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THE RELATIONSHIP BETWEEN THE NEUTROPHIL-TO-LYMPHOCYTE RATIO AND DIABETIC RETINOPATHY IN ADULTS.

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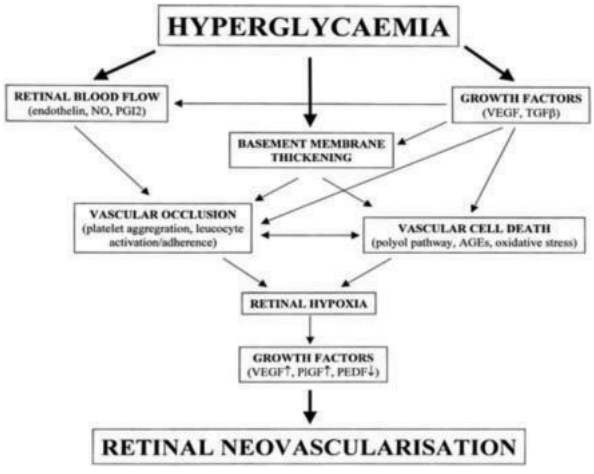
ABSTRACT

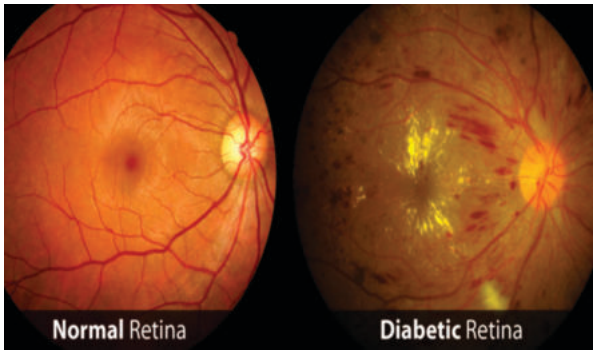
Background: Diabetic retinopathy (DR) is a common complication of diabetes mellitus (DM). Systemic inflammation is intimately associated with DR. The neutrophil-to-lymphocyte ratio (NLR) index is a relatively new indicator of inflammation. **Aims And Objective:** The aim of my study is to evaluate the association between Diabetic retinopathy and the Neutrophil Lymphocyte ratio and the Monocyte Lymphocyte Ratio. **Methods And Materials:** We consecutively enrolled 1030 patients with a definite diagnosis of type 2 diabetes mellitus (T2DM) from the enrolled a total of 1030 type 2 diabetic patients undergoing funduscopy from the department of Internal Medicine, Madhubani Medical College, Madhubani from September 2020 to February 2022. Based on funduscopy and family history checking, we excluded patients with a family history of hypertension and diabetes and finally enrolled 264 patients with DR and 206 patients with non-diabetic retinopathy (NDR). Through correlation analysis, univariate and multivariate regression, we further explore the association between NLR, PLR, and DR. On top of that, we investigate the effect of NLR and PLR on risk reclassification of DR. **Result:** Compared with NDR patients, NLR and PLR levels are significantly higher among DR patients (NLR: 2.36±1.16 in DR group versus 1.97±1.06 in NDR group, $p<0.001$; PLR: 11.62±4.55 in DR group versus 10.56±4.45 in NDR group, $p=0.012$). After fully adjusting co-founders, NLR, as both continuous and categorical variant, remains an independent risk factor for DR (OR (95%CI): 1.37 (1.06, 1.78) P=0.018). In addition, of PLR and NLR to the established factor hemoglobin (Hb) improved the discriminability of the model and assisted the reclassification of DR. **Conclusion:** Systemic inflammatory response indexes NLR and PLR were associated with the presence of DR among patients without associated family history and contributed to improvements in reclassification of DR in addition to Hb.

KEYWORDS : Type 2 diabetes mellitus, Diabetic retinopathy, and Neutrophil-lymphocyte ratio.

INTRODUCTION:

Diabetic retinopathy (DR) is a micro vascular complication of diabetes mellitus (DM) and is a primary cause of acquired blindness among working-age individuals [1]. Various mechanisms and factors mediate DR development, including pregnancy, diabetic nephropathy, obesity, family history, blood glucose fluctuations, hyperlipidemia, chronic diabetes, hypertension, and hyperglycemia [2,3,4]. The pathogenesis of DR is not fully understood; however, several studies suggested that inflammation plays an important role [5,6,7]. Many epidemiological studies highlighted the association between chronic inflammation and DM [8, 9]. Chronic inflammation may contribute to the development of microangiopathy and microangiopathy in patients with diabetes [10]. Several lines of evidence suggest that routine blood tests might provide adequate information to perform risk stratification [11, 12]. Specifically, peripheral blood leukocytes such as lymphocytes, neutrophils, basophils, eosinophils, and monocytes all have unique biological functions in systemic inflammation [13]. The neutrophil-to-lymphocyte ratio (NLR) can indicate systemic inflammation [14]. NLR represents the ratio of neutrophils to lymphocytes in peripheral blood, which integrates different but complementary immune pathways in circulating blood. Increased NLR may be the result of increased neutrophils, which can adhere to endothelial cells, resulting in vascular endothelial damage and widespread chronic inflammation [12, 15]. Furthermore, lymphocytes are the main cells of the body's immune response and have the ability to regulate inflammatory responses [16]. NLR has been used for mortality stratification in major cardiac events [17, 18], indicating infectious and inflammatory status or postoperative complications [19, 20]. NLR was also considered a prognostic and predictive factor for DM and its complications [21, 22]. Wang et al. found that NLR was related to DR in patients with diabetes who had no associated family history [23]. Nevertheless, further research is required to determine whether this is the same in different regions, populations, and types of diabetes.





AIMS AND OBJECTIVE:

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

MATERIAL AND METHOD:

Participants and study design

We consecutively enrolled a total of 1030 type 2 diabetic patients undergoing funduscopy from the department of Internal Medicine in Madhubani Medical College, Madhubani, from September 2020 to February 2022. (1 year 6 months). Diagnosis of type 2 diabetes was made according to the 1999 World Health Organization criteria. The diagnosis of diabetic was based on the 2002 International Clinical Classification Standard. And the non-diabetic retinopathy group (NDR) was defined as patients who had been clearly diagnosed with type 2 diabetes and had no diabetic retinopathy on fundus. Finally, we successfully enrolled 264 patients with DR and 206 patients without DR (the NDR group).

Clinical information and biochemical examination

All participants received routine examination and blood examination and were asked in detail about their disease history, medical history, and personal history. After collecting patients fasting peripheral blood, blood routine test and white blood cell classification were performed. Specifically, the blood routine and blood cell count were detected using a fully automated blood analyzer.

Inclusion criteria

Patients of both gender aged more than 18 years of age are selected.

Exclusion criteria

Patients with the following comorbidities are excluded - Hematological diseases, Hepatic failure - Renal failure - Cardiac failure - Any acute or chronic illness - Alcohol abuse - Pregnant women - Patients not capable of giving consent - Patients who are not willing to participate in the study. Besides patients with a family history of hypertension and diabetes, patients with severe systemic disease, glaucoma, trauma, non-diabetic retinopathy, pregnancy, malignant tumors, severe cardiovascular and cerebrovascular diseases, liver and kidney dysfunction, blood disease, recent surgery, infection or other severe stress condition were also excluded.

Procedure:

Statistical Analysis:

Distribution normality was initially tested through the Kolmogorov–Smirnov test. Continuous data are showed by the mean ± standard deviation (SD) and were compared by independent Student t test or one-way analysis of variance test. While variables without normality were expressed by median plus IQR. The Chi squared test or Fisher's exact test was used to compare categorical variables.

RESULT:

Univariate analysis

Our univariate regression analysis revealed that gender of female, presence of hypertension, long course of diabetes, higher levels of FPG, WBC, NLR, and TG adds risk to presence of DR, while higher counts of Hb was related to lower risk of DR. However, no association was found between age, BMI, HbA1c, TC, HDL-C, LDL-C, MLR and presence of DR. Compared with NDR patients, NLR and PLR levels are significantly higher among DR patients (NLR: 2.36±1.16 in DR group versus 1.97±1.06 in NDR group, $p<0.001$; PLR: 11.62±4.55 in DR group versus 10.56±4.45 in NDR group, $p=0.012$). After fully adjusting co-founders, NLR, as both continuous and categorical variant, remains an independent risk factor for DR (OR (95%CI): 1.37 (1.06, 1.78) P=0.018). In addition, of PLR and NLR to the established factor hemoglobin (Hb) improved the discriminability of the model and assisted the reclassification of DR.

Multivariate analysis

By conducting multivariate analysis, we found that NLR was associated with DR independent of other known factors. With a unit increase of NLR, the risk for DR would raise 37%. Furthermore, when treated as a category variate divided according to its quantile, the association of NLR and DR still exists. It was also demonstrated, from the crude model to simple or complex model, there was a 2.8 fold increased risk for DR in the highest quantile of NLR (OR, 95%CI 2.80 (1.32, 5.95) $p = 0.007$).

DISCUSSION:

Our research demonstrated the association of systemic inflammatory response index with diabetic retinopathy among type 2 diabetic patients without related family histories. First of all, we verified that levels of NLR and PLR but not MLR were higher in the DR group. Furthermore, according to our multivariate analysis, not only did NRL serve as an independent risk factor but also the highest quartile of both NLR and PLR added risk to DR. More importantly, addition of NLR and PLR to Hb-based model improved reclassification of DR. Through our study, we provide the simple and available blood-based index for DR, promoting the risk stratification of DR among type 2 diabetic patients without family history. Although the association between blood inflammatory index and DR drew much attention previously [24, 25–27], our study further deciphered the association and the clinical application of these indicators in T2DM patients without associated family history. 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 significantly improved discriminability and raised sensitivity compared with using Hb alone. Therefore, combining the three factors might be helpful in clinical practice to improve the identification of DR in T2DM patients without family history of diabetes and hypertension. Chronic inflammation plays an essential role in the initiation and progression of type 2 diabetes and further accelerates the deterioration of micro-angiopathy and macrovascular disease in patients with diabetes [28]. Previous studies have evidenced that peripheral blood leukocytes and their subgroups are associated with macrovascular and micro vascular complications among patients with type 2 diabetes [29]. Specifically, peripheral blood leukocytes include lymphocytes, basophils, neutrophils, eosinophils, and monocytes, each type of which holds a unique biological function in systemic inflammation. NLR and PLR are two indexes that represent the integration of two factors and are considered to be new markers of the systemic inflammatory response [30]. Increasing studies have confirmed their association with type 2 diabetes [30, 31]. DR is a common micro-angiopathic complication in diabetes. More and more evidence indicates that inflammation plays an important part in the early and progressive stage of DR [32–34], through inducing the formation of new blood vessels and macular edema [35], damaging the glial crosstalk and causing neuronal loss [36]. In addition, studies have also found that many inflammatory cytokines (such as CRP, TNF-α and VEGF, etc.) increase in patients with DR [37]. And intervention and regulation targeted at the inflammatory response in patients with diabetic retinopathy can prohibit the progression of diabetes and retinopathy.

CONCLUSION:

NLR levels correlated with an elevated risk of DR. NLR positively correlated with DR when its value was less than 4.778. Systemic inflammatory response indexes NLR and PLR were associated with the presence of DR among patients. However, these should be further confirmed by conducting prospective studies.

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