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Review

Elevated Neutrophil Lymphocyte Ratio as a Prognostic Biomarker for Stroke: A Review

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Abstract

Stroke remains a leading cause of morbidity and mortality worldwide, with inflammation playing a crucial role in its pathophysiology and prognosis. The neutrophil-lymphocyte ratio (NLR), a readily available and cost-effective biomarker, has emerged as a potential predictor of short-term mortality in stroke patients. This review explores the role of NLR in stroke, its underlying mechanisms, its prognostic significance, and its potential application in clinical practice.

Moreover, NLR has been shown to predict functional impairment at 90 days post-stroke. This biomarker's simplicity, cost-effectiveness, and easy accessibility make it an attractive tool for early risk stratification in stroke patients. However, variability in NLR cutoff values and the influence of confounding factors highlight the need for further research. Standardized NLR thresholds and prospective studies are essential to establish its utility in clinical decision-making. This review also explores the potential for therapeutic interventions aimed at modulating NLR as a means to improve stroke outcomes.

Keywords: Neutrophil-to-lymphocyte ratio (NLR), Stroke, Prognostic biomarker, Inflammation, Stroke severity, Short-term mortality.

INTRODUCTION

Stroke or Cerebrovascular accident is the sudden onset of the neurological deficit. It is the third leading cause of death and a major cause of disability worldwide. The global incidence of stroke has increased over the last few decades, with the most common subtype being ischemic stroke[1, 2]. Studies have therefore assessed the ability of various biological markers to predict stroke prognosis. Inflammatory markers have been reported to be

predictors of stroke[3, 4, 5]. Inflammation occurs when stagnant blood flow due to ischemic or hemorrhagic lesions results in the release and accumulation of pro-inflammatory mediators, which lead to the migration of neutrophils to the area of stroke. A decrease in lymphocyte count occurs due to lymphocyte adhesion to endothelial cells during inflammation and also due to lymphocyte migration to inflamed tissues which plays an essential role in the pathogenesis of brain damage [6]. Various types of inflammatory cells, including neutrophils, lymphocytes and monocytes are recruited to ischemic brain tissues, where they produce several types of inflammatory mediators. Both proinflammatory and anti-inflammatory mediators are involved in pathogenesis of ischemic stroke, an imbalance of which leads to inflammation. Thus, the combined increase in neutrophils and decrease in lymphocytes during inflammation manifests as an increased neutrophil-to-lymphocyte ratio (NLR)[7]. NLR is an emerging biomarker for assessing the systemic inflammatory status of an individual, as NLR is an easy and cost-effective investigation[8].

Pathophysiological Basis of NLR in Stroke

Inflammation and Stroke

Inflammation is a key contributor to both ischemic and hemorrhagic stroke. The acute phase of stroke triggers an immune response characterized by the activation of neutrophils and suppression of lymphocytes. This imbalance reflects systemic inflammation and immune dysregulation, which may contribute to neuronal injury and worsen clinical outcomes.

Neutrophils and Stroke

Neutrophils play a critical role in stroke pathophysiology by:

- Releasing reactive oxygen species (ROS) that contribute to oxidative stress.
- Promoting the breakdown of the blood-brain barrier (BBB) through matrix metalloproteinase (MMP) activation.
- Inducing neuronal apoptosis and ischemic injury.

Lymphocytes and Stroke

Lymphocytes, particularly regulatory T-cells, play a protective role in stroke by modulating the inflammatory response. A decrease in lymphocyte count suggests immune suppression, which has been associated with poor prognosis in stroke patients.

NLR as an Inflammatory Marker

NLR represents the balance between pro-inflammatory (neutrophils) and anti-inflammatory (lymphocytes) responses. A high NLR indicates an excessive inflammatory state, which has been linked to:

- Larger infarct size in ischemic stroke.
- Increased risk of hemorrhagic transformation.
- Higher short-term mortality rates.

Clinical Evidence of NLR in Stroke Prognosis

Several studies have investigated the prognostic value of NLR in stroke, with consistent findings across different populations:

1. NLR and Stroke Severity
    - High NLR levels on admission have been correlated with greater stroke severity, as assessed by the National Institutes of Health Stroke Scale (NIHSS).
    - Patients with severe strokes (NIHSS > 10) tend to have higher NLR values than those with milder strokes[6].
2. NLR and Short-Term Mortality
    - A meta-analysis of multiple studies suggests that an elevated NLR is significantly associated with increased in-hospital and 30-day mortality in stroke patients.
    - Higher NLR values have been linked to increased rates of complications, including pneumonia and sepsis, which further contribute to mortality[7].

3. NLR and Functional Outcomes

- Studies have demonstrated that stroke patients with high NLR values have worse functional outcomes at 90 days, as measured by the modified Rankin Scale (mRS).
- Patients with an NLR above a certain threshold (>5) have a significantly higher likelihood of poor recovery[8].

Potential Clinical Applications of NLR in Stroke

Given its prognostic value, NLR may have various applications in clinical practice:

1. **Early Risk Stratification** – NLR could be used as an early biomarker to identify high-risk stroke patients and guide treatment decisions.
2. **Therapeutic Targeting** – Modulating the inflammatory response to reduce NLR may improve stroke outcomes. Anti-inflammatory therapies targeting neutrophil activation are under investigation.
3. **Resource Allocation** – Patients with high NLR may require more intensive monitoring and early rehabilitation efforts.

Limitations and Future Directions

While NLR is a promising biomarker, several challenges remain:

- **Variability in NLR Cutoff Values**: Different studies use different NLR thresholds, making standardization difficult.
- **Confounding Factors**: Other inflammatory conditions, infections, and medications may influence NLR levels.
- **Need for Prospective Studies:** Large, multicenter prospective studies are required to validate NLR's predictive value in stroke outcomes.

Future research should focus on integrating NLR into stroke risk models, exploring its role in therapeutic interventions, and investigating its dynamic changes over time.

CONCLUSION

NLR is an emerging biomarker that provides valuable prognostic information in stroke patients. Its association with stroke severity, short-term mortality, and functional outcomes makes it a potential tool for risk stratification and clinical decision-making. However, further research is needed to establish standardized cutoff values and to explore its role in targeted therapeutic strategies.

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