

Original Research Article

## Relation of Neutrophilic Lymphocyte Ratio to Microvascular Complications of Diabetes Mellitus

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### ABSTRACT

**Introduction:-** Many epidemiological studies have highlighted that chronic low grade inflammation is associated with diabetes mellitus. Neutrophil-to lymphocyte ratio is a potential marker for inflammation in cardiac and non-cardiac disorders like diabetes and hypertension. Neutrophil lymphocyte ratio can be an important measure of systemic inflammation as it is cost effective, readily available and can be calculated easily.

**Materials and Methods-** The study was conducted in medical wards of a tertiary care hospital in Belgaum, Karnataka, India between January 2014 to January 2015. 40 patients were included in the study, patients were included retrospectively. Further laboratory data as a complete blood count (hemoglobin level, platelet count, neutrophil count, lymphocyte count, NLR), blood chemistry (urea, creatinine), fundoscopy was also done.

**RESULTS:-** In our study 21 out of the 40 cases had microvascular complications which was a significant number to assess the NLR ratio. Most of the cases had nephropathy and retinopathy together (n=15) in whom the NLR ratio was significantly on a higher side. Out of the 40 cases 21 cases had microvascular complications. From these 21 cases who demonstrated microvascular complications 15 cases revealed a NLR of >3.85 (p=0.001). In remaining 6 cases NLR was less than 3.85.

**Conclusion-** NLR serves an important function in predicting risk of microvascular complications. The nephropathy and retinopathy in our patients with diabetes might be due to vascular complications via chronic inflammation, and NLR may be helpful in estimating the prognoses of these patients. In conclusion, the NLR values of patients with diabetes must be calculated because NLR is a cheap marker with high predictive value for early microvascular complications.

**Key words-** Neutrophil to Lymphocyte Ratio (NLR), Diabetes Mellitus (DM).

### INTRODUCTION

Diabetes mellitus is a chronic and potentially disabling disease which is reaching an epidemic proportion in many parts of the world and a major growing threat to global public health. <sup>[1]</sup> Diabetes Mellitus has evolved into a global epidemic and India has the second largest population with diabetes. Diabetes and its complications caused 4.9 million deaths in

2014 and every seven second a person dies from diabetes or its complication. Based on the recent statistics of International Diabetes Association it is estimated that worldwide 387 million people have diabetes and by 2035 this will rise to 592 million. The prevalence in India is over 65 million and these figures are expected to increase to over 100 million by 2030. Diabetes Mellitus and its complications

lead to significant socioeconomic Burden in a country like India. The microvascular complications being diabetic nephropathy, neuropathy and retinopathy and macrovascular complications being atherosclerosis, ischemic heart disease, stroke and peripheral vascular disease pose a major economic burden on diabetic patients. Diabetic nephropathy is the single most common cause of end-stage renal disease. [1] In addition, through its association with the development of generalized vascular disease, diabetic nephropathy is the main cause of the excess mortality in diabetes. Also diabetic neuropathy and nephropathy pose significant problem. Thus identification of these complications at an early stage is necessary.

Many epidemiological studies have highlighted that chronic low grade inflammation is associated with diabetes mellitus. Systemic inflammation can be measured by using a variety of biochemical and haematological markers. Although novel disease specific biomarkers have been identified, most of which are time consuming and expensive. Observational studies have thoroughly investigated the role of C-reactive protein and total leukocyte count in different chronic conditions. Low grade inflammation measured by White Blood Cell (WBC) count has also been linked to the traditional risk factors of chronic diseases i.e. smoking, obesity, hypertension and elevated levels of triglycerides. [2,3]

Recent evidence indicated that the ratio of sub types of blood cells have a significant prognostic value for cardiovascular disease. Neutrophil-to lymphocyte ratio is a potential marker for inflammation in diabetes mellitus. Neutrophil lymphocyte ratio could be an important measure of systemic inflammation as it is cost effective, readily available and could be calculated easily. Little is known and published about

neutrophil lymphocyte ratio and its relationship with prevalent chronic conditions among general population. Therefore, the current study was conducted to investigate the neutrophil lymphocyte ratio as a measure of systemic inflammation and its relationship, with microvascular complications of diabetes mellitus. [4]

## **MATERIALS AND METHODS**

The study was conducted in medical wards of a tertiary care hospital (KLE hospital) in Belgaum, Karnataka, India between January 2014 to January 2015. All patients admitted in medical wards with complications of diabetes mellitus were included. 40 patients were included in the study, patients were included retrospectively. Patient demographic data including age, gender, disease duration were taken. The mean age of the patients was  $53.47 \pm 6.14$  years. Further laboratory data as a complete blood count (hemoglobin level, platelet count, neutrophil count, lymphocyte count, NLR), blood chemistry (urea, creatinine), fundoscopy was also done. The study excluded patients with active infection, leukocytosis, malignancy and patients on steroid. The data was analysed using SPSS statistical software version 20.0.

The data obtained was coded and entered into Microsoft excel spreadsheet and data was analysed using SPSS version 20. The categorical data was expressed in terms of rates, ratios and percentages and the continuous data was expressed in terms of mean $\pm$ standard deviation. The association between the NLR and complications was tested using Fisher's exact test. The discrimination of complications and NLR was made using the receiver operating characteristic curve (ROC curve). The accuracy of NLR in predicting complications was expressed in terms of sensitivity, specificity, positive predictive value and negative predictive value. A probability (p) value of  $\leq 0.050$  was considered as statistically significant.

## RESULTS

In our study 40 diabetic cases irrespective of sex, age and duration were screened for diabetic neuropathy, nephropathy and retinopathy. A neutrophil to leucocyte ratio was obtained from the haemogram. Factors like sepsis altering the neutrophil leucocyte ratio were ruled out.

In our study we found that diabetic distribution showed a male preponderance (n=28, male) (n=12, female). Age distribution showed majority of the diabetics belonged to middle aged population (51- 60yrs). Most of our cases had a 4 to 6 yrs history of diabetes and were on treatment. (table 1). Comorbid conditions like hypertension and ischemic heart disease were also screened to assess their effect on NLR which showed no alteration in NLR. In our study 21 out of the 40 cases had microvascular

complications which were a significant number to assess the NLR ratio. (table-2) Most of the cases had nephropathy and retinopathy together (n=15) in whom the NLR ratio was significantly on a higher side (table-3)

**Table.1 Duration of diabetes**

Duration (Years)	Distribution (n=40)	
	Number	Percentage
3 or less	12	30.00
4 to 6	15	37.50
7 to 9	11	27.50
> 9	2	5.00
Total	40	100.00

**Table.2 Complications**

Complications	Distribution (n=40)	
	Number	Percentage
Present	21	52.50
Absent	19	47.50
Total	40	100.00

**Table. 3 Frequency of complications**

Complications	Distribution (n=21)	
	Number	Percentage
Nephropathy	6	28.57
Nephropathy with retinopathy	15	71.43
Total	21	100.00

**Table. 4 Association of NLR with complications**

NLR	Complications				Total	
	Present		Absent		Number	Percentage
	Number	Percentage	Number	Percentage		
> 3.85	15	78.95	4	21.05	19	100.00
3.85 or less	6	28.57	15	71.43	21	100.00
Total	21	52.50	19	47.50	40	100.00
					p=	0.001

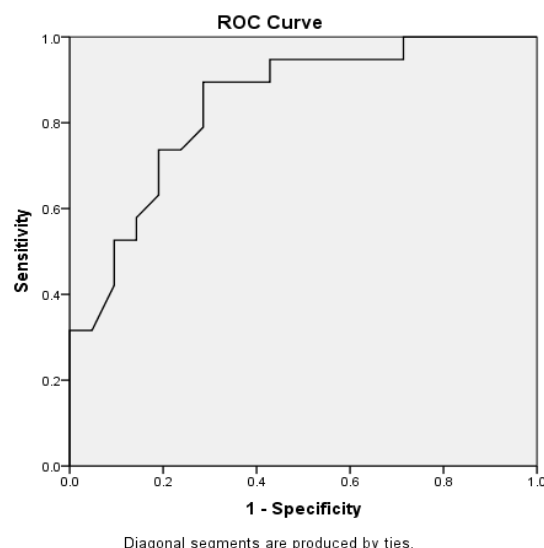
NLR Cut off - 3.85

In order to define a cut off for NLR in our study population we plotted a graph of all the NLR under a ROC (Receiver operating characteristics) curve to get the mean value relatively through which we found that 3.85 was the NLR cut off.

Out of the 40 cases 21 cases had microvascular complications. From these 21 cases who demonstrated microvascular complications 15 cases revealed a NLR of >3.85 (p=0.001). In remaining 6 cases NLR was less than 3.85. (table-4)

Following statistical values were analysed to state NLR as a positive predictor for microvascular complications.

Sensitivity	71.43
Specificity	78.95
PPV	78.95
NPV	71.43



## DISCUSSION

This study is the first to analyse the independent relationship between NLR

and all the microvascular complications in diabetics. Results showed that the NLR values were significantly higher in the diabetic patients with complications (nephropathy and retinopathy) than in the diabetic patients without microvascular complications and the healthy controls. Many epidemiological studies have determined that DM is associated with chronic inflammation, which may contribute to angiopathy development and acceleration, such as sensorineural hearing loss, retinopathy, and neuropathy in patients with DM. [5]

WBC count and its subtypes are cheap and readily available classic inflammatory markers, particularly in cardiovascular diseases. Studies have shown that neutrophilia and lymphocytopenia are independent predictors of many diseases, such as acute heart failure, coronary artery disease, and acute coronary syndromes. [6] Neutrophilia and relative lymphocytopenia are independent markers of many diseases, specifically DM complications. NLR is superior to other leucocyte parameters (e.g. neutrophil, lymphocyte and total leucocyte counts) because its stability is less influenced by physiological, pathological and physical factors.

Type 2 Diabetes Mellitus (T2DM) is characterized by insulin resistance and is associated with obesity and cardiovascular diseases. Several studies that explored the relationship between systemic inflammation and cardiovascular diseases indicated that chronic inflammation promotes the acceleration of diabetic microangiopathy in addition to the development of macroangiopathy in diabetic patients. [4] The immune response to various physiological challenges is characterized by increased neutrophil and decreased lymphocyte counts, and NLR is often recognized as an inflammatory marker to assess the severity of the disease. Calculating NLR is simpler and cheaper than measuring other

inflammatory cytokines, such as IL-6, IL-1 $\beta$  and TNF- $\alpha$ . NLR is a reliable index for predicting cardiovascular diseases that involve inflammation. Such diseases include coronary artery disease, acute coronary syndromes, and heart failure.

Several studies have explored the relationship between systemic inflammation and cardiovascular disease in patients with diabetes. Tsai *et al.* detected significant differences in the total leucocyte, neutrophil and monocyte counts between patients with diabetes and healthy subjects. They also determined that NLR is significantly high in the presence of ischaemic complications. However, previous studies have not specifically evaluated NLR values as an independent risk factor of DN. Thus, this study is the first to specifically address the relationship between NLR values and diabetic patients with DN. The NLR values were high in diabetic patients with microvascular complications. The prevalence of early-stage DN was dramatically higher in the diabetic patients with high NLR values than in the diabetic patients with low NLR values.

## CONCLUSION

NLR serves an important function in predicting risk of microvascular complications. The nephropathy and retinopathy in our patients with diabetes might be due to vascular complications via chronic inflammation, and NLR may be helpful in estimating the prognoses of these patients.

In conclusion, the NLR values of patients with diabetes must be calculated because NLR is a cheap marker with high predictive value for early microvascular complications. So our study demonstrated that high NLR values were independently related to microvascular complications.

### **Limitation:**

There were many limitations to our study, major being that the sample size was less and a control group was not taken

into consideration. Another limitation was that diabetic neuropathy patients were not taken into consideration.

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