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Study of neutrophil-lymphocyte ratio (NLR) in recent onset type 2 diabetes mellitus

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ABSTRACT

Introduction: The prevalence of type 2 diabetes mellitus (T2DM) is increasing steadily, assuming an epidemic proportion throughout the world. Most of this increased burden will come from developing countries. Studies show an increasing role of inflammation in the pathophysiology of diabetes. Estimation of neutrophil-lymphocyte ratio (NLR) could be a simple, inexpensive marker to stratify at-risk diabetes patients. This study aimed to estimate the NLR and CRP levels as a measure of systemic inflammation in diabetics compared to healthy controls. We also investigated if NLR was lower in diabetics with good glycemic control.

Methods: A cross-sectional comparative study, conducted in a tertiary hospital on 60 patients with T2DM and 69 healthy controls after voluntary informed consent. Anthropometric parameters, fasting plasma glucose, Lipid profile, CBC, CRP, and HbA1c were measured for all participants.

Results: The diabetic group showed significantly higher waist circumference(p=0.007) mean TG (p=0.003), VLDL-c (p=0.001), LDL-c (p=0.010), TG/HDL-c (p=0.001), HbA1c (p=0.00001), MPV (p=0.002), NLR (p=0.006), and CRP (p=0.004) values and lower HDL-c values (p=0.039) as compared to the control group. No significant difference was seen in BMI, Waist -Hip ratio, total cholesterol, and total cholesterol/HDL-c values between the two groups. Among the diabetics, only HDL-c (p=0.018) and TG/HDL-c ratio (p=0.049) differed significantly with glycemic control.

Conclusion: Diabetics had higher inflammatory markers (NLR, CRP) as compared to controls. Dyslipidemia (high TG, low HDL-c with high TG/HDL-c) and a higher waist circumference were seen in diabetics. Diabetics with fair control of glycemia (HbA1c < 7%) did not demonstrate lower NLR levels indicating that meticulous glycemic control may not ameliorate the chronic inflammation seen in diabetics until dyslipidemia is corrected.

Keywords: Diabetes Mellitus, Dyslipidemias, Inflammation, HbA1c
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INTRODUCTION

The prevalence of Type 2 Diabetes Mellitus (T2DM) assumes epidemic proportions, both in developed and developing countries worldwide. The estimates suggest that approximately 440 million adults or nearly 8% of the global population would be affected by T2DM by 2030. Almost 70% of this predicted increase in numbers is believed to be in developing countries like India.[1,2] Metabolic syndrome is a condition associated with a series of risk factors that predict many chronic diseases, including diabetes mellitus, obesity, and cardiovascular disease. The risk factors for metabolic syndrome are dyslipidemia, including high plasma triglycerides (TG), low levels of high-density lipoprotein cholesterol (HDL-c), and fasting hyperglycemia, and central obesity.[3]

It is increasingly believed that oxidative stress and inflammation are the common denominators linking the pathogenesis of obesity, insulin resistance, and T2DM. The rise in the prevalence of obesity and metabolic syndrome runs parallel with an increased incidence of T2DM.[4] It is thought that the chronic low-grade inflammation initially develops as an adaptive protective response to help ward off infections and permit tissue repair.[5] As body weight increases with age and obesity is established, a parallel state of low-grade chronic inflammation, characterized by an overproduction of proinflammatory cytokines like TNFα, IL-6, CRP, PAI-1 sets in, which induce molecular changes and switch metabolic endpoints of insulin sensitivity leading to T2DM.[4] This inflammation is associated with increased cardiometabolic risk, and atherosclerosis.[6,7]

Studies have established a relationship between leukocytosis and the pathogenesis of atherosclerosis and metabolic syndrome.[8,9] A high total WBC count shows a positive correlation with inflammation in cardiovascular diseases, but as its stability is influenced by physical, physiological, and pathological factors, it serves as a crude measure of the inflammatory status. Neutrophil to lymphocyte ratio (NLR) has been recently discovered as a novel and stable inflammatory marker reflecting the inflammatory status, superior to other individual leukocyte

parameters. Its stability is less subject to pathophysiological variation and can easily be calculated. It is a simple, cheap, and reliable index for predicting diseases that involve inflammation. It is easier and more cost-effective than measuring proinflammatory cytokines like TNF-α, IL-1β, and IL-6 or other inflammatory biomarkers like monocyte chemoattractant protein 1 (MCP-1), lipoprotein-associated phospholipase A2 (Lp-PLA2), or quantitative fibrinogen levels, and may serve as an immediate indicator of the degree of inflammation present.[10]

An increasing consensus is emerging that inflammation plays a central and critical role in the pathophysiology of T2DM, which has led to numerous recent studies studying the relationship between NLR and insulin resistance. Studies have shown higher NLR values in T2DM patients than healthy controls and a positive, independent correlation of NLR with insulin resistance.[11,12] Sefil and co-workers demonstrated that NLR was positively correlated with HbA1c levels indicating that patients of T2DM with poor glycemic control had higher NLR levels.[12]

Data on Asian Indian diabetic patients have shown a positive correlation of NLR with differing grades of glucose tolerance and insulin resistance. NLR levels showed a statistical difference in patients of T2DM with and without complications and thus an emerging role of it as a surrogate prognostic marker for predicting macrovascular and microvascular complications in such patients.[13,14]

The study aimed to compare NLR and CRP levels in patients with T2DM and healthy controls. It was also proposed to investigate if NLR was lower in diabetics with good glycemic control (as determined by HbA1c). We also evaluated the anthropometric parameters and presence of dyslipidemia in the patient and control group.

METHODS

A cross-sectional comparative study was conducted in a tertiary-care garrison hospital after approval from the Institutional Research Committee and Ethics committee (IEC/ACMS/NP-9/2016 – Army College of Medical Sciences, Delhi Cantt). The study was conducted among diabetic patients with recent-onset T2DM (< 5 years). The patients reported for follow-up with the outpatient medical/ endocrinology department consecutively from Jan- Jun 2016. Patients < 18 years of age, or suffering from type 1 diabetes mellitus, hypertension, asthma, cancer, chronic liver disease, lymphoproliferative disorder, acquired immunodeficiency disorder (AIDS), smokers and patients with total white blood cell (WBC) counts less than 4,000 per mm^3 (leukopenia) or more than 12,000 per mm^3 (leukocytosis) or with active infection were excluded. Patients who had consumed alcohol in the past week and hospitalized patients with micro or macrovascular complications were also excluded.

After applying inclusion/exclusion criteria, a total of 60 patients with T2DM were selected randomly. 70 healthy age and sex-matched subjects from hospital staff who did not have any acute or chronic illness were enrolled as controls. Informed, voluntary written consent was obtained from both patients and controls before the commencement of the study. One of the control subjects' samples was hemolyzed, but as he declined a repeat blood collection, he was excluded. Hence, a total of 60 patients of T2DM and 69 controls were included.

Diagnosis of diabetes was established based on the World Health Organization Consulting criteria, i.e., fasting plasma glucose FPG of ≥ 126 mg/dl or 2 – hour post glucose value ≥ 200 mg/dl).[15]

None of the subjects included (patients or controls) reported any intake of oral or topical steroids / anti-inflammatory drugs or statins at the time of the study. Weight measurement was done with the patient either barefoot or wearing socks with an Indian Standards Institution (ISI) certified digital scale with a measuring accuracy of 100 grams. Height measurement was recorded in a standing position after the removal of shoes against a wall-mounted scale. It was recorded to the nearest 0.5 centimeters (cm). Height obtained in cm was converted to meters for the estimation of BMI. BMI was calculated by dividing the weight obtained in kilograms by the height in meters squared. Waist circumference was taken just above the iliac crest at the end of normal expiration. The maximum circumference around the buttocks was taken as the hip circumference. Waist to hip ratio (W/H ratio) was calculated.

Fasting venous samples were collected to estimate plasma glucose and lipid profile on a fully automated Biochemistry analyzer - EM360 (Erba, Mannheim), with commercially available kits from the same manufacturer. Lipid profile included an estimation of total cholesterol, triglyceride (TG), and high-density lipoprotein cholesterol (HDL-c). Since all patients had TG values < 400mg/dl, very low-density lipoprotein cholesterol (VLDL-c) values were obtained by dividing TG values obtained in mg/dl by 5, and low-density lipoprotein cholesterol values (LDL-c) was calculated as per the Friedwalds equation. All ratios, namely TG/HDL-c, total cholesterol/HDL-c, and LDL-c/HDL-c, were determined from the lipid profile.

HbA1c was estimated in the Nycocard reader (Axis Shield, Oslo, Norway). C-reactive protein was estimated on a semi-auto analyzer Erba chem Pro (Transasia, Erba, Mannheim), with a kit from Spinreact, S.A, Santa Coloma, Spain. Complete blood counts were performed on a three-part automated hematology autoanalyzer, Sysmex KX-21 (Sysmex Corporation, Kobe, Japan). Standardization, calibration of instruments, quality control, and sample processing were done according to the manufacturer's instructions. NLR was calculated as the ratio of the percentage of neutrophils to the percentage of lymphocytes from the same fasting blood sample.

Statistical analysis was performed on IBM SPSS Statistics for Windows, Version 24.0 (Armonk, NY: IBM Corp). Continuous variables are expressed as Mean ± Standard Deviation (SD). The Shapiro-Wilk test and Levene's test were used to assess the normality of continuous variables and equality of variances, respectively. An independent samples t-test or Mann-Whitney U-test was used as appropriate to compare groups. A p-value of < 0.05 was considered to be statistically significant.

RESULTS

A total of 60 patients and 69 controls were included in the study. The patient group comprised 52% males and 48% females, whereas males comprised 53% and females comprised 47% of the control group. The mean age of patients and controls was 50.4 ± 10.64 years and 49.7 ± 8.87 years.

An independent samples t-test and Mann Whitney U-test was used to compare the diabetic and control groups. The patient group showed significantly higher waist circumference, mean TG, VLDL-c, TG/HDL-c, HbA1c, MPV, NLR, and CRP values compared to the control group, whereas the mean HDL-c values in patients were significantly lower. No significant difference was seen in BMI, W/H ratio, total cholesterol values, and total cholesterol/HDL-c, LDL-c/HDL-c ratios between the two groups (Table 1, 2; Fig.1, 2).

Table 1. Anthropometric and inflammatory variables in diabetics vs. controls

Variable	Groups	N	Mean	SD	Significance
Body Mass Index	Diabetic	60	25.01	4.23	t = 0.715, p = 0.477
	Control	69	24.57	2.40	
Waist Circumference	Diabetic	60	36.09	3.12	**t = 2.745, p = 0.007****
	Control	69	34.70	2.61	
Waist-Hip Ratio	Diabetic	60	0.92	0.045	t = 1.434, p = 0.154
	Control	69	0.90	0.054	
C-Reactive Protein (CRP)	Diabetic	60	5.24	10.05	**U = 1464.0, p = 0.004****
	Control	69	1.91	2.11	
Neutrophil-Lymphocyte Ratio (NLR)	Diabetic	60	2.02	0.71	**U = 1483.0, p = 0.006****
	Control	69	1.65	0.56	
Mean Platelet Volume	Diabetic	60	11.71	1.62	**t = 3.234, p = 0.002****
	Control	69	10.89	1.18	
Hemoglobin A1c	Diabetic	60	7.12	1.77	**U = 158.5, p = 0.00001****
	Control	69	5.19	0.18	

*Significant at p<0.05 level; **Significant at p<0.01 level; t = test statistic for independent samples t-test; U = test statistic for Mann Whitney U test.

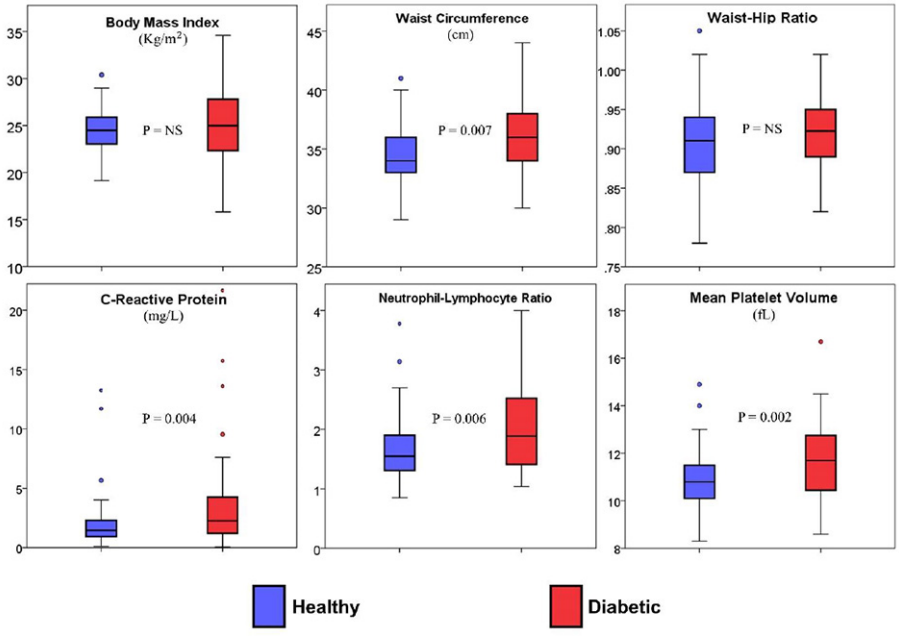

Figure 1. Anthropometric and inflammatory variables in diabetics vs. controls. The p-values obtained by comparison of continuous measures. Means were compared using an independent samples t-test, and medians were compared using a Mann-Whitney U test as appropriate.

Patients with T2DM (n=60) were further sub-grouped depending on the degree of glycemic control, dichotomized by an HbA1c value of 7%. A total of 20 patients had HbA1c > 7%, and 40 had HbA1c ≤ 7%. The two groups were compared using a Mann-Whitney U test for NLR, CRP, TG, HDL, TG/HDL-c ratio, total cholesterol, total cholesterol/HDL-c ratio, and LDL-c/HDL-c ratio (Table 3). NLR values were comparable in both groups. CRP values were higher in patients with poor glycemic control than patients with good glycemic control. However, these differences were not statistically significant. TG and TG/HDL-c ratios were high, and mean HDL-c levels were low in patients with poor glycemic control. Only mean HDL-c levels and TG/HDL-c ratio were seen to be statistically significant.

DISCUSSION

This study aimed to evaluate the presence of dyslipidemia and inflammation in T2DM patients visiting the outpatient clinic of a tertiary hospital as compared to healthy controls. Diabetics showed higher NLR (p=0.006) and CRP (p=0.004) as compared to controls (Table 1; Fig.1). Studies have shown T2DM to be associated with chronic low-grade inflammation, also known as meta inflammation.[7,11,16] This results in an increased secretion of proinflammatory cytokines like CRP, IL-6, IL-1β, and TNF-α, leading to a chronically elevated neutrophil granulocytic count demonstrating a chronic proinflammatory metabolic state.

Data from a few studies demonstrate NLR to correlate positively with HbA1c levels.[12,13] However, the NLR did not vary significantly with the degree of glycemic control in our study. This possibly suggests that once T2DM is established, the low-grade inflammation present is in a continuous state of dynamic change due to the relatively short life of neutrophils,

Table 2. Lipid variables in diabetics vs. controls

Variable	Group	N	Mean	SD	Significance
Total Cholesterol	Diabetic	60	165.18	34.19	t = -1.249, p = 0.214
	Healthy	69	172.84	35.19	
Low Density Lipoproteins (LDL-c)	Diabetic	60	93.40	30.93	**t = -2.609, p = 0.010****
	Healthy	69	107.27	29.38	
High Density Lipoprotein (HDL-c)	Diabetic	60	38.91	9.43	**U = 1633.0, p = 0.039***
	Healthy	69	42.82	10.38	
Triglycerides (TG)	Diabetic	60	158.93	97.81	**U = 1430.5, p = 0.003****
	Healthy	69	110.76	50.44	
Very Low-Density Lipoprotein (VLDL-c)	Diabetic	60	33.20	21.03	**U = 1373.0, p = 0.001****
	Healthy	69	22.25	10.26	
Total Cholesterol/HDL-c ratio	Diabetic	60	4.42	1.23	t = 1.501, p = 0.136
	Healthy	69	4.13	0.86	
Triglyceride/HDL-c ratio	Diabetic	60	4.47	3.23	**U = 1333.0, p = 0.001****
	Healthy	69	2.73	1.47	
LDL-c/HDL-c Ratio	Diabetic	60	2.50	0.99	t = -0.533, p = 0.595
	Healthy	69	2.58	0.77	

*Significant at p<0.05 level; **Significant at p<0.01 level; t = test statistic for independent samples t-test; U = test statistic for Mann Whitney U test

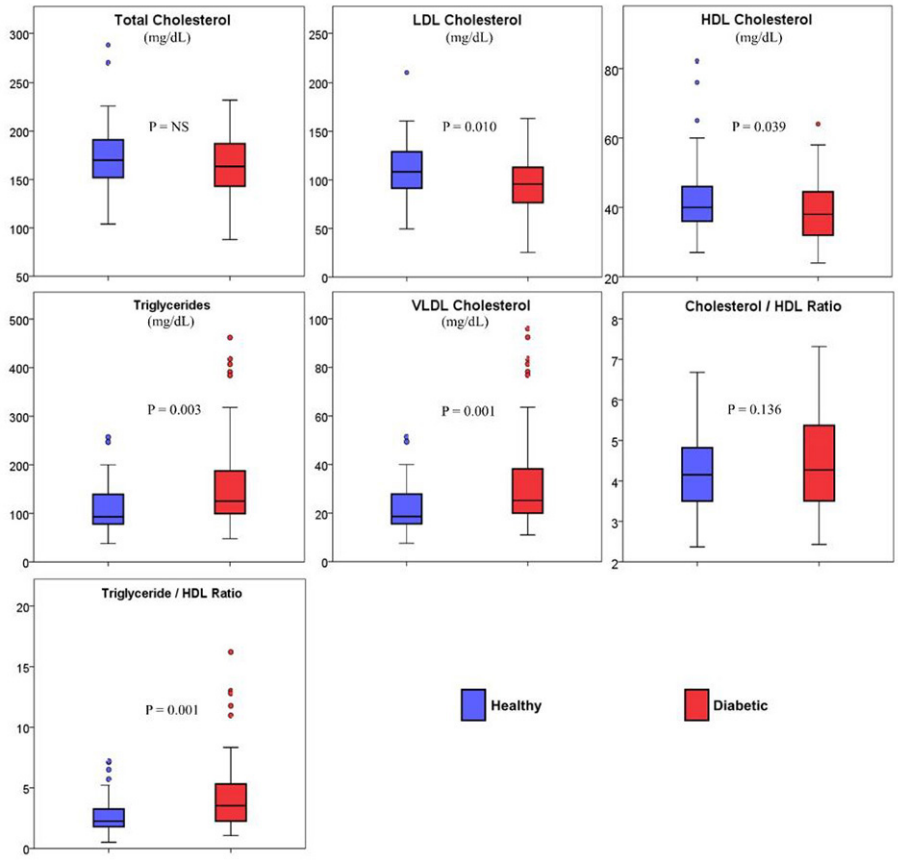

Figure 2. Lipid variables in diabetics vs. controls. The p-values obtained by comparison of continuous measures. Means were compared using an independent samples t-test, and medians were compared using a Mann-Whitney U test as appropriate.

and this change may not always reflect in parallel with HbA1c levels, which are indicative of glycemic control over a more extended period. Hence, meticulous control of glycemia may not lead to a reduction in NLR. Likewise, CRP levels also did not show a statistically significant difference between both groups.

Though obesity (as determined by BMI) is an accepted risk factor in the development of T2DM, BMI does not provide information about the distribution of body fat in various body sites. In our study, both the patient and control groups did not significantly differ in BMI or W/H ratio. However, diabetics documented a larger waist circumference than controls, which was statistically significant (Table 1; Fig.1). Our findings appear to be in concordance with other studies that have documented waist circumference positively correlated with inflammatory markers like IL-6 and TNF.[17] Even though obesity rates are soaring worldwide, body fat distribution assumes greater importance than BMI per se, as the intra-abdominal visceral fat accumulation has been shown to correlate with an atherogenic, prothrombotic, and proinflammatory metabolic profile. A significantly higher MPV (p=0.002) in our diabetic group seems to corroborate this. Lemieux and co-workers have also reported similar findings.[18] However, the risk does not appear to be similar in all ethnicities worldwide. At any given waist circumference, Asians are believed to have a higher degree of insulin resistance, hyperinsulinemia, and diabetes due to the increased amount of visceral fat.[19]

Our patients demonstrated a significantly higher TG (p=0.003), TG/HDL-c ratio (p=0.001), and lower HDL-c values (p=0.039) as compared to healthy controls. Values of total cholesterol (p=0.214), total cholesterol / HDL-c ratio (p=0.136) did not vary significantly between both groups (Table 2; Fig.2), indicating that dyslipidemia comprising of high TG values along with low HDL-c was more prevalent in diabetic patients. Dyslipidemia has been frequently observed in diabetics.[20,21] The HDL–c values are reported to be lower in this group, along with elevated small dense LDL-c particles that are believed to be the

Table 3. **Patients with poor vs fair glycemic control**

Variable	HbA1c	N	Mean	SD	Significance
Neutrophil-Lymphocyte ratio (NLR)	> 7%	20	1.94	0.61	U = 381.0, p = 0.766
	≤ 7%	40	2.06	0.77	
C – Reactive Protein (CRP)	> 7%	20	7.01	14.25	U = 338.5, p = 0.335
	≤ 7%	40	4.36	7.17	
Triglycerides (TG)	> 7%	20	191.85	117.63	U = 286.0, p = 0.074
	≤ 7%	40	142.47	83.07	
High Density Lipoprotein Cholesterol (HDL-c)	> 7%	20	35.50	5.74	**t = -2.446, p = 0.018***
	≤ 7%	40	40.62	10.46	
Triglyceride/HDL-c ratio	> 7%	20	5.64	3.71	**U = 275.0, p = 0.049***
	≤ 7%	40	3.89	2.84	
Total Cholesterol	> 7%	20	165.25	41.49	t = 0.011, p = 0.992
	≤ 7%	40	165.15	30.49	
Total Cholesterol/HDL-c ratio	> 7%	20	4.73	1.31	t = 1.395, p = 0.168
	≤ 7%	40	4.26	1.18	
Low Density Lipoprotein (LDL-c) / HDL-c Ratio	> 7%	20	2.52	1.00	t = 0.080, p = 0.937
	≤ 7%	40	2.49	1.00	

*Significant at p<0.05 level; t = test statistic for independent samples t-test; U = test statistic for Mann Whitney U test.

primary carrier of ceramides that promote both inflammation and insulin resistance.[22] This potentially explains increased inflammation in diabetics in the absence of obesity, which was also observed in our study. Patients with poor glycemic control showed a significantly higher TG/HDL-c ratio (p=0.049) and lower HDL-c values (p=0.018) than patients with good control of glycemia. These ratios may better reflect the inflammatory state than total cholesterol, total cholesterol/ HDL-c ratio, or LDL-c / HDL-c ratio, which were not statistically significant (Table 3).

A high NLR in patients with T2DM is also believed to herald the presence of ischemic complications in these patients, as suggested by various authors.[10,23] However, we could not assess this in our study, as the patients' enrolled in our study were recent-onset diabetics who did not report any macro or microvascular complications.

The possibility that dyslipidemia, namely, a high TG and low HDL-c, is the driver of inflammation and leads to high NLR and CRP levels in T2DM patients is slowly gaining credence.[24,25] It may be the common link connecting inflammation, endothelial dysfunction, platelet reactivity, atherothrombosis, and metabolic syndrome, which needs to be addressed on priority. Correcting underlying dyslipidemia in patients with poor glycemic control may be paramount in managing this disease.

This study was limited by the relatively small sample size. We could not undertake a follow-up study to determine the incidence of complications in these patients. NLR can only be interpreted appropriately with the absence of any concomitant hematologic disease, cancer, immunodeficiency, and acute or chronic inflammatory states. Studies need to be extended to a larger, multiethnic population group, so appropriate dietary guidelines and lifestyle modifications may be enforced.

CONCLUSION

Patients of T2DM exhibit high NLR, CRP values compared to controls suggesting a chronic steady-state of inflammation in these subjects. However, the degree of glycemic control did not affect the NLR and CRP values. Additionally, these patients showed dyslipidemia, with high TG and low HDL-c levels compared to controls. Waist circumference was larger in diabetics as compared to controls. BMI and waist-hip ratio did not show any significant difference between both groups. These results emphasize the importance of screening patients by simple, inexpensive parameters like waist circumference, TG, HDL-c, and NLR values as highly useful tools, or a relevant first-step approach, in stratifying the risk of developing complications in diabetics, thus ensuring optimal utilization of limited resources, especially in developing countries.

AUTHORS CONTRIBUTION

All authors contributed equally to the study.

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DISCLOSURES

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