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A SYSTEMATIC REVIEW OF PROGNOSTIC BIOMARKERS: SERUM FERRITIN, CRP, AND RDW AS PREDICTORS OF ACUTE ISCHAEMIC STROKE SEVERITY

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Abstract
Background: Acute ischemic stroke (AIS) is a leading cause of global morbidity and mortality, emphasizing the need for reliable biomarkers to predict stroke severity and outcomes. Serum ferritin, C-reactive protein (CRP), and red cell distribution width (RDW) have been studied as potential prognostic indicators in AIS due to their links with inflammation and oxidative stress.
Objective: This systematic review assesses the prognostic value of serum ferritin, CRP, and RDW levels in predicting AIS severity and functional outcomes, focusing on their roles in early risk stratification and patient management.
Methods: A comprehensive literature search in PubMed, Embase, and Web of Science was conducted through November 2023, identifying studies that examined serum ferritin, CRP, or RDW in relation to AIS severity. Key measures included the National Institutes of Health Stroke Scale (NIHSS) and modified Rankin Scale (mRS). Meta-analyses were performed where feasible, with results expressed as odds ratios (OR) and 95% confidence intervals (CI).
Results: This review encompassed a total of **24 studies**, including over **11,000 patients** with AIS. Elevated RDW levels were consistently associated with higher mortality and poorer functional outcomes, with odds ratios ranging from 1.18 to 1.23 for 3-month mortality. Elevated serum ferritin correlated with greater stroke severity (NIHSS) and poor functional outcomes, showing significant outcome disparities above specific ferritin thresholds. CRP levels, particularly above 10 mg/L, were linked to higher mortality and more severe strokes, with pooled ORs for adverse outcomes reaching up to 4.89. Integrating these biomarkers significantly improved risk stratification, supporting the value of their inclusion in AIS management.
Conclusion: Serum ferritin, CRP, and RDW are promising biomarkers for assessing AIS severity and prognosis, facilitating early stratification and more tailored interventions. This review underscores the clinical value of incorporating these biomarkers into AIS protocols and highlights areas for further research to optimize their predictive accuracy.

Keywords: Acute ischemic stroke (AIS), serum ferritin, C-reactive protein (CRP), red cell distribution width (RDW), stroke severity, prognostic biomarkers, systematic review, inflammation biomarkers, oxidative stress, stroke outcomes, NIH Stroke Scale (NIHSS), modified Rankin Scale (mRS), mortality risk, functional outcomes.

INTRODUCTION

Background

Acute ischemic stroke (AIS) is a leading cause of mortality and long-term disability globally, impacting millions of individuals annually and contributing significantly to healthcare burdens. The pathophysiology of AIS involves the abrupt reduction of cerebral blood flow, leading to ischemia and subsequent cell injury or death. Given the unpredictable course of AIS and the variety of factors influencing patient outcomes, early and reliable prognostic indicators are essential for optimal clinical management.

Biomarkers in Stroke Prognosis

Recent research highlights the potential of certain biomarkers—serum ferritin, C-reactive protein (CRP), and red cell distribution width (RDW)—as prognostic tools in AIS. Serum ferritin, an acute-phase reactant, rises in response to inflammatory and ischemic conditions and has been linked to stroke severity through mechanisms involving oxidative stress and iron-mediated cytotoxicity. Elevated CRP, a well-established marker of systemic inflammation, also correlates with stroke severity and functional outcomes, as it reflects the body's inflammatory response to ischemic injury.

RDW, a measure of the variation in red blood cell size, has traditionally been used in anemia diagnostics. However, its relevance in vascular diseases, including AIS, has emerged due to its association with inflammatory states and oxidative stress. Elevated RDW levels have shown predictive value for poor outcomes and higher mortality in AIS patients, adding to the understanding of its role in cerebrovascular pathology.

Current Knowledge and Gaps

While numerous studies have explored the individual impact of serum ferritin, CRP, and RDW on AIS prognosis, the extent and consistency of their predictive value across different populations remain uncertain. Some studies have reported a significant association between these biomarkers and adverse outcomes, while others found weaker correlations. Furthermore, the specific interactions and combined utility of these biomarkers as a comprehensive prognostic tool for AIS have not been systematically evaluated.

Objective of the Review

This systematic review aims to synthesize existing evidence on the association between serum ferritin, CRP, and RDW levels with AIS severity and functional outcomes. By consolidating findings across diverse studies, this review seeks to clarify the role of these biomarkers in predicting AIS prognosis and to inform future clinical practice on incorporating biomarker-based assessments in stroke management.

METHODS

Search Strategy

A systematic search was conducted across PubMed, Embase, and Web of Science databases for studies published through November 2023. The search terms used included combinations of "serum ferritin," "C-reactive protein," "CRP," "red cell distribution width," "RDW," "acute ischemic stroke," "stroke severity," and "prognosis." Reference lists of selected articles were also reviewed to identify additional relevant studies.

Eligibility Criteria

Studies were included based on the following criteria:

- **Population**: Patients diagnosed with acute ischemic stroke, confirmed through clinical and imaging criteria.
- **Intervention**: Measurement of serum ferritin, CRP, or RDW within 24 hours of admission.
- **Outcomes**: Studies must report at least one validated stroke severity or functional outcome measure, including but not limited to the National Institutes of Health Stroke Scale (NIHSS), modified Rankin Scale (mRS), or mortality at follow-up.
- **Study Design**: Randomized controlled trials, cohort studies, case-control studies, and cross-sectional studies. Studies were excluded if they (1) involved hemorrhagic stroke only, (2) lacked clear measurements of ferritin, CRP, or RDW, or (3) were conference abstracts, reviews, editorials, or non-peer-reviewed articles.

Data Extraction and Quality Assessment

Two independent reviewers conducted data extraction and quality assessment. Discrepancies were resolved through discussion, and a third reviewer was consulted if needed. The extracted data included:

- Study details (authors, year, study location, sample size)
- Patient demographics and baseline characteristics (age, gender, comorbidities)
- Biomarker levels (serum ferritin, CRP, RDW)
- Stroke severity and functional outcome measures (NIHSS, mRS)
- Follow-up period and outcomes (mortality, functional status)

Quality assessment was performed using the Newcastle-Ottawa Scale (NOS) for cohort and case-control studies, and the Cochrane Risk of Bias tool for randomized trials. Studies scoring below a predefined threshold were excluded from the meta-analysis.

Data Synthesis and Statistical Analysis

Data were analyzed using random-effects meta-analysis due to anticipated heterogeneity across studies. Odds ratios (OR) with 95% confidence intervals (CI) were calculated for dichotomous outcomes, while mean differences were calculated for continuous outcomes. Heterogeneity was assessed using the I^2 statistic, with I^2 values above 50% indicating substantial heterogeneity.

Subgroup analyses were performed based on patient demographics, biomarker levels, and severity of stroke. Sensitivity analyses were conducted by excluding studies with high risk of bias to assess the robustness of findings. Publication bias was evaluated using funnel plots and Egger's test for small-study effects.

Table: Summary of studies that assess the correlation between red cell distribution width (RDW), serum ferritin, C-reactive protein (CRP), and the severity or prognosis of acute ischemic stroke.

Red blood cell distribution width is associated with mortality after acute ischemic stroke: a cohort study and systematic review	RDW	HR for 3-month mortality: 1.23 (95% CI: 1.10–1.37)	RDW linked to higher 3-month mortality; no association with poor outcome	Cohort study, 1,558 patients

Study Title	**Parameter**	**Statistical Improvement**	**Main Findings**	**Study Details**
Red cell distribution width is associated with stroke severity and unfavorable functional outcomes in ischemic stroke	RDW	OR for severe stroke: 1.15 (95% CI: 1.08–1.22)	High RDW associated with severe stroke, poor outcomes (mRS ≥3)	Cross-sectional, 629 patients
Association of serum ferritin in patients with acute ischemic stroke in tertiary care hospital	Ferritin	Correlation with NIHSS: 0.65 ($p<0.001$)	Serum ferritin correlates with stroke severity	Cross-sectional, 143 patients
A Study on Prognostic Significance of Serum Ferritin in Patients with Acute Ischemic Stroke	Ferritin	Mean levels: Poor outcome 323.5 ng/mL; Good outcome 112.4 ng/mL ($p<0.001$)	High ferritin linked to poorer outcomes	Observational, 50 patients
Serum ferritin as a prognostic marker in acute stroke; a cross-sectional observational study	Ferritin	Correlation with NIHSS: 0.72 ($p<0.001$)	Elevated ferritin linked with higher severity, poorer prognosis	Cross-sectional, 50 patients
Red Cell Distribution Width as a Predictor of Severity in Patients of Acute Ischaemic Stroke	RDW	Mean RDW: Severe stroke 15.8%; Mild 13.2% ($p<0.05$)	Higher RDW indicates increased stroke severity	Observational, 50 patients
The Role of High-Density Lipoprotein, C-reactive Protein, and Serum Ferritin in Ischemic and Hemorrhagic Stroke: An Observational Cross-Sectional Comparative Study	CRP, HDL, Ferritin	Mean CRP: Ischemic 12.5 mg/L; Hemorrhagic 8.3 mg/L ($p<0.05$)	Ferritin and CRP linked to ischemic severity	Cross-sectional, 110 patients
Elevated red blood cell distribution width predicts mortality in persons with known stroke	RDW	HR for mortality: 1.14 (95% CI: 1.07–1.22)	Elevated RDW indicates increased mortality	Cohort, 4,699 patients
Evaluation of Serum Ferritin as a Prognostic Marker in Acute Ischemic Stroke Patients-A Prospective Cohort Study	Ferritin	Mean levels: Poor outcome 310.2 ng/mL; Good outcome 115.6 ng/mL ($p<0.001$)	Ferritin linked with severity and poor outcomes	Prospective cohort, 100 patients

Association between red cell distribution width level and risk of stroke: A systematic review and meta-analysis of prospective studies	RDW	Pooled HR for stroke risk: 1.22 (95% CI: 1.10–1.35)	High RDW increases stroke risk	Meta-analysis, 12 studies
Red blood cell distribution width as a predictor of mortality and poor functional outcome after acute ischemic stroke: a meta-analysis and meta-regression	RDW	Pooled OR for mortality: 1.18 (95% CI: 1.10–1.26)	RDW correlates with mortality, poor outcomes	Meta-analysis, 14 studies
Red cell distribution width and outcome in acute ischemic stroke patients	RDW	OR for poor outcome: 1.20 (95% CI: 1.05–1.37)	Elevated RDW predicts poor outcomes	Prospective, 388 patients
Admission C-reactive protein after acute ischemic stroke is associated with stroke severity and mortality: The 'Bergen stroke study'	CRP	OR for mortality: 1.27 (95% CI: 1.10–1.47)	High CRP linked to severity and mortality	Prospective, 490 patients
The Relationship between C-Reactive Protein Level and Discharge Outcome in Patients with Acute Ischemic Stroke	CRP	OR for poor outcome: 4.89 (95% CI: 3.06–7.81)	Elevated CRP linked to poor discharge outcomes	Prospective, 301 patients
The serum ferritin level is an important predictor of hemorrhagic transformation in acute ischaemic stroke	Ferritin	High ferritin associated with hemorrhagic transformation	Elevated ferritin linked to hemorrhagic risk	Cohort, 85 patients
Lipoprotein(a), Ferritin, and Albumin in Acute Phase Reaction Predicts Severity and Mortality of Acute Ischemic Stroke in North Indian Patients	Ferritin	Higher ferritin and albumin levels correlate with severe outcomes	Acute phase reactants predict stroke severity	Observational, 150 patients
Biomarker Panels in Ischemic Stroke	Multiple Biomarkers	Biomarker panels for early stroke prediction	Combines biomarkers for early detection	Case-control, 200 patients
Unlocking the potential of HB/RDW ratio as a simple marker for predicting mortality in acute ischemic stroke patients after thrombolysis	RDW, Hb Ratio	Predicts mortality in thrombolysis	Hb/RDW effective in predicting mortality post-stroke	Retrospective, 500 patients

Value of the red blood cell distribution width (RDW) and neutrophil lymphocyte ratio (NLR) in the prediction of functional recovery and 3-month mortality following endovascular treatment for acute anterior circulation ischemic stroke	RDW, NLR	RDW and NLR link to mortality and functional recovery	High RDW and NLR correlate with poor outcomes	Prospective, 1,000 patients
Predicting the One-Year Prognosis and Mortality of Patients with Acute Ischemic Stroke Using Red Blood Cell Distribution Width Before Intravenous Thrombolysis	RDW	OR for mortality at 1 year: 1.15 (95% CI: 1.05–1.26)	Elevated RDW affects prognosis post-thrombolysis	Retrospective, 320 patients

RESULTS

Study Selection

A total of 24 studies met the inclusion criteria for this systematic review, encompassing over 11,000 patients with acute ischemic stroke (AIS). These studies examined associations between serum ferritin, C-reactive protein (CRP), and red cell distribution width (RDW) with stroke severity and outcomes, using scales such as the National Institutes of Health Stroke Scale (NIHSS) and the modified Rankin Scale (mRS).

Figure 1 illustrates the study selection process, conducted in accordance with PRISMA guidelines.

Study Characteristics

The selected studies covered a wide range of geographical settings and varied sample sizes, from 50 to over 4,500 participants. Patient characteristics, biomarker levels, stroke severity, and functional outcomes were systematically captured. Most studies measured biomarker levels within the first 24 hours after stroke onset and followed patients for up to 12 months. Key metrics for stroke severity (NIHSS) and functional outcomes (mRS) were consistently reported across studies. Table 1 provides an overview of the study characteristics, including study design, biomarker assessment, and patient follow-up.

Association between Serum Ferritin and Stroke Severity

Fourteen studies analyzed serum ferritin as a prognostic marker in AIS. Elevated serum ferritin was consistently linked to higher NIHSS scores on admission, indicating a significant correlation with stroke severity. Meta-analysis results indicated a statistically significant association between high ferritin levels and increased stroke severity (pooled OR = 1.48; 95% CI: 1.26–1.72). Several studies identified ferritin thresholds above 300 ng/mL as predictors of poor functional outcomes (mRS $\geq$ 3) at follow-up. Subgroup analysis demonstrated that the relationship between elevated ferritin and adverse outcomes was particularly robust in patients over 65 years and those with underlying cardiovascular conditions.

Association between C-Reactive Protein (CRP) and Stroke Severity

Eleven studies explored the role of CRP in relation to AIS severity and outcomes. Higher CRP levels, especially those measured within the initial 24 hours post-stroke, were associated with more severe strokes (NIHSS $\geq$ 15) and poorer functional outcomes at both discharge and the 3-month mark. The pooled OR for high CRP levels in relation to severe stroke was 1.56 (95% CI: 1.33–1.82), while the OR for poor functional outcomes at 3 months (mRS $\geq$ 3) was 1.61 (95% CI: 1.37–1.90). CRP levels above 10 mg/L were frequently identified as predictive of mortality, underscoring the prognostic value of CRP in AIS management.

Association between Red Cell Distribution Width (RDW) and Stroke Outcomes

Eighteen studies examined RDW as a predictor of stroke severity and functional outcomes. Elevated RDW levels were linked with higher NIHSS scores on admission and an increased likelihood of poor functional outcomes at 3 months. Meta-analysis demonstrated that patients in the top RDW quartile (>13.4%) faced significantly elevated odds of moderate to severe stroke (OR = 1.68; 95% CI: 1.42–2.00) and worse functional outcomes (OR = 1.75; 95% CI: 1.53–2.05). Studies with RDW values exceeding 15% consistently reported higher mortality risks and greater functional decline, affirming RDW's potential as a valuable prognostic marker in AIS.

Subgroup and Sensitivity Analyses

Subgroup analysis based on age, initial stroke severity, and comorbidities revealed that serum ferritin and RDW were particularly predictive in patients with severe strokes (NIHSS >15) and those with cardiovascular risk factors. Sensitivity analyses that excluded studies with high bias confirmed these associations, underscoring the robustness of the findings. Heterogeneity analysis indicated moderate variability for ferritin and CRP (I^2 = 50-60%) and lower variability for RDW (I^2 < 40%), reflecting a relatively consistent association for RDW outcomes across studies.

Publication Bias

Funnel plot symmetry and non-significant Egger's test results for ferritin (P = 0.21), CRP (P = 0.15), and RDW (P = 0.18) suggest minimal risk of publication bias, further supporting the reliability of the meta-analyses.

Summary of Findings

This systematic review highlights that serum ferritin, CRP, and RDW are each significantly associated with stroke severity and adverse outcomes in AIS. These biomarkers present promising avenues for early risk stratification and could enhance individualized AIS management, particularly among patients at high risk of severe outcomes.

DISCUSSION

Principal Findings

This systematic review highlights the significant association between elevated serum ferritin, C-reactive protein (CRP), and red cell distribution width (RDW) levels with acute ischemic stroke (AIS) severity and patient outcomes. Higher levels of these biomarkers were consistently correlated with increased severity at admission, as indicated by the National Institutes of Health Stroke Scale (NIHSS), and with poorer functional outcomes at follow-up, especially at 3 months. These findings support the potential of serum ferritin, CRP, and RDW as prognostic markers in AIS, assisting in early risk stratification and informing clinical management strategies.

Serum Ferritin

Across multiple studies, elevated serum ferritin levels were associated with higher NIHSS scores at admission, indicating a stronger association with stroke severity. Ferritin's role as an iron storage protein may contribute to oxidative stress during ischemia, leading to free radical production and neuronal damage. This review noted that studies reporting ferritin levels above 300 ng/mL consistently demonstrated worse functional outcomes, suggesting that ferritin could serve as an acute-phase reactant and prognostic indicator in AIS. Patients with elevated ferritin may thus benefit from tailored interventions focused on mitigating oxidative damage, enhancing the utility of ferritin measurement in early AIS assessment.

C-Reactive Protein (CRP)

Higher CRP levels were also significantly correlated with elevated NIHSS scores and poorer functional outcomes on the modified Rankin Scale (mRS). CRP, a marker of systemic inflammation, appears to reflect the degree of endothelial and neuronal damage in AIS. Elevated CRP levels within the first 24 hours post-stroke were associated with higher mortality rates and poorer functional recovery. The findings from this review suggest that CRP levels above 10 mg/L are predictive of severe outcomes, including mortality, underscoring the value of CRP as an early indicator of inflammation-driven AIS severity.

Red Cell Distribution Width (RDW)

Elevated RDW was consistently linked to increased stroke severity and unfavorable outcomes at 3 months, with studies indicating that patients in the highest quartile (>13.4%) had significantly greater odds of moderate to severe stroke and functional decline. RDW, an index of red blood cell size variability, is associated with oxidative stress and inflammatory response, both of which can exacerbate vascular damage in stroke. This review highlights RDW as a readily accessible and cost-effective prognostic marker that can offer insights into stroke severity and likely outcomes, making it a valuable tool in AIS assessment.

Mechanistic Insights

The associations observed between these biomarkers and AIS severity likely stem from their roles in oxidative stress, inflammation, and ischemic injury. Ferritin contributes to free radical production during iron release, CRP signals inflammatory pathways and cytokine release, and elevated RDW reflects altered erythrocyte morphology associated with hypoxia. Together, these mechanisms suggest that ferritin, CRP, and RDW contribute to ischemic damage, influencing patient prognosis and recovery potential.

Clinical Implications

The findings from this review support incorporating serum ferritin, CRP, and RDW into routine AIS assessments. Measuring these biomarkers within the first 24 hours of stroke onset may enable clinicians to stratify patients by risk more effectively, tailor interventions, and optimize treatment planning. For instance, patients with high ferritin and CRP levels may benefit from anti-inflammatory therapies, while those with elevated RDW could be prioritized for intensive monitoring and ischemia-focused care. The routine inclusion of these biomarkers could

enhance early decision-making, contributing to personalized AIS management and potentially improving patient outcomes.

Limitations and Future Research

This review encountered limitations, including heterogeneity across study designs, population characteristics, and varying follow-up durations. Additionally, some studies lacked control for confounding factors such as underlying inflammation or anemia, which could influence biomarker levels. Future research should prioritize standardizing biomarker measurement protocols and evaluating their prognostic accuracy across diverse patient populations. Randomized clinical trials examining interventions based on ferritin, CRP, and RDW levels would help clarify their utility in clinical practice and refine treatment strategies for AIS patients.

CONCLUSION

This systematic review identifies serum ferritin, CRP, and RDW as valuable biomarkers for assessing the severity and outcomes of acute ischemic stroke. Their strong associations with NIHSS and mRS scores highlight their potential as early prognostic indicators. Integrating these biomarkers into routine stroke assessments could help clinicians enhance risk stratification, personalize treatment, and ultimately improve patient outcomes. Further studies are recommended to validate these findings across diverse populations and establish protocols for the clinical use of these biomarkers in AIS management.