

Evaluation Of Neutrophil-To-Lymphocyte Ratio As A Biomarker For Chronic Inflammation In Type2 Diabetes Mellitus

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ABSTRACT

BACKGROUND

Type 2 diabetes is on the rise worldwide that can cause complications in long term or uncontrolled diabetes mellitus. Inflammatory processes have a significant role in the onset and progression of type 2 diabetes. Leukocytes, including Neutrophil-to-Lymphocyte Ratio (NLR) have been identified as novel markers of inflammation. Neutrophil-to-Lymphocyte Ratio (NLR) has lately become a prominent inflammatory marker, and studies have shown that a high NLR negatively influences the prevalence and prognosis of coronary artery disease

AIMS & OBJECTIVES

To assess the correlation between NLR and glycaemic control in T2DM patients.

MATERIALS & METHODS

A hospital-based cross-sectional study was carried out amongst 60 T2DM patients, wherein NLR measured from venous blood samples. HbA1c estimated using HPLC method. Pearson's correlation was used to analyse the relationships between HbA1c and NLR with a p-value < 0.05 considered statistically significant.

RESULTS

The mean age of our study subjects was found to be 54.25± 8.50 yrs. Our study population showed a clear male predominance, with a male-to-female (M: F) ratio of 1:0.57. Further, we found the mean BMI to be 27.95 ± 4.02 kg/m². 55 patients were found to have HbA1C level above 6.5%. 49 patients had a normal NLR value, whereas 11 patients had an NLR value above 3.50. It is observed that increasing HbA1C levels found to correlate strongly with increase in NLR Ratio.

CONCLUSION

There was a significant positive correlation between the Neutrophil-to-Lymphocyte Ratio and HbA1C levels in type 2 diabetes mellitus patients. Higher NLR was linked to poor glycaemic control, indicating it's role as an independent marker of inflammation. We conclude NLR as a reliable, easily available, cost-effective marker which can forecast systemic inflammation in a variety of chronic inflammatory disorders.

Keywords: Glycaemia, Neutrophil Lymphocyte Ratio, Diabetes Mellitus, Neutrophil, Lymphocyte

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INTRODUCTION

Diabetes mellitus (DM) is a public health problem with a gradually increasing prevalence, on a worldwide scale.¹ Type 2 diabetes is on the rise worldwide, and it is approaching an epidemic level in many countries, particularly India.^{2,3}

Type 2 diabetes mellitus (T2DM) is associated with various complications such as cardiovascular disease, nephropathy, neuropathy, retinopathy, lower limb amputations. this may lead to reduced life expectancy, quality of life and higher mortality rates.⁴

In recent years, T2DM is being recognized as a chronic metabolic disorder which is linked to persistant low-grade inflammation. Poor glycaemic control may

further exacerbate this inflammatory process which increases the risk of complications.^{4,5}

Many pathophysiological pathways suggest that inflammatory processes have a significant role in the onset and progression of T2DM. Subclinical inflammation may be associated with an increased risk of cardiovascular disease in individuals with diabetes.⁵

Because of the strong association between diabetes mellitus and cardiovascular disease, the NCEP-ATP III guidelines identify diabetes as a coronary heart disease risk equivalent, placing affected individuals at the same risk level as patients with established coronary artery disease. Biomarkers such as high-sensitivity C-reactive

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protein (hs-CRP), interleukin-6 (IL-6), tumour necrosis factor-alpha (TNF- α), fibrinogen, P-selectin, and serum amyloid A are commonly used to assess systemic inflammation, which plays a key role in the pathogenesis of atherosclerosis.^{1,6}

However, inflammatory markers such as CRP and IL-6 are costly and not easily available in low-resource settings, thereby increasing the financial burden on patients. In this context, the neutrophil-to-lymphocyte ratio (NLR), derived from a routine complete blood count, serves as a simple, inexpensive, and cost-effective marker of systemic inflammation^{1,2}.

Leukocytes including Neutrophil-to-Lymphocyte Ratio (NLR) has lately become a prominent inflammation marker, and studies have shown that a high NLR negatively influences the prevalence and prognosis of coronary artery disease.^{2,9} Many studies have shown that diabetes-related macrovascular and microvascular problems increase the NLR rate. NLR is regular investigations that is affordable and simple to conduct.

Therefore, this study was carried out to assess the relationship between glycaemic control parameters and the Neutrophil-to-Lymphocyte Ratio (NLR) in patients with type 2 diabetes mellitus, with particular focus on how HbA1c variations influence NLR.

AIMS & OBJECTIVES

To assess the correlation between NLR and glycaemic control in T2DM patients.

MATERIALS & METHODS

The study was conducted in Raja Rajeswari Medical College and Hospital, Karnataka, India, Institutional ethical clearance was obtained before starting the study. Participants were recruited for the study after explaining the procedure in detail and taking a written consent.

❖ Study design: Hospital-based cross-sectional observational study.

❖ Sample size: 60 T2DM patients, selected by simple random sampling.

Inclusion Criteria

❖ Patients aged 21 years and above diagnosed with Type 2 Diabetes Mellitus as per ADA(American Diabetes Association) criteria within the last 2 years

❖ Individuals willing to give informed written consent

❖ Clinically stable individuals without acute complications

Exclusion Criteria

❖ Patients on statins, thiazolidinediones (TZDs), aminoglycosides, aspirin, or other anti-inflammatory drugs affecting inflammatory markers

❖ Patients with acute or chronic infections, malignancy, autoimmune disorders, or inflammatory diseases

❖ Patients with extreme BMI values that may independently influence inflammatory markers

Methodology

Clinical and Anthropometric Assessment

General and systemic examinations were performed. Resting pulse, blood pressure, and temperature were recorded. Anthropometric measurements included height, weight, BMI (as per South Asian guidelines), waist circumference, hip circumference, and waist-hip ratio.

Sample Collection

Venous blood was collected from the antecubital vein by trained personnel under aseptic precautions. About 6 ml of fasting blood (after at least 8 hours of overnight fasting) and 2 ml of postprandial blood (2 hours after breakfast) were obtained.

Laboratory Analysis

Complete blood count was performed using an automated hematology analyzer, and Neutrophil-Lymphocyte Ratio (NLR) was calculated. Fasting blood glucose and postprandial glucose were measured using standard enzymatic methods. Glycated hemoglobin (HbA1c) was estimated by High-Performance Liquid Chromatography (HPLC).

Statistical Analysis

Data was collected & statistical analysis was carried out using IBM SPSS 26.0 software. Descriptive statistics for discrete variables were utilized to characterize the data through the implementation of frequency analysis and percentage analysis.

Pearson's correlation was used to analyse the relationships between HbA1c and NLR with a p-value < 0.05 considered statistically significant.

RESULTS

The mean age of our study subjects was found to be 54.25 \pm 8.50 yrs. (Fig 1) We had definite male predominance, with a male-to-female (M:F) ratio of 1:0.57. (Fig 2).

Further, we found the mean BMI to be 27.95 \pm 4.02 kg/m². Majority of the patients 55 (91.67%) patients were found to have HbA1C level above 6.5%.

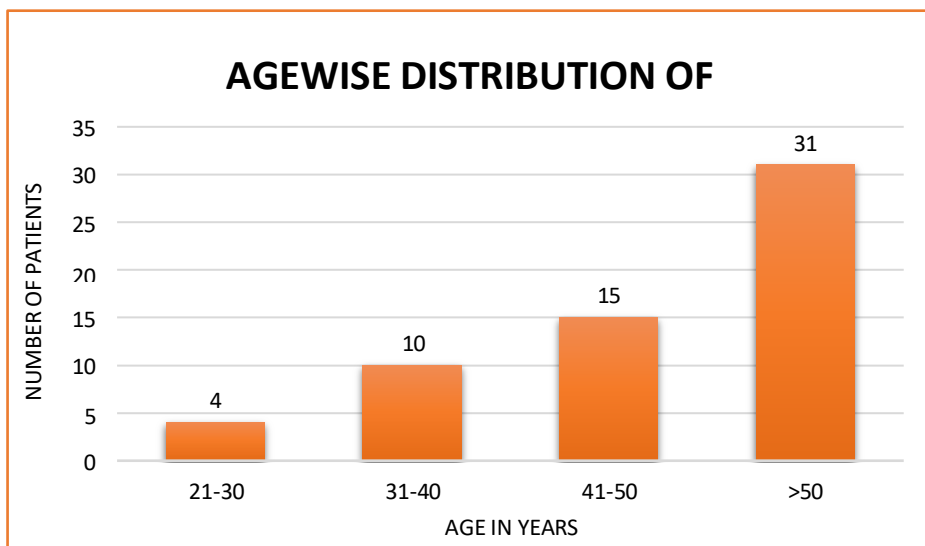


Fig 1: Age distribution

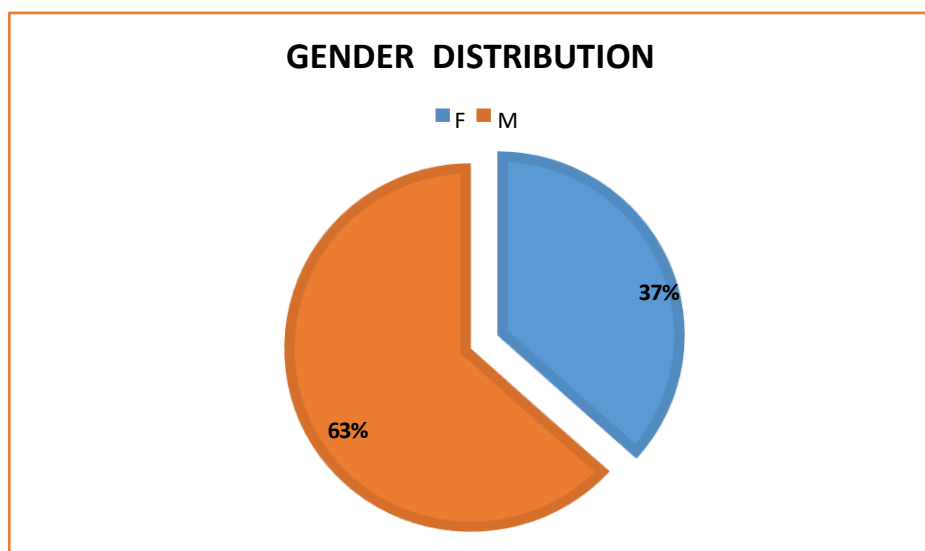


Fig 2: Gender distribution

NLR Ratio*	No of cases	Percentage
Up to 3.50	49	82%
> 3.50	11	18%
Total	60	100%

* NLR Ratio = Neutrophils to Lymphocytes Ratio

Table 1: NLR ratio

Mean HbA1C	No of Cases	Mean NLR Ratio
4.85	2	1.12
6.24	3	2.02
7.34	13	2.94
9.40	35	3.40
10.12	7	4.36
Pearson correlation Coefficient		
R	0.832	strong positive correlation
P	<0.00001	significant

Table 2: Correlation of HbA1C and NLR Ratio

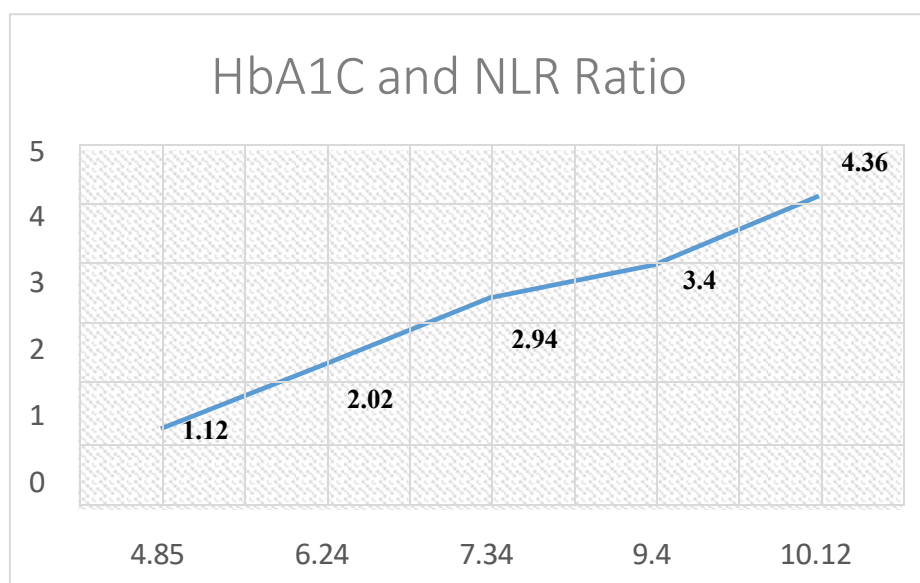


Figure 3: HbA1C and NLR Ratio

HbA1C levels showed a strong positive correlation with NLR Ratio (R= 0.832) (Table 2, Fig 3)

DISCUSSION

Type II DM are increasing at an astonishing pace worldwide, with it reaching epidemic proportions across various countries, India being one of them.²

Blood glucose levels have been conventionally used to assess & diagnose diabetes. Glycated hemoglobin (HbA1c) is used to measure the long-term glycaemic control amongst diabetic patients. However, both these commonly used parameters fail to forecast the ongoing inflammatory process in diabetic, which is one of the main pathways related to diabetes associated complications.^{2,10-12}

Over the years, Neutrophil-Lymphocyte Ratio (NLR) has gained importance, as it can easily detect & monitor inflammatory process.¹³ A high neutrophil value is a marker of the ongoing, destructive, nonspecific inflammatory process. On the contrary, a low lymphocyte count points to somewhat inadequate immune regulation, apart from a quiescent immunity pathway. Therefore, high NLR levels indicate the functional status of the immune system during chronic inflammation.¹⁰

The mean age of T2DM subjects in our study is 54.25 ± 8.50 years, which is in accordance to Dayama N et al.,² who reported a mean age of 54.10 years among controlled T2DM patients and 55.3 years among those with uncontrolled T2DM. Similar age distributions have also been reported by Shamshirgaran et al.⁷ and Fox et al.⁸, indicating that T2DM is most prevalent during the fifth decade of life.

Similar findings were reported by Akin S et al.¹, who observed that the mean body mass index (BMI) among both good and poor glycaemic control groups was approximately 28 kg/m². In the same study, Akin et al. performed a detailed assessment of glycaemic status and reported that the mean HbA1c levels were 6.7% in patients with good glycaemic control and 10.1% in those with poor glycaemic control.

In contrast to our observations, Sefil et al.¹⁴ reported no significant association between BMI and the neutrophil-to-lymphocyte ratio (NLR). However, they demonstrated a strong positive correlation between NLR and HbA1c levels, indicating that NLR is more closely related to glycaemic status rather than adiposity.

According to current international and national guidelines, the recommended target HbA1c level is below 7% for patients with Type 1 diabetes mellitus and uncomplicated Type 2 diabetes mellitus. In patients with established complications, particularly those with cardiovascular or neurological comorbidities and in the elderly population, a relatively less stringent HbA1c target of approximately 8% is advised^{15, 16}.

In the present study, the majority of patients, 55 (91.67%), had HbA1c levels above 6.5%, indicating suboptimal glycaemic control. Sonmez et al. demonstrated a significant association between elevated NLR values and both the presence and complexity of coronary artery disease. The relationship

between diabetes mellitus and NLR has therefore gained increasing attention as an area of active research⁶.

In recent years, NLR has emerged as a novel and reliable marker of systemic inflammatory response across a wide range of diseases¹⁰. The exact mechanism responsible for elevated NLR levels in patients with uncontrolled Type 2 diabetes mellitus is not fully understood; consequently, multiple etiopathogenetic mechanisms have been proposed¹⁷.

In recent years, the neutrophil-to-lymphocyte ratio (NLR) has emerged as a novel and reliable marker of systemic inflammation across a wide range of clinical conditions¹⁰. Multiple studies have demonstrated a significant association between elevated NLR values and poor glycaemic control in patients with diabetes mellitus.

In the present study, 49 (81.67%) patients had normal NLR values, while 11 (18.33%) patients exhibited NLR values greater than 3.50. A strong positive correlation was observed between increasing HbA1c levels and rising NLR values, indicating worsening glycaemic control.

Yilmaz et al.²¹ evaluated the role of NLR in gestational diabetes mellitus and reported significantly higher NLR values in pregnant women with gestational diabetes compared to healthy controls. They proposed an NLR cut-off value of >2.93 , which showed a sensitivity of 76% and specificity of 94% for the diagnosis of gestational diabetes mellitus.

Shiny et al.¹⁵ also examined the relationship between glucose intolerance and NLR and reported higher NLR values in patients with impaired glucose metabolism.

Dayama N et al.² reported that 40.48% of controlled diabetics and 63.29% of uncontrolled diabetics had NLR values greater than 2, indicating a higher inflammatory burden in poorly controlled diabetes.

Similarly, Devamsh et al.²² demonstrated a significant positive correlation between NLR and glycaemic control, with elevated NLR values being associated with increased HbA1c levels and poor glycaemic status.

Akin S et al.¹ reported mean NLR values of 2.07 in patients with good glycaemic control and 2.48 in those with poor glycaemic control. Duman et al.²³ found that median NLR values were significantly higher in patients with Type 2 diabetes mellitus compared to healthy controls and showed a strong correlation with HbA1c levels.

Hussain et al.²⁴ further supported these findings by demonstrating that increased NLR was significantly associated with poor glycaemic control in patients with Type 2 diabetes mellitus.

Chronic low-grade inflammation plays a pivotal role in the development and progression of diabetic complications and is often reflected by elevated leukocyte counts. This inflammatory milieu is considered a potential etiopathogenetic mechanism for both microvascular and macrovascular complications of diabetes mellitus^{10, 18, 19}.

The neutrophil-to-lymphocyte ratio represents a balance between two opposing immune pathways. Neutrophils contribute to endothelial injury through oxidative stress, release of proteolytic enzymes, and promotion of vascular inflammation, while lymphocytes exert anti-atherosclerotic and regulatory immune effects. An increase in neutrophils combined with a reduction in lymphocytes results in an elevated NLR, reflecting heightened inflammatory activity^{18,19}. Studies have also suggested that patients with Type 2 diabetes mellitus exhibit impaired lymphocyte proliferation. Hyper-glycaemia induced lymphopenia further contributes to an increased NLR, thereby linking poor glycaemic control to systemic inflammation²⁰.

Based on existing evidence, NLR can be considered a reliable biomarker of low-grade systemic inflammation. It has been shown to be useful in various inflammatory and metabolic conditions such as diabetes mellitus, obesity, hypertension, metabolic syndrome, thyroiditis, inflammatory bowel disease, irritable bowel disease, cardiovascular diseases, COVID-19 infection, and malignancies. NLR has also been identified as an independent predictor of morbidity, mortality, and long-term survival^{10,25}.

The present study has certain limitations, including a relatively small sample size, a single-center study design, a non-randomized sample, and the absence of multiple observers. To overcome these limitations, future studies should involve larger sample sizes, multicentric participation, randomized sampling, and standardized multi-observer assessments.

CONCLUSION

Hence, the Neutrophil-to-Lymphocyte Ratio (NLR) can be considered a simple, easily available, and cost-effective inflammatory marker in patients with T2DM. The significant positive correlation observed between NLR and HbA1c levels indicates that increasing systemic inflammation parallels worsening glycaemic control. Therefore, NLR may serve as a useful tool to predict disease progression and identify patients at risk of poor glycaemic control. Incorporating NLR into routine clinical evaluation may assist clinicians in early risk stratification and enable more effective planning and optimization of management strategies, thereby potentially reducing the burden of diabetes-related complications.

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