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The Correlation and Predictive Value of Hematological Inflammatory Indices in Diabetic Retinopathy: A Commentary

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About the Study

Diabetic Retinopathy (DR), a leading cause of blindness in diabetic populations, necessitates early detection strategies beyond conventional fundus photography. This review synthesizes evidence on hematological inflammatory indices as potential biomarkers for DR screening. The Neutrophil-to-lymphocyte Ratio (NLR) emerges as the most consistent independent risk factor, with composite indices like SII and SIRI showing diagnostic value. Pathophysiologically, these indices reflect systemic inflammation driven by neutrophil-mediated vascular damage, monocyte-induced insulin resistance, and platelet-leukocyte interactions. While NLR correlates strongly with proliferative DR, PLR/SII demonstrate utility in non-proliferative stages. Current limitations include lack of standardized cut-offs and susceptibility to transient confounders. Future research should prioritize multicenter validation and integration with glycemic/hemodynamic parameters to enhance predictive models.

Diabetic Retinopathy (DR), a prevalent microvascular complication of Diabetes Mellitus (DM), has emerged as the primary cause of blindness and irreversible visual impairment in diabetic populations worldwide. The asymptomatic nature of early-stage DR underscores the critical importance of timely screening and intervention in disease management. Current clinical practice relies predominantly on fundus photography-based screening, which necessitates specialist interpretation by ophthalmologists [1]. This approach poses substantial challenges to healthcare systems, particularly given the overwhelming prevalence of DR affecting more than one million patients globally [2]. To address this disparity, there is an urgent need to identify cost-effective and scalable biomarkers that can facilitate early diagnosis and mitigate disease progression.

The pathophysiology of DR is characterized by multifactorial mechanisms, with chronic inflammation recognized as a central driver of disease initiation and advancement [3-5]. This inflammatory inflammatory cascade triggers leukocyte activation and cytokine-mediated endothelial dysfunction, ultimately leading to retinal capillary degeneration. Notably, hematological inflammatory indices derived from routine Complete Blood Count (CBC) tests provide a quantifiable proxy for systemic inflammation. Their non-invasive accessibility and clinical feasibility have positioned these biomarkers as promising candidates for large-scale DR screening programs, a hypothesis that has gained substantial traction in recent translational research

Association between Hematological Inflammatory Indices and DR

Emerging evidence underscores the pathophysiological connection between systemic inflammation and Diabetic Retinopathy (DR), with hematological inflammatory indices serving as clinically accessible proxies for this relationship. Among the most extensively studied markers are Neutrophil-to-lymphocyte Ratio (NLR), Platelet-to-lymphocyte Ratio (PLR) and Monocyte-to-lymphocyte Ratio (MLR).

To capture the multidimensional nature of systemic inflammation, composite indices such as the Systemic Immune-Inflammation Index (SII), Systemic Inflammation Response Index (SIRI), Aggregate Index of Systemic Inflammation (AISI), and Pan-immune Inflammation Value (PIV) have been developed, providing a holistic assessment of inflammatory status. Clinical correlations from cross-sectional studies reveal that these indices are significantly elevated in DR patients compared to diabetic controls without retinopathy [6-9]. Notably, NLR exhibits a strong association with Proliferative DR (PDR) [10,11], suggesting its role in advanced disease progression.

PLR and SII correlate with Non-proliferative DR (NPDR) [9], implicating their potential in early-stage disease stratification. These findings collectively highlight the diagnostic and prognostic utility of inflammatory biomarkers in DR management.

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Pathophysiological Mechanisms Linking Inflammation to DR

The pathogenesis of Diabetic Retinopathy (DR) involves differential contributions from distinct immune cell populations, each playing a unique role in disease progression. Neutrophils primarily drive vascular damage through the secretion of pro-inflammatory cytokines (e.g., TNF-α, IL-6), which disrupt endothelial barrier integrity and promote capillary leakage. Monocytes contribute to metabolic dysfunction by releasing hormones and cytokines (e.g., resistin, leptin) that exacerbate insulin resistance, thereby accelerating the progression of Type 2 Diabetes Mellitus (T2DM). Lymphocytes serve a dual role in immune surveillance and inflammation regulation. A decline in lymphocyte count correlates with dysregulated immune responses and a systemic pro-inflammatory state [12,13]. Platelets act as immune modulators, expressing bioactive mediators (e.g., P-selectin, CD40 ligand) that enhance leukocyte activation via platelet-leukocyte adhesion complexes [14], amplifying the inflammatory cascade in retinal microvasculature. This multicellular interplay underscores the complex immunopathology of DR, highlighting potential therapeutic targets for anti-inflammatory interventions.

Current Controversies and Inconsistencies in Research

The current body of research presents a nuanced picture regarding the relationship between inflammatory indices and Diabetic Retinopathy (DR). While existing studies demonstrate inconsistent associations across different biomarkers, NLR emerges as the most consistently validated independent risk factor for DR, supported by multiple robust studies [15-17]. In contrast, the clinical utility of other indices like PLR and MLR remains less conclusive, with findings varying significantly across different patient cohorts. For example, while certain studies report statistically significant elevation of PLR and MLR in DR patients [9,18], others fail to replicate these associations [7,16]. This heterogeneity in results may stem from methodological variations, including differences in study populations, geographic distribution, sample sizes, and importantly, the spectrum of DR severity stages examined. These factors collectively contribute to the discrepancies observed in the literature, highlighting the need for standardized, large-scale prospective studies to clarify the clinical significance of these inflammatory biomarkers in DR.

Clinical Utility and Future Directions

These hematological inflammatory indices offer practical clinical value as complementary screening tools, enabling clinicians to efficiently stratify diabetic patients at high risk of DR within large-scale populations. Current diagnostic performance, as evidenced by AUC values ranging from 0.55 [9] to over 0.9 [19], demonstrates moderate-to-high discriminatory capability for DR. Notably, combinatory use of multiple indices yields enhanced predictive accuracy (larger AUC) and shows promising potential in distinguishing DR severity stages. However, clinical implementation faces key limitations: 1) lack of standardized cut-off values across studies; 2) Vulnerability to transient confounders (e.g., infections, acute stress). Future research priorities should include: 1) Large-scale, multicentre prospective studies to validate and standardize these biomarkers; 2) Integration with established risk models (incorporating HbA1c, disease duration, blood clinical practice.

pressure) to develop comprehensive predictive tools; 3) Longitudinal assessment of biomarker stability and clinical utility. Addressing these challenges will be critical for translating these findings into routine

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