal survival [63], while miR-124 plays a key role in neuroprotection and regeneration, helping reduce tissue damage caused by ischemic stroke [86]. Additionally, protein markers carried by exosomes, such as heat shock protein 70 (HSP70) and tissue plasminogen activator (tPA), are also considered potential biomarkers for predicting ischemic stroke prognosis [87]. These proteins play important roles in neuroprotection and repair. Studies have found that HSP70 in exosomes reduces cell damage caused by ischemia-reperfusion through anti-inflammatory and anti-oxidative mechanisms, while tPA effectively alleviates ischemic stroke severity by dissolving thrombi and restoring blood flow [88]. [**Figure 3: see original paper**] illustrates the mechanisms of miRNA and exosomes in predicting cerebral infarction prognosis.

Despite the tremendous potential of exosomes as prognostic biomarkers for ischemic stroke, their clinical translation faces several challenges. The primary issue is significant interindividual variability in exosome composition and function, which challenges their reliability as uniform biomarkers. Secondly, the long-term effects and safety of exosomes in humans have not been fully elucidated, limiting their clinical feasibility and effectiveness. Finally, exosome extraction, purification, and detection technologies lack standardization, hindering their widespread clinical application. Therefore, future research should focus on developing standardized technologies, exploring mechanisms of action, and conducting large-scale clinical validation to effectively apply this emerging biomarker in ischemic stroke prognostic assessment and treatment strategies, ultimately improving patient outcomes and quality of life.

This review has summarized the importance and potential mechanisms of various biomarkers in ischemic stroke prognostic assessment, including hematological indices, cytokines (IL-6, TNF-α, and Lp-PLA2), ω-3 PUFA, miRNAs (miR-21, miR-155, and miR-126), and exosomes. Blood cell analysis, as a routine clinical test, provides crucial information for prognosis judgment due to its rapid and convenient nature. Inflammatory cytokines IL-6, TNF-α, and

Lp-PLA2 significantly influence ischemic stroke prognosis by regulating inflammatory responses. Notably, hematological indices such as RDW are also associated with ischemic stroke prognosis, with elevated baseline RDW correlating with increased recurrent stroke risk and inversely associated with time to recurrence. Additionally, ω-3 PUFA demonstrates important value in predicting and improving prognosis, while specific miRNAs play key roles by regulating apoptosis, inflammatory responses, and angiogenesis. Exosomes, as a research hotspot in recent years, show great potential in stroke prognosis assessment through their carried miRNAs and proteins.

Although current research has preliminarily revealed the application prospects of these biomarkers, their clinical promotion still faces numerous challenges. For each marker, this review elaborates on its clinical advantages and limitations, and points out that future research should focus on: first, developing standardized extraction and analysis techniques to ensure consistent and reliable results; second, deeply investigating the specific roles of exosomes and miRNAs in stroke pathology and repair mechanisms; third, conducting large-scale, rigorously designed preclinical and clinical studies (including cross-sectional, case-control, cohort, and randomized controlled trials) with clear specification of sample types, sample sizes, ethnic distributions, and collection methods to validate the application effects and reliability of these biomarkers in different patient populations; and finally, systematically evaluating their long-term effects and safety in vivo to provide solid scientific evidence for clinical application. Through further in-depth research and clinical validation, these biomarkers are expected to play more precise roles in stroke prognosis assessment and treatment, advancing the development of personalized diagnosis and treatment strategies. In particular, if these biomarkers are established, specific application strategies in disease assessment and therapeutic target selection should be strengthened to significantly improve stroke patient outcomes, enhance quality of life, and reduce economic burden on families and society.

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Note: Figure translations are in progress. See original paper for figures.