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ASSOCIATION BETWEEN NEUTROPHIL TO LYMPHOCYTE RATIO AND PLATELET TO LYMPHOCYTE RATIO WITH DIABETIC RETINOPATHY AMONG TYPE-II DIABETIC PATIENT AT A TERTIARY CENTER

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ABSTRACT
Introduction: Diabetic retinopathy (DR) is important microvascular complication of diabetes mellitus (DM) and one of the main causes of blindness worldwide, but an effective screening is challenging due to limited available retina specialists. Developing new biomarkers could help clinical decision in prioritizing ophthalmological consultation in patients at risk of developing severe DR. **Aim:** To evaluate the association between Diabetic retinopathy and the Neutrophil Lymphocyte ratio, and the Platelet Lymphocyte Ratio **Methods:** Hospital based Case Control study on 360 diabetic patients . 180 patients were taken as cases who have DM with retinopathy and 180 patients were taken as controls who have DM without retinopathy with age between 18 to 65 years at Mahatma Gandhi Hospital, Jaipur from September 2022 to August 2023. **Results:** Compared with control patients, NLR and PLR levels are signifcantly higher among cases (NLR: 2.29 ±1.21 in controls versus 2.91 ±1.98 in cases and $p<0.001$; PLR: 108.13 ±75.21 137.89 ±26.98 and $p<0.001$). **Conclusion:** High NLR and PLR increase the risk of Diabetic Retinopathy and these insights emphasize the importance of comprehensive diabetic management strategies that not only target blood glucose levels but also monitor and manage inflammatory markers to improve patient outcomes and reduce the burden of diabetic retinopathy.
Keywords: Type 2 diabetes mellitus, Diabetic retinopathy, Neutrophil-to-lymphocyte ratio, Platelet-tolymphocyte ratio.

INTRODUCTION
Diabetic retinopathy (DR), a progressive and potentially sight-threatening complication of diabetes, is a significant public health concern [1]. It is one of the most common microvascular complications of diabetes, and its prevalence is on the rise, mirroring the global diabetes epidemic [2]. Among the various complications associated with diabetes, Diabetic retinopathy poses a unique challenge due to its insidious onset and asymptomatic nature in the early stages, which often results in delayed diagnosis and intervention [3]. Understanding the risk factors and early markers associated with diabetic retinopathy is paramount for timely identification, intervention, and prevention of vision loss in individuals with type-II diabetes [4].

Over the years, considerable research has been dedicated to unraveling the intricate pathophysiology of diabetic retinopathy. The disease is primarily characterized by vascular abnormalities, including microaneurysms, hemorrhages, exudates, and neovascularization. However, it is becoming increasingly evident that Diabetic retinopathy is not just a localized ocular complication; it is intertwined with systemic factors, particularly inflammation and dysregulation of the immune response [5-6]. In this context, hematological markers such as the neutrophil to lymphocyte ratio (NLR) and the platelet to lymphocyte ratio (PLR) have emerged as intriguing candidates for further investigation.

NLR and PLR are simple yet informative hematological indices that reflect the relative proportions of different white blood cell types in the peripheral blood [7]. Neutrophils, lymphocytes, and platelets, each plays a distinct role in the immune response and inflammatory processes, and imbalances in these cell types are often indicative of systemic inflammation [8]. As such, NLR and PLR have been used as surrogate markers of inflammation and have shown promise in predicting a range of medical conditions, including cardiovascular diseases, cancers, and autoimmune disorders [7]. It is this connection between systemic inflammation and various health conditions

that has sparked interest in exploring the potential link between NLR, PLR, and diabetic retinopathy among individuals with type-II diabetes.

The association between NLR, PLR, and diabetic retinopathy represents a multifaceted and evolving field of research that warrants in-depth investigation. Understanding the connection between these hematological markers and diabetic retinopathy can offer valuable insights into the underlying inflammatory and vascular processes that contribute to the development and progression of this ocular complication. By examining the associations between NLR, PLR, and diabetic retinopathy, researchers seek to uncover potential early indicators, risk factors, and predictors that could aid in the identification of individuals at higher risk of developing Diabetic retinopathy. Such insights could not only enable earlier diagnosis and intervention but also pave the way for more personalized treatment strategies to mitigate the impact of diabetic retinopathy.[9]

As we embark on this journey of exploration, it is important to acknowledge that the pathogenesis of diabetic retinopathy is complex and multifactorial. It involves various biochemical, cellular, and molecular mechanisms, such as advanced glycation end-products, oxidative stress, and the release of pro-inflammatory cytokines [10]. In this intricate web of events, the role of immune cells and their ratios, as quantified by NLR and PLR, remains a subject of active investigation.

AIMS & OBJECTIVES

The aim of study is to evaluate the association between Diabetic retinopathy and the Neutrophil Lymphocyte ratio, and the Platelet Lymphocyte Ratio.

MATERIAL AND METHODS

Hospital based Case Control study on 360 diabetic patients . 180 patients were taken as cases who have DM with retinopathy and 180 patients were taken as controls who have DM without retinopathy with age between 18 to 65 years at Mahatma Gandhi Hospital, Jaipur from September 2022 to August 2023.

Inclusion criteria for cases

- All patient's > 18 years to <65 years of age in both gender with Type 2 DM with retinopathy were included.

Inclusion criteria for controls

- All patient's > 18 years to <65 years of age in both gender with Type 2 DM without retinopathy were included.

Exclusion criteria:

Patients with the following comorbidities were excluded:

- Hematological diseases
- Hepatic failure
- Renal failure
- Cardiac failure
- Any acute or chronic illness
- Alcohol abuse
- Hypertension
- On drugs that alter platelet function or causes retinopathy
- Pregnant women

RESULTS

Table 1 : Age distribution of Study population

	Diabetes Mellituswithout Retinopathy (DM) N=180	**Diabetic Retinopathy (DR) N=180**	p-Value
Age (Years)	56.33±16.19	57.48±19.11	0.5383

The study included 180 patients in each group, with a mean age of 56.33 years (±16.19) for those with DM and 57.48 years (±19.11) for those with DR, showing no statistically significant difference (p = 0.5383).

Table 2: Gender distribution of study population

Sex	**Diabetes Mellitus without Retinopathy (DM)**	**Diabetic Retinopathy (DR) N=180**	**p-Value**

	N=180		
Male	99 (55.0)	128 (71.11)	<0.0001
Female	81 (45.0)	52 (28.89)	

In this study, the participants were categorized based on their sex, revealing noteworthy disparities in the occurrence of Diabetic Retinopathy among males and females. Among the male participants, 55.0% were diagnosed with Diabetes Mellitus, and 71.11% of them manifested concurrent Diabetic Retinopathy. In contrast, 45.0% of the female participants had Diabetes Mellitus, with 28.89% of them exhibiting Diabetic Retinopathy.

Table 3: Duration of DM in DM & DR study population

	Diabetes Mellitus without Retinopathy (DM) N=180	**Diabetic Retinopathy (DR) N=180**	**p-Value**
Duration of DM (Months)	46 (4–78)	122 (46–159)	0.001

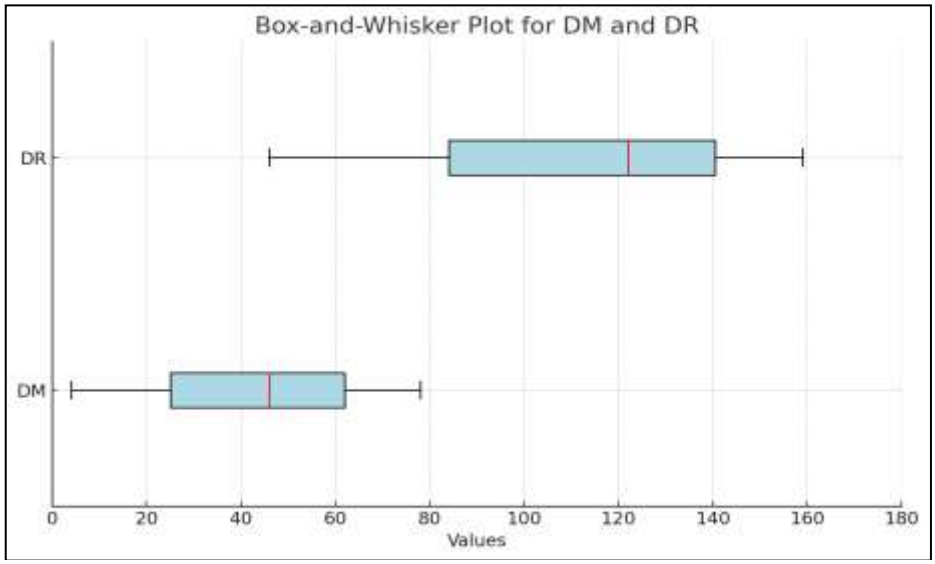

Fig. 3: Duration of DM (Median) in DM & DR study population

The present study, the participants were meticulously characterized by the duration of their diabetes, and the analysis revealed compelling findings. The median duration of diabetes in the overall cohort was 46 months, with a wide interquartile range (4–78 months). Notably, among individuals with Diabetic Retinopathy, the median duration of diabetes substantially escalated to 122 months, accompanied by a narrower interquartile range (46–159 months). Statistical analysis yielded a significant p-value of 0.001, underscoring a robust association between the duration of diabetes and the likelihood of developing Diabetic Retinopathy.

Table 4: NL, & PL ratio in DM & DR groups

	Diabetes Mellitus without Retinopathy (DM) N=180	**Diabetic Retinopathy (DR) N=180**	p-Value
NL Ratio	2.29 ±1.21	2.91 ±1.98	0.0004
PL Ratio	108.13 ±75.21	137.89 ±26.98	0.00001

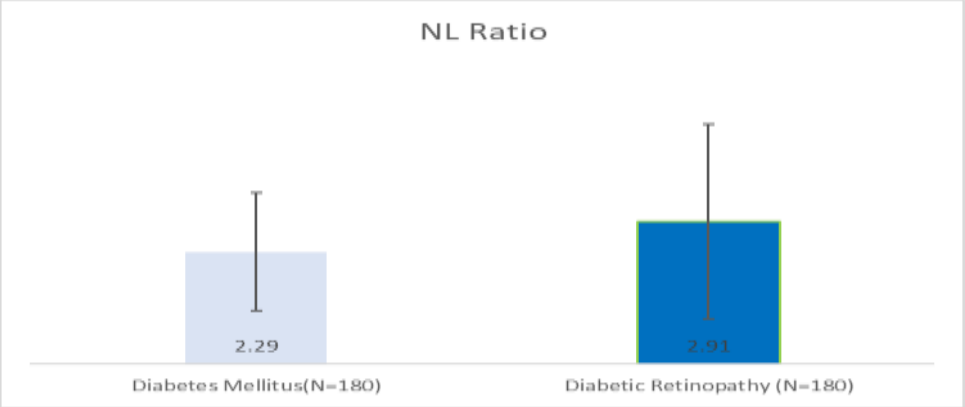

Fig. 1: NL ratio in DM & DR groups

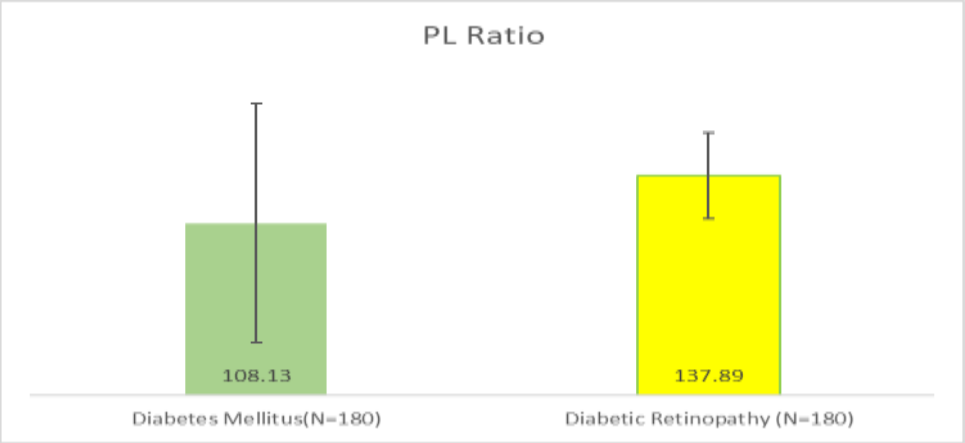

Fig. 2: PL ratio in DM & DR groups

The Neutrophil-to-LymphocyteRatio was significantly higher in the DR group (2.91 ± 1.98) compared to the DM group (2.29 ± 1.21) with a p-value of 0.0004. Similarly, the Platelet-to-Lymphocyte Ratio demonstrated a marked elevation in the DR group (137.89 ± 26.98) in contrast to the DM group (108.13 ± 75.21) with a highly significant p-value of 0.00001.

DISCUSSION

Although the association between blood inflammatory index and DR drew much attention previously [11,12], Herein, we investigate the association between the indicators and DR more comprehensively in a larger population (n=470) and revealed that a combination of NLR, PLR and Hb displayed signifcantly improved discriminability and raised sensitivity compared with using Hb alone. Therefore, combining the three factors might be helpful.

Gender distribution demonstrated a significant difference between DM and DR groups, with a higher prevalence of males in the DR group (71.11% vs. 55.0%, $p<0.0001$). This trend continued within the DR subgroup, where males were more likely to have NPDR (84.4%) compared to PDR (71.9%, $p<0.001$). These findings align with previous studies that have highlighted gender as a potential risk factor for the development and progression of diabetic retinopathy [13].

The duration of diabetes was significantly longer in individuals with DR compared to those with DM alone. Prolonged hyperglycemia is known to cause microvascular damage, which can lead to the development and progression of diabetic retinopathy [14].HbA1c and fasting blood sugar levels were significantly higher in DR patients (HbA1c: p=0.0061; FBS: p=0.0030), indicating poorer glycemic control in these individuals. Poor glycemic control is a well-established risk factor for the development and progression of diabetic retinopathy [15].

Both NLR and PLR were significantly higher in DR patients compared to those with DM alone (NLR: p=0.0004; PLR: p=0.00001). These ratios were also higher in patients with PDR compared to NPDR, indicating a potential association between these inflammatory markers and the severity of retinopathy. Elevated NLR and

PLR have been proposed as biomarkers for systemic inflammation and have been linked to diabetic complications, including retinopathy [16].

The study highlights that NLR, a marker of systemic inflammation, is significantly elevated in individuals with diabetic retinopathy compared to those with diabetes mellitus alone. This elevation suggests a link between systemic inflammation and the pathogenesis of diabetic retinopathy. Specifically, higher NLR levels correlate with increased severity of retinopathy, indicating that chronic inflammation may exacerbate microvascular damage and contribute to the progression of DR [17].

Similarly, the study findings reveal that PLR, another marker of inflammation reflecting the balance between platelets and lymphocytes, is also elevated in patients with diabetic retinopathy compared to those without retinopathy. Elevated PLR levels are associated with more severe forms of diabetic retinopathy, suggesting a potential role of platelet activation and inflammation in the development and progression of retinal vascular complications [18].

The elevated NLR and PLR to diabetic retinopathy are multifactorial. Chronic hyperglycemia in diabetes triggers oxidative stress and inflammatory responses, leading to endothelial dysfunction and microvascular damage in the retina. Neutrophils and platelets play pivotal roles in these processes by promoting inflammation, thrombosis, and tissue injury, which are central to the pathophysiology of diabetic retinopathy [19].

From a clinical perspective, measuring NLR and PLR can serve as valuable biomarkers for assessing the inflammatory status and predicting the risk of diabetic retinopathy in patients with diabetes mellitus. These ratios offer a non-invasive and cost-effective means to identify individuals at higher risk of developing or progressing to diabetic retinopathy. Early identification of inflammatory markers like NLR and PLR could prompt intensified management strategies aimed at reducing inflammation and mitigating the risk of diabetic complications [20].

These correlations are crucial as they underscore the interplay between glycemic control, systemic inflammation, and diabetic retinopathy risk. The positive correlations with disease duration and fasting blood sugar levels suggest that both chronic and acute hyperglycemia contribute to systemic inflammation, as evidenced by elevated NLR and PLR. Conversely, the negative correlations with HbA1c levels suggest that optimizing long-term glycemic control may help reduce systemic inflammation and potentially mitigate the risk of diabetic complications.

CONCLUSION

High NLR and PLR increase the risk of Diabetic Retinopathy and these insights emphasize the importance of comprehensive diabetic management strategies that not only target blood glucose levels but also monitor and manage inflammatory markers to improve patient outcomes and reduce the burden of diabetic retinopathy. For more precise and reliable guidance for clinical diagnosis, further large multi-center prospective clinical studies and basic researches are also required to elucidate the relationship between the PLR, NLR and Diabetic Retinopathy.

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