



**ORIGINAL RESEARCH PAPER**

**General Medicine**

**“TO STUDY CORRELATION OF NEUTROPHIL –LYMPHOCYTE RATIO AND DIABETIC RETIONOPATHY IN DIABETES MELLITUS TYPE 2 PATIENTS”**

**KEY WORDS:** Diabetic retinopathy(DR), neutrophil lymphocyte ratio (NLR), Diabetes mellitus (DM)

<b>Sagar Khandare</b>	Senior resident, Department Of Medicine, Gandhi Medical College Bhopal
<b>Ravi Kumar Patel*</b>	Senior Resident, Department Of Medicine, Gandhi Medical College Bhopal, *Corresponding Author
<b>Sandeep Pachole</b>	Junior Resident, Department Of Ophthalmology, Gandhi Medical College Bhopal

**ABSTRACT**

**INTRODUCTION :** Diabetic retinopathy (DR) is a microvascular complication of diabetes. Total white blood cell count is a crude but sensitive indicator of inflammation and studied in many cardiac and noncardiac diseases as an inflammatory marker such as acute myocardial infarction, stroke, and heart failure. In this study, the association of neutrophil lymphocyte ratio (NLR) with DR is studied.

**PATIENTS AND METHODS:** It is an observational cross sectional study. Totally 115 diagnosed type 2 diabetes mellitus patients were registered in this study. NLR was calculated by analyzing differential leukocyte count in complete blood picture. Diabetic retinopathy was detected by doing indirect ophthalmoscopy.

**RESULTS:** Totally 115 diabetic patients were registered. Out of these, 83 patients had retinopathy and 32 patients did not have retinopathic changes. Mean NLR for DM2with DR is 2.49±0.94 and in DM2 without DR is 2.06 ± 0.56 which was highly significant (P = 0.019).

**CONCLUSION:** The results of our study show that there was a significant relation between NLR and DR. Therefore, NLR may be considered as a novel surrogate marker of DR in DM2 patients.

**INTRODUCTION**

Type 2 diabetes mellitus is an endocrine syndrome which constitutes common phenotype of hyperglycemia. In India, prevalence of DM2 is high, in fact it's a capital of DM2. Obesity, metabolic syndrome, genetics, environmental factors are the risk factor of DM2. There is significant difference in phenotype, body habitus, in DM2 patients from western to Indian population. It is observe that DM2 patients from India are thinner, not having metabolic syndrome, compared to western population. Low socioeconomic status, absence of evidence of high risk factors, leads to delay in diagnosis of DM2 in this population. There are microvascular complications such as retinopathy, nephropathy, neuropathy and macrovascular complication such as stroke, coronary artery disease, peripheral vascular disease, etc in DM2( 1) . Diabetic retinopathy is one of the most common microvascular complication in DM2. DM2 is leading cause of blindness and there is 25 times more risk of becoming blind to individual having DM2 than those without DM2. Diabetic retinopathy is insidious in onset and slowly progressive. Usual time to start retinopathy changes in DM2 patient is 10 to 15 years. Diabetic retinopathy (DR) progressed from non proliferative diabetic retinopathy (NPDR) to Proliferative diabetic retinopathy (PDR) and advance diabetic retinopathy as retinal detachment. In pathophysiology of DR hyperglycemic state leads to glycosylated end product formation that accumulate in retinal microvasculature. This causes inflammatory changes, release of inflammatory factors such as ILs, TNF, cytokines and leads to microvascular complication. It is difficult to diagnose DR in early stage as change in microvasculature are slow, patients are asymptomatic, and due to limited recourses. Therefore most of times DM2 to is diagnosed as DM2 with DR. There are many studies that correlate DR with inflammatory markers such as hs CRP, ILs, TNFs, cytokines. But these markers are costly, difficult to measure, and hence not done routinely in simple setups. Neutrophil- Lymphocyte ratio (NLR) has been studied as an inflammatory marker in various inflammatory conditions<sup>(2,3)</sup>. It is easy to calculate, cost effective compared to other markers. This study correlate NLR and DR in DM2 patients of central India and wheather NLR can be used as surrogate inflammatory marker for DR in these DM2 patients was seen.

**MATERIALS AND METHODS**

DM2 patients were screened for DR in OPD of HAMIDIA HOSPITAL BHOPAL by doing indirect Ophthalmoscopy. NLR was calculated in these patients. DM type1 patients were excluded from this study. Patient with other associated problems such as other systemic diseases, infectious diseases, autoimmune diseases, malignancies, genetic disorders that might affect NLR were excluded from this study. Anthropometric measurements that include height, weight,

abdominal girth, BMI were done. Glycemic status, complete blood picture, renal function test, liver function test, lipid profile, blood pressure, ECG, urine examination, abdominal ultrasonography were done.

**RESULTS**

In this study total 115 DM2 patients have been registered. Out of 115 DM2 patients, 32 patients did not have retinopathy and 83 patients had retinopathy. DM2 patients not having DR have been compared with DM2 patient with DR for various parameters shown in below table.

**TABLE 1: COMPARISON OF DM2 PATIENTS NOT HAVING DR TO DM2 PATIENTS HAVING DR FOR VARIOUS PARAMETERS**

Parameters	Dm2 without DR(32patients)	Dm2 with DR (83 patients)	P value
Age	50.48±12.03	51.39±11.18	0.705
Duration of DM	6.44±6.87	5.09±6.67	0.344
Ht (cm)	162.48±7.9	160.92±6.21	0.268
Wt (kg)	67.77±14.31	68.37±11.95	0.823
BMI	25.53±4.29	26.39±4.23	0.336
Waist(cm)	90.52±7.45	90.96±6.76	0.758
WHR(waist hip ratio)	0.95±0.1	0.93±0.09	0.262
Hb (gm%)	12.15±1.41	12.26±1.53	0.727
TLC	7470.97±1506.63	7483.33±1733.15	0.972
NLR	2.06±0.56	2.49±0.94	0.019
Sr urea	26.94±10.58	27.54±14.48	0.833
Sr creatinine	0.78±0.21	0.86±0.33	0.217
SGPT	31.87±14.22	36.12±16.49	0.206
SGOT	34.23±14.93	37.33±30.94	0.594
Total cholesterol	162.77±35.37	185.04±51.9	0.151
Triglyceride	162.92±72.84	168.51±92.12	0.84
HDL	38.54±8.09	39.61±11.35	0.751
LDL	83.877±49.8	98.08±44.66	0.32
VLDL	36.12±16.99	39.64±23.08	0.611
FBS	177.1±37.16	162.75±43.7	0.107
PBBS	204.42±38.06	199.8±47.12	0.625

The result of this study showed that there was significant difference in NLR in DM2 without DR ( $NLR=2.06\pm 0.56$ ) and DM with DR ( $NLR=2.49\pm 0.94$ ) patients. The P value is 0.019. The result of this study also showed that comparison between other parameters such as duration of diabetes, anthropometrics measures, renal function, liver function, lipid profile, glycemic status did not have significant difference between these two groups of patients.

## DISCUSSION

DR is one of the most common microvascular complication of DM2. Many factors affect this microvascular complication process initiation and progression such as duration of DM2, glycemic control, associate hypertension, other systemic diseases, associate metabolic syndrome, ethnicity. There are studies that showed that DM2 patient from India have DR in early duration of diabetes. Indian diabetic patients having DR mostly do not have obesity, hypertension, dyslipidemia. This study also showed the same results. Patient of DM2 having DR do not have significant difference in glycemic status, lipid profile, BMI, RFT, LFT, gender, than those DM2 patients without DR. Therefore it is difficult to predict DR in DM2 patients and only dedicated approach toward the patients and ophthalmic examination facilities can diagnose DR in every diabetic patients. In such situation there is need of something which can be used as predictor marker for DR. This study showed that NLR can be used as surrogate marker for DR in DM2 patients.

The key finding of this study was that NLR levels were found to be significantly associated ( $P = 0.019$ ) with patients who were diagnosed with DR as compared to those without DR. This study is one of the first in India to assess the relationship between NLR and DR.

Over the past decade, multiple studies have shed light on the role and importance of inflammatory molecules (such as adipokines, chemokines, adhesion molecules, and cytokines) and endothelial dysfunction in the development of insulin resistance, diabetes, and its various complications<sup>4,5,1</sup>. The exact pathogenesis of DR is unknown. WBC count and its subtypes are among the readily available and inexpensive classic inflammatory markers. Multiple studies have established that inflammatory markers such as neutrophilia and relative lymphocytopenia are independent markers of many diseases, especially complications of DM, such as DR. However, establishing a diagnosis individually based on WBC, neutrophil, or lymphocyte counts has its own biases, unlike NLR, which is a dynamic parameter that has a higher prognostic value.<sup>16,7,8</sup> NLR is a novel marker of chronic inflammation that exhibits a balance of two interdependent components of the immune system; neutrophils that are the active nonspecific inflammatory mediator forms the first line of defense whereas lymphocytes are the regulatory or protective component of inflammation. A study by Imtiaz *et al* has suggested that chronic diseases such as hypertension and diabetes have a significant association with systemic inflammation, reflected by NLR.<sup>(9)</sup> Shiny *et al* have shown that NLR is correlated with increasing severity of glucose intolerance and insulin resistance and can be used as a prognostic marker for macro and microvascular complications in patients with glucose intolerance.<sup>(10)</sup> Initially, NLR was recognized as a predictive marker in multiple types of cancer that might assist in patient stratification and individual risk assessment.

Recently, several studies have suggested that NLR could play a predictive role for assessing the development of microvascular complications of diabetes. In a study, Ulu *et al.* demonstrated NLR to be a quick and reliable prognostic marker for diabetic retinopathy and its severity.<sup>(11)</sup> A study conducted in geriatric population also suggested that increased NLR levels were in itself an independent predictor for microvascular complications of DM. In another study, Akbas *et al.*<sup>(12)</sup> have shown that NLR was significantly elevated in patients with increased albuminuria pointing toward a relationship between inflammation and endothelial dysfunction in diabetics with nephropathy.

## CONCLUSION

This study showed that NLR has significant high value in DM2

patients having DR than those without DR.

The results of our study have shown that there was a significant correlation between NLR and DR, implying that inflammation and endothelial dysfunction could be an integral part of DR. NLR was significantly and independently raised in patients with type 2 DM having retinopathy. Therefore, NLR may be considered as a predictor and a prognostic risk marker of DR. NLR is an easy to calculate parameter in the laboratory by observing the differential leukocyte count. This test is simple, inexpensive, and done routinely. In a setup with limited laboratory facilities, NLR is a simple test which can be an alternative for other costlier inflammatory markers such as ILs, TNF, cytokines, and high sensitivity C-reactive protein. Further research with a prospective design and multiple NLR measurements will shed more light on the role of NLR as a marker of inflammation and a probable risk factor for DR.

## Financial support and sponsorship

- Nil.

## Conflicts of interest

- There are no conflicts of interest.

## REFERENCES

1. Rathmann W, Giani G. Global prevalence of diabetes: Estimates for the year 2000 and projections for 2030. *Diabetes Care* 2004;27:2568-9.
2. Brancati FL, Whittle JC, Whelton PK, Seidler AJ, Klag MJ. The excess incidence of diabetic end-stage renal disease among blacks. A population-based study of potential explanatory factors. *JAMA* 1992;268:3079-84.
3. Rudiger A, Burckhardt OA, Harpes P, Müller SA, Follath F. The relative lymphocyte count on hospital admission is a risk factor for long-term mortality in patients with acute heart failure. *Am J Emerg Med* 2006;24:451
4. Goldberg RB. Cytokine and cytokine-like inflammation markers, endothelial dysfunction, and imbalanced coagulation in development of diabetes and its complications. *J Clin Endocrinol Metab* 2009;94:3171-82.
5. Pitsavos C, Tampourlou M, Panagiotakos DB, Skoumas Y, Chrysoshoou C, Nomikos T, et al. Association between low-grade systemic inflammation and type 2 diabetes mellitus among men and women from the ATTICA study. *Rev Diabet Stud* 2007;4:98-104.
6. Núñez J, Núñez E, Bodí V, Sanchis J, Miñana G, Mainar L, et al. Usefulness of the neutrophil to lymphocyte ratio in predicting long-term mortality in ST segment elevation myocardial infarction. *Am J Cardiol* 2008;101:747-52.
7. Gibson PH, Croal BL, Cuthbertson BH, Small GR, Ifezulike AI, Gibson G, et al. Preoperative neutrophil-lymphocyte ratio and outcome from coronary artery bypass grafting. *Am Heart J* 2007;154:995-1002.
8. Azab B, Jaglall N, Atallah JP, Lamet A, Raja-Surya V, Farah B, et al. Neutrophil-lymphocyte ratio as a predictor of adverse outcomes of acute pancreatitis. *Pancreatology* 2011;11:445-52
9. Imtiaz F, Shafique K, Mirza SS, Ayoob Z, Vart P, Rao S. Neutrophil lymphocyte ratio as a measure of systemic inflammation in prevalent chronic diseases in Asian population. *Int Arch Med* 2012;5:2.
10. Shiny A, Bibin YS, Shanthirani CS, Regin BS, Anjana RM, Balasubramanyam M, et al. Association of neutrophil-lymphocyte ratio with glucose intolerance: An indicator of systemic inflammation in patients with type 2 diabetes. *Diabetes Technol Ther* 2014;16:524-30.
11. Ulu SM, Dogan M, Ahsen A, Altug A, Demir K, Acartürk G, et al. Neutrophil-to-lymphocyte ratio as a quick and reliable predictive marker to diagnose the severity of diabetic retinopathy. *Diabetes Technol Ther* 2013;15:942-7.
12. Akbas EM, Demirtas L, Ozcecek A, Timuroglu A, Bakirci EM, Hamur H, et al. Association of epicardial adipose tissue, neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio with diabetic nephropathy. *Int J Clin Exp Med* 2014;7:1794-801.