*Original Article*

# Comparison of Neutrophil-Lymphocyte Ratio in between Type 2 Diabetic Patients and Normoglycemic Individuals

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***ABSTRACT***

*Neutrophil-lymphocyte ratio (NLR) acts as an indicator of subclinical inflammation. A cross-sectional study was carried out in the Department of Physiology, Dhaka Medical College, Dhaka, Bangladesh, between January and December 2021, to assess the status of neutrophil-lymphocyte ratio in patients with type-2 diabetes mellitus (T2DM) and normoglycemic individuals in a Bangladeshi population. A total of 180 subjects were selected aged between 20 and 79 years. Among them, 60 relatively healthy subjects were selected as control group (group A), while 120 type 2 diabetic patients were included as study group (group B) for comparison. Participants' age, gender, height, weight, waist circumference (WC) and blood pressure were recorded. Body mass index (BMI) was calculated. Then, blood samples were taken from the participants to see complete blood count (CBC), HbA1c, random blood glucose, serum creatinine and serum ALT were estimated. Receiver operating characteristic (ROC) curve was plotted to assess the NLR's performance in diabetes mellitus prediction. The power of diabetes mellitus prediction was quantified by the area under the curve (AUC) with 95% confidence intervals. No differences were found between the groups in terms of participants' age, gender, BMI, systolic and diastolic blood pressure ($p>0.05$). However, total WBC count, neutrohil count and neutrophil-lymphocyte ratio (NLR) was found higher and lower lymphocute count in type-2 diabetic patients compared to healthy controls ($p<0.001$). Measuring the predictive value of neutrophils-lymphocyte ratio in predicting diabetes mellitus, we found area under the curve (AUC) value of 0.819, SE 0.031 with 96.7% sensitivity and 70% specificity ($p<0.001$) through ROC curve analysis. Therefore, our data suggests that NLR can be used as prognostic tool during the follow up of the diabetic patients.*

***Keywords:*** *Type 2 diabetes mellitus, neutrophil-lymphocyte ratio, glycemic control, glycated haemoglobin.*

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## INTRODUCTION

Type-2 diabetes mellitus is a major public health problem regionally and globally and is a leading cause of death in most countries[1]. According to the International Diabetes Federation (IDF), 463 million (9.3%) people worldwide have diabetes and by 2045, the number may rise to 700 million (10.9%). It has also been estimated that globally as many as 193 million people, or half (50.1%) of all people with diabetes, are unaware of their disease, and many of these cases present with diabetes-related complications at the time of diagnosis. Around 88

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million people with diabetes live in low-income or middle-income countries in South-East Asia[2]. In Bangladesh, the prevalence of diabetes has been steadily rising and diabetes creates a substantial burden on the Bangladeshi population, in terms of health and well-being and lost productivity[2]. Inadequate control of glycemia in diabetic patients is the key factor for the occurrence of both micro and macrovascular complications[3].

Diabetes mellitus is a clinical condition characterized by chronic hyperglycemia. The chronic hyperglycemia of diabetes is associated with long-term damage, dysfunction, and failure of various organs, especially the eyes, kidneys, nerves, heart, and blood vessels[4]**.** It is strongly associated with both macrovascular complications, e. g., stroke, coronary artery diseases, and peripheral arterial diseases and microvascular complications e. g., diabetic retinopathy, neuropathy, and nephropathy[5]. In hyperglycemia, there is increased nonenzymatic glycation of proteins and the rate of the glycation proportionately depends upon the blood level of glucose. Thus, there is increased formation of glycated proteins due to hyperglycemia[6]. HbA1c is the example of glycated protein which are used in assessing the status of hyperglycemia in DM. These glycated proteins cause activation of pro-inflammatory mediators and produce chronic inflammation in the body[7]. This chronic inflammation causes increased activity of neutrophils which is key inflammatory cell involved in atherosclerosis that leads to endothelial dysfunction and later is can be responsible for chronic complications[8].

The increased chronic inflammation causes increased production of inflammatory markers like CRP and exhaustion of antioxidant system of the body producing oxidative stress. Increased oxidative stress is responsible for cardiovascular events and other complications occurring in diabetes mellitus[9,10]. Various tests are available to estimate the oxidative stress in the body like CRP, IL-6, TNF-á, and many others. However, those tests are expensive and not easily available at all centers. Neutrophil-lymphocyte ratio (NLR), on the other hand, has been recently discovered as a novel and stable inflammatory marker which may serve as an immediate indicator of the degree of inflammation present[11], which is got by simply division of neutrophil count by lymphocyte count in a haemogram[12]. Neutrophil-lymphocyte ratio is superior to other leukocyte parameters, because its stability is less influenced by physiological, pathological, and physical factors[13].

Neutrophil-lymphocyte ratio (NLR) is a potential marker to determine inflammation in various disorders because it has a superior predictive, diagnostic and discriminative ability than the total WBC count. Even patients with increased NLR but normal total lymphocyte count could have an increased risk of atherosclerosis-related diseases[14]. Neutrophil-lymphocyte ratio has been linked with hypertension, the severity of glucose intolerance, and insulin resistance[15]. The predictive value of NLR is comparable to various other inflammatory markers such as C-reactive protein (CRP), tumor necrosis factor, and interleukin-6 in the detection of subclinical inflammation, and endothelial dysfunction in various clinical studies[16]. Neutrophil-lymphocyte ratio can also serve as an important predictor for the presence of microvascular diabetic complications, namely retinopathy, neuropathy, and or nephropathy in patients with type 2 diabetes[13,17,18].

Zahorec et al. described an NLR meter, where NLR ratio range 1-2 is said to be normal range, 2-3 indicate low inflammation and stress, 3-7 indicates mild to moderate inflammation, 7-11 indicated moderate inflammation with stress and >11 indicates severe inflammation and stress[19].

In spite of extensive clinical studies of NLR in diabetic patients, limited data is available to determine the effect of NLR on glycemic control. However, NLR can predict ongoing inflammation and diabetes-associated complications which are not predicted by HbA1c precisely. Neutrophil-lymphocyte ratio is a simple, easily available, safe and cost-effective test. Neutrophil-lymphocyte ratio can also guide the physicians in resource-poor settings like Bangladesh when evaluating a patient with T2DM for microvascular and macrovascular complications. However, there is no published study of observing the status of NLR in patients with T2DM in our country to the best of our knowledge. Hence, the present study was designed to observe the status of NLR in Bangladeshi patients with T2DM and to compare with that of normoglycemic individuals as well as its capacity to predict diabetes mellitus.

## METHODS

This cross-sectional study was conducted in the Department of Physiology, Dhaka Medical College, Dhaka, Bangladesh, between January and December of 2021. According to selection criteria 120 diagnosed patients of type-2 DM attending the Outpatient Department (OPD) of Endocrinology & Metabolism, Dhaka Medical College Hospital, Dhaka, Bangladesh, were selected as group B (case). Then 60 age and sex matched apparently healthy individuals were selected (hospital staff, patient attendants and visitors by personal contact) for comparison as group A (control). Counseling of healthy individuals was also done and asked them to come with at least 8 hours fasting. Data were collected in a data collection sheet including particulars of the patients including age, gender, history and relevant investigations. Among the study subjects, height and body weight were measured to calculate body mass index (BMI). Blood pressure was measured to assess the cardiovascular condition of the subjects. In this study, details history was taken from study subjects regarding personal, family, drug and medical history. Fasting blood glucose, HbA1c, serum creatinine, serum alanine aminotransferase (ALT) level and complete blood count were done to exclude cardiac diseases, kidney diseases, liver diseases and presence of any infection or inflammatory condition respectively.

With all aseptic precautions, 6 ml venous blood sample was collected from median cubital vein of each study participants and out of 6 ml blood, 2 ml was mixed with potassium EDTA with gentle push to avoid hemolysis and used for estimation of HbA1c and complete blood count (CBC), another 2 ml blood was taken in a glucose tube with sodium fluoride anticoagulant, another 2 ml blood was taken in red cap tube without any anticoagulant to measure serum creatinine and serum ALT. Blood sample of CBC tube was analyzed for estimation of total count of WBC in the Department of Hematology of the same institution. Glucose tube containing blood and red cap tube containing blood were send to the Department of Clinical Pathology, Dhaka Medical College Hospital and was analyzed for estimation of fasting blood glucose level. The serum from the red cap tube containing blood sample was analyzed for estimation of serum creatinine and serum ALT.

After data collection, collected data were checked and verified; then data cleaning, coding and recording were done. Data was expressed as mean±SD (standard deviation) and range as well as frequency and percentage where applicable. Quantitative variables were compared by using the Unpaired Student's-t test, while qualitative variables were compared by using Chi-square test. Then NLR was evaluated as a tool to predict diabetes mellitus for each study subject. Receiver operating characteristic (ROC) curve was plotted to assess the performance of NLR. The power of diabetes mellitus prediction was quantified by the area under the curve (AUC) with 95% confidence intervals, i.e., a larger AUC reflecting better predictive accuracy. All statistical analyses were conducted using SPSS version 27.0. for Windows (SPSS, Chicago, IL, USA). The difference was considered statistically significant at P value <0.05 based on a 2-sided probability.

This study was approved by the Ethical Review Committee of Dhaka Medical College, Dhaka, Bangladesh.

## RESULTS

The mean age was found 52.27±6.56 years in group A and 45.20±11.74 years in group B; however, no difference was observed in age between the groups ($p>0.05$). Male predominance was observed in both groups. No difference was also observed in gender distribution between the groups ($p>0.05$). No differences were found between the groups in terms of participants' BMI, systolic and diastolic blood pressure ($p>0.05$) (Table-I). Regarding blood related parameters, significant differences were observed between the groups in terms of total WBC count, neutrophil count, lymphocyte count and particularly neutrophil-lymphocyte ratio ($p<0.001$) (Table-II). Measuring the predictive value of neutrophils-lymphocyte ratio in predicting diabetes mellitus, we found area under the curve (AUC) value of 0.819, SE 0.031 and 96.7% sensitivity and 70% specificity ($p<0.001$) through receiver operating characteristics (ROC) curve analysis (Table-III, Fig.1).

**Table-I:** *General characteristics of the study participants in different groups (N=180)*

| Parameters | Group A (n=60) (Mean±SD) | Group B (n=120) (Mean±SD) | p-value |
|---|---|---|---|
| Age (years) | 52.27±6.56 (32-59) | 45.20±11.74 (24-70) | 0.074 |
| Gender | | | |
| Male | 33(55.0%) | 81(67.5%) | 0.235 |
| Female | 27(45.0%) | 39(32.5%) | |
| BMI (Kg/m²) | 23.84±1.58 (19.7-28.2) | 24.18±1.91 (19.7-29.4) | 0.235 |
| Systolic pressure (mmHg) | 121.27±10.27 (100-145) | 120.73±8.61 (100-140) | 0.710 |
| Diastolic pressure (mmHg) | 76.32±6.87 (60-90) | 75.28±7.06 (60-90) | 0.348 |

Results were expressed as mean±SD with range and as frequency and percentage where applicable. Unpaired Student's t-test and Chi-square test were performed to compare between two groups, NS= not significant

**Table-II:** *Comparison of blood parameters between two groups (N=180)*

| Variables | Group A (n=60) | Group B (n=120) | p-value |
|---|---|---|---|
| Total WBC ($\times 10^3/\mu l$) | 7.84±1.62 (4.73-11.47) | 9.28±1.99 (4.08-14.60) | <0.001* |
| Neutrophil count ($\times 10^3/\mu l$) | 57.19±4.50 (48.1-66.2) | 64.79±8.19 (42.6-76.1) | <0.001* |
| Lymphocyte count ($\times 10^3/\mu l$) | 36.14±4.36 (25.2-47.7) | 28.16±6.33 (18-44.8) | <0.001* |
| Neutrophil-lymphocyte ratio (NLR) | 1.62±0.29 (1.01-2.34) | 2.47±0.77 (0.95-4.0) | <0.001* |

Data were expressed as mean±SD and range. Unpaired Student t-test was performed to compare between two groups, *=significant

**Table-III:** *Predictive value of neutrophils -lymphocyte ratio in predicting diabetes mellitus*

| Neutrophil-lymphocyte ratio cut off value | Case | | Control | | Total | |
|---|---|---|---|---|---|---|
| | Frequency | Percentage | Frequency | Percentage | Frequency | Percentage |
| >2.08 | 84 | 70% | 2 | 3.33% | 86 | 47.77% |
| ≤2.08 | 36 | 30% | 58 | 96.66% | 94 | 52.22% |
| Total | 120 | 100% | 60 | 100% | 180 | 100% |
| Predictive value | | | | | | |
| AUC | | | 0.819 | | | |
| SE | | | 0.031 | | | |
| Sensitivity | | | 96.7% | | | |
| Specificity | | | 70% | | | |
| p-value | | | <0.001 | | | |
| 95% CI Lower | 0.758 | | | | | |
| Upper | 0.879 | | | | | |

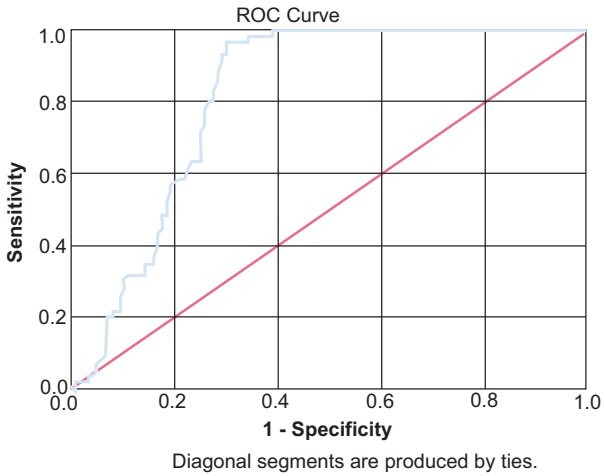


**Fig. 1:** *ROC curve of neutrophils-lymphocyte ratio (NLR) showing its predictability of diabetes mellitus in study participants*

## DISCUSSION

The present study, we noticed a higher NLR (2.47±0.77) among diabetic patients than that of non-diabetic control group (1.62±0.29) ($p<0.001$). As per NLR meter given by Zahorec et al. Any NLR ratio between 2-3 indicates low inflammation and stress. In our study, NLR in DM group is 2.47±0.77 indicating low grade inflammation with stress[19].

In our study, ROC curve analysis shows that best cut off point of NLR was 2.08. It is also observed that 84 diabetics has their NLR ratio >2.08. Thus, 70% of diabetics were having NLR ratio >2.08. Similarly, we also observed that 58 non diabetics were having their NLR ratio <2.08. In this study, the sensitivity and specificity of NLR ratio to detect T2DM comes out to be 96.7% and 70% respectively. There is reported data that shoed increased NLR as a marker of disease related inflammation[20]. Few studies also reported that NLR ratio is linked with higher HbA1c and poor glycemic control in T2DM[21] Several studies have observed that uncontrolled diabetes is associated with high NLR. A study done by Fawwad et al. reported that subjects with normal TLC but increased NLR had increased risk of atherosclerosis which is a key pathological process of cardiovascular complications in diabetics[17]. Lou et al. reported significantly higher NLR ratio was associated with insulin resistance in newly diagnosed type-2 diabetics. They also proposed raised NLR as a predictive marker of insulin resistance[22]. Selfil et al. reported raised NLR may be associated with high HbA1c in T2DM[23]. Akin et al. suggested that NLR might be used as an easily measurable, noninvasive, and cost-effective parameter for the follow-up of diabetic patients[24].

NLR represents a combination of two markers where neutrophils represent the active nonspecific inflammatory mediator initiating the first line of defense, whereas lymphocytes represent the regulatory or protective component of inflammation[25]. Patients with T2DM are in a state of low-degree chronic inflammation that induces hypersecretion of inflammatory factors, such as CRP, IL-6, TNF-á, and MCP-1, which may interact in haematopoiesis in bone marrow results in a constantly elevated neutrophilic granulocyte count and thus, cause an increase in inflammatory haemogram indices such as NLR. Moreover, chronic hyperglycemia tends to release more reactive oxygen species from neutrophils. Hyperglycemia or advanced glycation end products induce persistent activation of neutrophils, as seen by the increased activity of neutrophil alkaline phosphatase and causes neutrophilia. Besides, type-2 diabetic patients have insufficient proliferation of lymphocytes due to low expression of interleukin-2 receptors and lymphopenia is linked with inflammation[23,26]. Apart from that another suggested mechanism is that increased NLR in diabetic patients could be caused by differential influence of hyperglycemia on neutrophils and lymphocytes. Increased apoptosis in lymphocytes and increased oxidative DNA damage in peripheral blood lymphocytes has been demonstrated in patients with T2DM. In contrast, hyperglycemia has been shown to reduce the apoptosis in neutrophils, leading to impaired neutrophil clearance and prolonged inflammation in diabetes[27]. However, the exact mechanism demands further research.

There are some limitations of this study. The sample was taken purposively and conveniently. Hence, there may be chance of bias which can influence the result. The study was conducted in a selected hospital. Therefore, the study population might not represent the whole community.

## CONCLUSION

Our data suggests that Neutrophil-Lymphocute Ratio (NLR) is significantly higher in patients with T2DM than that of apparently healthy adults. Moreover, it is a simple, readily available and inexpensive examination; it shows an AUC value of 0.819, SE 0.031

with 96.7% sensitivity and 70% specificity ($p<0.001$) through ROC curve analysis. Therefore, NLR can be used as prognostic and disease monitoring tool during the follow-up of diabetic patients in our country.

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