

Neutrophil Lymphocyte Ratio (NLR) is an Indicator of Coronary Artery Disease (Cad) in Type 2 Diabetes Mellitus Patients

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Research Article

Volume 2 Issue 1

Received Date: October 22, 2018

Published Date: November 01, 2018

DOI: 10.23880/cprj-16000112

Abstract

Background: Coronary artery disease (CAD) is the leading cause of death in type 2 diabetes mellitus (DM) patients. DM is a significant risk factor in atherosclerotic cardiovascular disease (CVD). We aimed to investigate relationship between Neutrophil lymphocyte ratio (NLR) and CAD proven with angiography in type 2 DM and to establish NLR as a useful indicator of CAD in type 2 DM patient.

Objective: To assess the NLR as a predictive marker for CAD in patients with type 2 diabetes mellitus.

Methods: This case control study was conducted in the Department of Clinical Pathology in collaboration with Department of Cardiology, Bangabandhu Sheikh Mujib Medical University (BSMMU), Shahbag, and Dhaka from March 2014 to February 2015. Total 134 patients were enrolled in this study who were waiting for further percutaneous coronary intervention (PCI) in the Department of Cardiology, BSMMU; 84 cases were considered as Group I (DM with CAD) and 50 controls were Group II (DM without CAD). A 2 ml of blood was collected in EDTA tube from the patients prior to PCI for complete blood count (CBC) were measured by hematology auto analyzer, rechecked manually and NLR was calculated in the Department of Clinical Pathology, BSMMU. Coronary artery disease with 50% coronary artery stenosis and more critical lesion that were diagnosed by PCI were included in this study as cases. Coronary artery disease with less than 50% coronary artery stenosis that was diagnosed by PCI was included in this study as control. The statistical analysis was done by Chi-square test and unpaired sample 't' test.

Results: NLR was higher in CAD (+) group compared to group without CAD (-) (2.76 (±0.74) vs 1.56 (±0.15), p<0.001).

Conclusion: NLR was higher in DM patients with angiographically proven CAD compared to those DM patients without CAD. NLR may be a useful marker to predict the presence of CAD in type 2 DM patients.

Keywords: Neutrophil lymphocyte ratio; Diabetes mellitus; Coronary artery disease

Abbreviations: CAD: Coronary Artery Disease; CVD: Cardiovascular Disease; NLR: Neutrophil Lymphocyte Ratio; PCI: Percutaneous Coronary Intervention; CBC: Complete Blood Count; BSMMU: Bangabandhu Sheikh Mujib Medical University; CHD: Chronic Heart Disease; WBC: White Blood Cell; ESR: Erythrocyte Sedimentation Rate; FPG: Plasma Glucose- Fasting; PPBG: Plasma Glucose 2 Hours After 75 G Glucose; HBA1c: Glycated Hemoglobin; ALT: Alanine Amino Transferase.

Introduction

Diabetes is a group of metabolic disorders characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both [1]. According to WHO report, Bangladesh had 3.2 million of diabetic subjects in 2000 and the number is expected to increase to a staggering 11.1 million by 2030 [2]. Type 2 DM is a chronic disease associated with many complications. There is two to four fold increased risk of cardiovascular disease in type 2 DM patients. (Tables 1 & 2) About 52% cause of death in type 2 DM is cardiovascular disease [3]. Several mechanisms are likely to contribute to the accelerated atherosclerosis and increased chronic heart disease (CHD) risk in patients with type 2 diabetes mellitus. Important factors of premature coronary atherosclerosis include dyslipidemia, hypertension, hypercoagulability, poor glycemic control, smoking, obesity and lack of physical activity [4]. Most important factors are hyperglycemia affecting the vessel wall, diabetic dyslipidemia, hyperglycemia against dyslipidemia and chronic inflammation in the vessel wall [5].

	Group-I Mean \pm SD (n=84)	Group-II Mean \pm SD (n=50)	P value*
HbA1c (%)	7.40 \pm (1.04)	6.13 \pm (0.65)	<0.001

Table 1: Mean difference between Group-I (DM with CAD) and Group-II (DM without CAD) with HbA1c (%) (n=134). * Unpaired sample t test was done to measure level of significance.

Lipid profile	Group I (n=84)	Group II (n=50)	P value*
TC (mg/dl)	187.75 (\pm 39.16)	150.0 (\pm 17.87)	<0.001
Range	115-320	96-183	
HDL (mg/dl)	30.61 (\pm 6.12)	44.22 (\pm 11.55)	<0.001
Range	22-60	28-90	
LDL (mg/dl)	108.77 (\pm 17.83)	83.20(\pm 10.02)	<0.001
Range	68-170	51-108	
TG (mg/dl)	179.35 (\pm 19.60)	142.02(\pm 17.65)	<0.001
Range	118-230	118-230	

Table 2: Mean difference between Group-I and Group-II with lipid profile (n=134).

* Unpaired sample t test was done to measure level of significance

TC = <0.001

HDL = <0.001

LDL = <0.001

TG = <0.001.

The relationship between various inflammatory markers and CAD has been established [6]. Among these markers, the levels of white blood cell (WBC) subtypes confirmed inflammatory markers that play a crucial role in the pathogenesis of atherogenesis and atherothrombosis [7], have received significant attention. It has been established that the WBC count and levels of WBC subtypes not only play an important role in the development of CAD, but can also be used to predict the clinical outcomes of patients with CAD [8].

Neutrophil lymphocyte ratio (NLR) is the sign of balance between Neutrophil lymphocyte levels in the body and an indicator of systemic inflammation [9]. NLR is a new indicator for cardiovascular risk and mortality and by which we can predict the risk of coronary artery disease in type 2 DM patients [10]. Increased NLR is associated with major adverse cardiac events in diabetic patients [11,12].

In this study, we aimed to investigate relationship between NLR and CAD proven with angiography in type 2 DM and to establish NLR as a useful indicator of CAD in type 2 DM patient (Table 3).

	Sex		P-value*
	Male Mean \pm SD	Female Mean \pm SD	
NLR	2.44(\pm 0.82)	1.92(\pm 0.76)	0.008
Range (min-max)	1.23-7.0	1.25-5.0	

Table 3: Distribution of mean NLR with sex (n=134). * Unpaired sample t test was done to measure level of significance.

Methods

This case control study was conducted at the Department of Clinical Pathology in collaboration with the Department of Cardiology, Bangabandhu Sheikh Mujib Medical University (BSMMU), Shahbag, Dhaka from March 2014 to February 2015. 134 type 2 DM patients were enrolled in this study; 84 cases were considered as Group I (DM with CAD) and 50 controls were Group II (DM without CAD).

Type 2 DM patients with coronary artery disease who have $\geq 50\%$ stenosis, adults (18 years and above) patients, patients of both sexes were included in this study. Recurrent myocardial infarction, patients with congenital cardiac disease as shunt or vascular anomalies, pulmonary hypertension (both primary or secondary), acute or chronic infectious diseases, uncontrolled hypertension, known case of patients with cerebrovascular diseases, patients with documented malignancy, hematological disorders, patients with hepatic and renal impairment were excluded from the study. In this study patient's complete blood counts were measured by hematology auto analyzer (SYSMEX 4000i), rechecked manually and NLR was calculated in the Department of Clinical Pathology, BSMMU.

After selection, all the patients were thoroughly informed about the aims, objectives and procedure of the study and were encouraged for their voluntary participation (Tables 4 & 5). Then an informed written consent was taken from each subject. A detail personal, medical, occupational, educational and smoking history was recorded in a preformed data schedule and thorough physical examinations were done and documented. Tests done in Dept. of Clinical Pathology: CBC with PBF including differential count of WBC, erythrocyte

sedimentation rate (ESR) and Neutrophil lymphocyte ratio (NLR). Reports collected from patient's file were: plasma glucose- fasting (FPG), plasma glucose 2 hours after 75 g glucose (PPBG), glycated hemoglobin (HbA1c), serum lipid profile, serum creatinine, alanine amino transferase (ALT).

	Group-I Mean \pm SD	Group-II Mean \pm SD	P value*
NLR (Ratio)	2.76 (\pm 0.74)	1.56 (\pm 0.15)	<0.001
Range (min-max)	2.0-7.0	1.23-1.74	

Table 4: Mean NLR difference between Group-I and Group-II (n=134).

* Unpaired sample t test was done to measure level of significance.

Cut off value of NLR was 1.74.

	Cut of value	Sensitivity	Specificity	Accuracy
Neutrophil lymphocyte ratio (NLR)	1.74	98%	58%	p<0.001

Table 5: Neutrophil lymphocyte ratio and Group-I (DM with CAD) for evaluation of coronary artery disease (CAD).

Results

A total 134 type 2 DM patients were included in the study. 84 cases were considered as Group I (DM with CAD) and 50 controls were Group II (DM without CAD).

The mean age of the DM with CAD (Group I) was 54.73 \pm 8.94 years, the mean age of the DM without CAD (Group II) was 53.10 \pm 9.47 years (Figure 1).

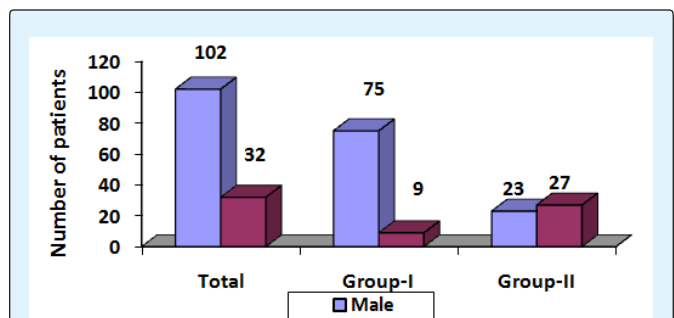


Figure 1: Sex distribution of the study population (n=134).

*Chi-square test was done to measure level of significance (P <0.001).

Discussion

Neutrophil lymphocyte ratio (NLR) is the sign of balance between neutrophil and lymphocyte levels in the body and an indicator of systemic inflammation [13]. NLR is a new predictor for cardiovascular risk and mortality. NLR could play an important role in early detection of atherosclerosis in diabetic patients and by which we can initiate early treatment [14].

Coronary artery disease occurs at any adult age, but it is the disease of middle and old age. In our study, the mean age of the patients in Group I (DM with CAD) was 54.73 (± 8.94) years as compared to 56.59 ± 13.63 years and 58.01 ± 12.9 years, studies done by Assiri AS, et al. and Al-Saif SM, et al. [15,16]. It was 52.0 ± 8.6 years in a study reported by Siddique MA, et al. [17] and 56.6 years by Ullah M, et al. [18] in Bangladesh.

There was clear male predominance in Group I (89.28%). In Group II there was 46% male. The difference was statistically significant between the groups ($p < 0.001$). Our study is consistent with findings of study done by Bittencourt C, et al. [19]. They also found male predominance. They found that in patients with CAD group, male patient was 61.2% and in the other group male patient was 40%. There was also statistically significant association between the groups ($p < 0.001$). Our findings are also similar with the results found in the study conducted by Sonmez O, et al., Sayeed MA, et al., Paudel R, et al., Joshi P [20-22].

Glycemic control, measured here by HbA1c, was associated with CAD among type 2 DM patients. In our study, it was observed that mean HbA1c % was significantly higher in the DM with CAD group (7.40 ± 1.04 vs 6.13 ± 0.65) ($p < 0.001$). Our results reinforce the concept that glycemic control plays an important role in the presence of CAD, at least in this group of type 2 DM patients with high cardiovascular risk [23]. Even in non-diabetic individuals HbA1c can be associated with CAD and its severity [24].

Our lipid profile findings are similar with a study conducted by Rani S, et al. [25]. They observed that mean levels of total cholesterol in patients (DM with coronary heart disease) is 199.4 ± 27.2 mg/dl and that of the controls (DM without coronary heart disease) is 130 ± 28.6 mg/dl.

The mean levels of LDL in the serum of diabetics and controls were found to be 135.56 ± 32.57 mg/dl and

92.5 ± 8.3 mg/dl respectively and were statistically significant ($p < 0.05$). Our observation is also similar with other studies conducted by Sahin S, et al., Sattar N, and Wilson P W [26-27].

In this study, we found a relation of NLR with the presence of coronary artery disease. There is no doubt in cardiovascular medical science that atherosclerosis is a chronic inflammatory disease [28-30]. In our study mean NLR in Group I was 2.76 (± 0.74), whereas it was 1.56 (± 0.15) in Group II. There was statistically significant association between two groups in this regards ($p < 0.001$). Our findings are similar to a study conducted by Sahin S, et al. [9]. They also found higher mean NLR in patients with CAD group (1.98 ± 0.85 vs 2.69 ± 1.74) ($p < 0.001$). Sonmez O, et al. (2013) also found higher mean NLR in patients with coronary artery disease (2.3 vs 1.6) ($p < 0.001$).

Blood NLR is a new indicator of the overall inflammatory status of the body. It is a simple, inexpensive and useful marker of subclinical inflammation. Increased NLR is associated with major adverse cardiac events in diabetic patients [11,12].

NLR can be a useful tool to detect and measure the future prognosis of CAD. In this study, we found a relationship between NLR and CAD proven with angiography and NLR is a useful indicator of presence of CAD.

Limitation

This study was a non-randomized single center study that included a relatively small number of patients was subject to selective bias. We did not compare the prognostic value of NLR with other inflammatory markers such as: CRP, interleukin-1 (IL-1), interleukin-6 (IL-6) and TNF- α etc. We also did not exclude the stressful condition and autoimmune disease because of financial resource and short hospital stay of patients.

Conclusion

Increased Neutrophil lymphocyte ratio (NLR) is a risk factor for developing coronary thrombosis leading to coronary artery disease (CAD). By the assessment of NLR we can take preventive measure and precaution to reduce the risk of coronary artery disease in type 2 diabetic patients. NLR is a simple, cost effective, readily available test and could be calculated easily to predict the risk of CAD and can take extra measure and preventive

intervention to prevent CAD. It can also use as a simple tool for an independent indicator, prognosis and follow up of CAD in type 2 diabetes mellitus patients.

Acknowledgement

Authors of this study are thankful to the authority of the Department of Cardiology, BSMMU and the Department of Clinical Pathology, BSMMU, for their nice cooperation during sample collection, laboratory procedure and also thankful to the study subjects for their active and enthusiastic participation.

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