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Hematological Harbingers: Exploring the Neutrophil - to - Lymphocyte and Platelet - to - Lymphocyte Ratios as Novel Biomarkers for Diabetic Neuropathy

Dr. Rahul Garg

MBBS, MD (Medicine), Associate Professor, Department of Medicine, F H Medical College and Hospital, Etmadpur, Agra

Abstract: ***Diabetic neuropathy is a prevalent and debilitating complication of diabetes mellitus. This review explores the potential of two hematological markers, the Neutrophil - to - Lymphocyte Ratio (NLR) and Platelet - to - Lymphocyte Ratio (PLR), as novel biomarkers for diabetic neuropathy. Recent studies have shown significant associations between elevated NLR and PLR values and the presence and severity of diabetic neuropathy in both type 1 and type 2 diabetes. These ratios reflect underlying chronic inflammation and immune dysregulation characteristic of diabetes and its complications. Proposed cut - off values for NLR range from 1.7 to 4.3, while PLR cut - off values ranging from 92 to 120 have been suggested, with varying sensitivities and specificities across studies. The mechanisms linking these ratios to diabetic neuropathy involve complex interactions between inflammation, oxidative stress, and vascular dysfunction. While the evidence is promising, challenges remain, including the need for standardization of cut - off values, consideration of confounding factors, and longitudinal studies to establish causality. Despite these limitations, NLR and PLR show potential as simple, cost - effective tools for early screening, risk stratification, and monitoring of diabetic neuropathy progression. Their use as complementary markers alongside established tests could improve the accuracy of neuropathy prediction and guide personalized treatment strategies. Further research, particularly large - scale longitudinal studies and standardization efforts, is needed to fully establish the clinical utility of NLR and PLR in the context of diabetic neuropathy management.***

Keywords: Diabetic Peripheral Neuropathy (DPN), Neutrophil Lymphocyte Ratio (NLR), Platelet Lymphocyte Ratio (PLR), Type 2 Diabetes Mellitus, Type 1 Diabetes Mellitus

1. Introduction

Diabetic neuropathy is a common and debilitating complication of diabetes mellitus, affecting a significant proportion of patients with both type 1 and type 2 diabetes [1]. Early detection and management of diabetic neuropathy are crucial for preventing its progression and improving patient outcomes. In recent years, there has been growing interest in the use of simple, cost - effective hematological markers as potential indicators of diabetic complications, including neuropathy.

Two such markers that have gained attention are the Neutrophil - to - Lymphocyte Ratio (NLR) and the Platelet - to - Lymphocyte Ratio (PLR). These ratios, derived from routine complete blood count tests, have been proposed as indicators of systemic inflammation and potential predictors of diabetic neuropathy. This narrative review aims to explore the current evidence surrounding the utility of NLR and PLR as markers for diabetic neuropathy, their potential mechanisms of action, and their clinical implications.

Neutrophil - to - Lymphocyte Ratio (NLR), Platelet - to - Lymphocyte Ratio (PLR) and Diabetic Neuropathy

The NLR has emerged as a promising marker for various inflammatory conditions, including diabetic complications whereas PLR is also emerging as a marker for diabetic neuropathy. Several studies have investigated the relationship between NLR, PLR and diabetic neuropathy, with many reporting significant associations. (Table 1)

Author	Type of Diabetes	NLR (in patients with DPN)	NLR (in patients without DPN)	PLR (in patients with DPN)	PLR (in patients without DPN)	Sensitivity	Specificity
Liu et al (2017) [2]	T1DM	1.7	-	-	-	63%	72%
Xu et al (2017) [3]	T2DM	2.58±0.5	2.18±0.61	-	-	81%	48%
Fawwad et al (2018) [4]	T2DM	4.3±3.32	-	-	-	-	-
Ranjith et al (2018) [5]	T2DM	2.26	-	-	-	88%	57%
Senyigit (2018) [6]	T2DM	4.17±3.85	2.32±1.29	-	-	-	-
Demirdal and Sen (2018) [7]	T1DM and T2DM	9.8±11.5	-	285.8±207.4	-	42.1% for NLR 31.6% for PLR	76.9% for NLR 94.9% for PLR
Abou Raya et al (2020) [8]	T2DM	2.44±1.11	1.92±0.89	-	-	-	-

Zhang et al (2021) [9]	T2DM	-	-	119.35±33.84 In DFU: 171.19±60.73	-	-	-
Chen et al (2021) [10]	T1DM and T2DM	In previously diagnosed DPN - T1DM: 1.74 T2DM: 2.0 In newly diagnosed DPN (T1DM and T2DM): 2.88	TIDM: 1.37 T2DM: 1.80 T1DM and T2DM: 1.57	In previously diagnosed DPN - T1DM: 115.35±37.31 T2DM: 92.2 In newly diagnosed DPN (T1DM and T2DM): 96.46	T1DM: 84.03±27.02 T2DM: 85.42 T1DM and T2DM: 83.63	38% for NLR 55.4% for PLR	79% for NLR 70.4% for PLR
Gao et al (2024) [11]	T2DM	1.98 (Subclinical DPN)	-	-	-	-	-

T1DM: Type 1 Diabetes Mellitus, T2DM: Type 2 Diabetes Mellitus, NLR: Neutrophil Lymphocyte Ratio, PLR: Platelet Lymphocyte Ratio, DPN: Diabetic Peripheral Neuropathy, DFU: Diabetic foot ulcer

Table 1: Neutrophil - to - Lymphocyte Ratio (NLR) and Platelet - to - Lymphocyte Ratio (PLR) Cut - off Values and Predictive Accuracy for Diabetic Neuropathy

Mechanisms Linking NLR and PLR to Diabetic Neuropathy

The potential mechanisms underlying the association between NLR, PLR, and diabetic neuropathy are multifaceted and involve complex interactions between inflammation, oxidative stress, and vascular dysfunction.

1) *Chronic Inflammation*: Diabetes is associated with a state of chronic low - grade inflammation, which plays a crucial role in the development and progression of diabetic complications, including neuropathy. Elevated NLR and PLR reflect an imbalance in the immune system, with an increase in neutrophils and platelets (pro - inflammatory) relative to lymphocytes (anti - inflammatory). This imbalance may contribute to the inflammatory processes that damage peripheral nerves [12, 13].
2) *Oxidative Stress*: Chronic hyperglycemia in diabetes leads to increased oxidative stress, which is a key factor in the pathogenesis of diabetic neuropathy. Neutrophils are a major source of reactive oxygen species (ROS), and an elevated neutrophil count (reflected in a higher NLR) may indicate increased oxidative stress. This oxidative environment can damage nerve fibers and contribute to neuropathy [14].
3) *Vascular Dysfunction*: Both NLR and PLR have been associated with endothelial dysfunction and microvascular complications in diabetes. Impaired microvascular function can lead to reduced blood flow to peripheral nerves, contributing to the development of neuropathy. The relationship between these hematological ratios and vascular function may partly explain their association with diabetic neuropathy [15].
4) *Platelet Activation*: Elevated PLR may reflect increased platelet activation, which has been implicated in the pathogenesis of diabetic complications. Activated platelets can release pro - inflammatory mediators and growth factors that may contribute to nerve damage and impaired regeneration in diabetic neuroathy [16].
5) *Immune Dysregulation*: The imbalance between different immune cell populations, as reflected by NLR and PLR, may indicate a dysregulated immune response in diabetes. This dysregulation could affect nerve repair mechanisms and contribute to the progression of neuropathy [17].

2. Limitations and Considerations

Despite the promising evidence, there are several limitations and considerations to keep in mind when interpreting the results of studies on NLR and PLR in diabetic neuropathy:

1) *Study Heterogeneity*: The studies reviewed have varying designs, sample sizes, and populations, making direct comparisons challenging. Cut - off values for NLR and PLR vary between studies, highlighting the need for standardization.
2) *Confounding Factors*: NLR and PLR can be influenced by various factors, including infections, medications, and other inflammatory conditions. Studies need to account for these potential confounders.
3) *Causality*: While associations between elevated NLR/PLR and diabetic neuropathy have been demonstrated, causality has not been established. Longitudinal studies are needed to clarify the temporal relationship.
4) *Specificity*: NLR and PLR are markers of systemic inflammation and may be elevated in various conditions. Their specificity for diabetic neuropathy needs further investigation.
5) *Standardization*: There is a lack of standardized cut - off values for NLR and PLR in the context of diabetic neuropathy. Large - scale, multicenter studies are required to establish these reference ranges across different populations.

3. Clinical Implications

The growing body of evidence supporting the use of NLR and PLR as markers for diabetic neuropathy has several potential clinical implications:

1) *Early Screening and Risk Stratification*: NLR and PLR could be used as simple, cost - effective tools for early screening and risk stratification of diabetic patients. Patients with elevated ratios may be identified for more intensive monitoring and earlier intervention to prevent or delay the onset of neuropathy [2, 3, 10].
2) *Monitoring Disease Progression*: These ratios may be useful for monitoring the progression of diabetic

neuropathy over time. Regular assessment of NLR and PLR could help clinicians track the effectiveness of interventions and adjust management strategies accordingly [18].

3) *Complementary Markers*: NLR and PLR could be used in conjunction with other established markers, such as HbA1c, to improve the accuracy of predicting diabetic neuropathy. This multi - marker approach may provide a more comprehensive assessment of a patient's risk profile [18].
4) *Guiding Treatment Decisions*: Knowledge of a patient's NLR and PLR status could potentially inform treatment decisions. Patients with elevated ratios might benefit from more aggressive management of inflammation and vascular risk factors [13].
5) *Research Applications*: These ratios could serve as valuable endpoints in clinical trials evaluating new therapies for diabetic neuropathy. Changes in NLR and PLR over time may provide insights into the efficacy of interventions targeting inflammation and oxidative stress [19].

4. Future Directions

Future research directions should focus on addressing the limitations and gaps in current knowledge:

1) *Longitudinal Studies*: Most of the current evidence comes from cross - sectional studies. Longitudinal studies are needed to better understand the temporal relationship between changes in NLR/PLR and the development and progression of diabetic neuropathy [14].
2) *Mechanistic Studies*: Further research is needed to elucidate the precise mechanisms linking NLR and PLR to the pathogenesis of diabetic neuropathy. Understanding these mechanisms could lead to new therapeutic targets [12].
3) *Standardization*: Large - scale, multicenter studies are required to establish standardized cut - off values for NLR and PLR in the context of diabetic neuropathy across different populations [11].
4) *Integration with Other Biomarkers*: Studies exploring the combined use of NLR and PLR with other emerging biomarkers for diabetic neuropathy could enhance our ability to predict and monitor this complication [18].
5) *Intervention Studies*: Clinical trials evaluating whether interventions targeting the reduction of NLR and PLR can prevent or slow the progression of diabetic neuropathy would provide valuable insights into the clinical utility of these markers [13].

5. Conclusion

The Neutrophil - to - Lymphocyte Ratio (NLR) and Platelet - to - Lymphocyte Ratio (PLR) have emerged as promising markers for diabetic neuropathy. A growing body of evidence suggests that these simple, cost - effective hematological ratios may have value in predicting the development and progression of diabetic neuropathy, as well as other microvascular complications of diabetes.

Studies across various populations have consistently shown higher NLR and PLR values in patients with diabetic neuropathy compared to those without. The proposed cut - off values for NLR range from 1.7 to 4.3, while for PLR cut - off values ranging from 92 to 120 have been suggested. These ratios reflect the underlying chronic inflammation and immune dysregulation characteristic of diabetes and its complications. Elevated ratios may indicate a pro - inflammatory state and increased oxidative stress, which contribute to nerve damage and impaired regeneration in diabetic neuropathy.

Despite these challenges, the potential clinical applications of NLR and PLR in diabetic neuropathy management are significant. These ratios could enhance early screening, risk stratification, and monitoring of disease progression. Their use as complementary markers alongside established tests like HbA1c could improve the accuracy of neuropathy prediction and guide personalized treatment strategies.

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