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Original Research Article

THE ASSOCIATION BETWEEN NEUTROPHIL/LYMPHOCYTE RATIO, PLATELET/LYMPHOCYTE RATIO AND ALBUMINURIA AS MARKERS IN DIABETIC KIDNEY DISEASE: A TEACHING HOSPITAL BASED STUDY

Jasneet Kaur Sandhu[1], Manoj Kumar Yadav[2], Ashish Bajaj[3]

[1]Associate Professor, Department of Pathology, World College of Medical Sciences Research and Hospital, Jhajjar, India.
[2]Associate Professor, Department of Biochemistry, World College of Medical Sciences Research and Hospital, Jhajjar, India.
[3]Assistant Professor, Department of Microbiology, World College of Medical Sciences Research and Hospital, Jhajjar, India.

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Corresponding Author:
Dr. Ashish Bajaj,
Email: drbajaj03@gmail.com

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Abstract

Background: Diabetes mellitus's high treatment costs and associated problems have made it a global public health concern. Albuminuria, a symptom of diabetic nephropathy, is an inflammatory condition that precedes end-stage renal failure. As emerging intermediate indicators of diabetic kidney disease (DKD), the neutrophil–lymphocyte ratio (NLR) and platelet–lymphocyte ratio (PLR) show promise. **Material and Methods:** Based on their urine albumin-to-creatinine ratio, 96 patients with type 2 diabetes mellitus were split up into three groups: Individuals with type 2 diabetes who had normoalbuminuria (urinary albumin-to-creatinine ratio <30 mg/g), microalbuminuria (urinary albumin-to-creatinine ratio = 30–299 mg/g), or macroalbuminuria (urinary albumin-to-creatinine ratio ≥300 mg/g). The three groups' levels of inflammatory indicators, such as the neutrophil-to-lymphocyte and platelet-to-lymphocyte ratios, have been assessed and analysed. **Results:** Patients with macroalbuminuria had significantly longer duration of diabetes and increased prevalence of hypertension. NLR and the duration of diabetes, HbA1c, GFR, albumin/creatinine ratio, CRP, and PLR were revealed to be significantly correlated by Pearson correlation analysis. **Conclusion:** Diabetic nephropathy was substantially correlated with higher neutrophil-to-lymphocyte and platelet-to-lymphocyte ratios, suggesting that these ratios could be used as predictive risk markers and predictors of diabetic nephropathy.

INTRODUCTION

The prevalence and incidence of diabetes mellitus (DM), a major hazard to world health, are rising. In 2019, 463 million people had diabetes mellitus. The International Diabetes Federation (IDF) predicts that by 2045, this figure will have risen to 700 million.[1]Hyperglycemia, or elevated blood sugar, is a hallmark of diabetes mellitus (DM), a chronic metabolic disorder that can be caused by either cellular resistance to insulin or impaired insulin secretion.[2]Type 1 diabetes is characterized by the pancreas's inability to create insulin, while type 2 diabetes is characterized by insufficient insulin secretion or the body's inability to effectively respond to it.[3]In addition to stroke, cardiovascular diseases (CVDs), and peripheral vascular diseases (macrovascular complications), diabetes mellitus (DM) generates major consequences like diabetic nephropathy (DN), diabetic retinopathy, and diabetic neuropathy (microvascular complications).[4]The prevalence of diabetic nephropathy has significantly increased due to the growing number of individuals with diabetes.[5] The most common cause of chronic kidney disease is diabetic nephropathy, a metabolic illness with a high morbidity and death rate that affects 20% to 40% of individuals with type 2 diabetes mellitus.[6,7] Due to accelerated atherosclerosis, the risk of cardiovascular death from atherosclerosis is 10–20 times higher in individuals with chronic kidney disease (CKD) than in the general population.[8] Since an elevated leukocyte count starts a chain reaction of inflammation in the artery wall, its

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significance in the pathophysiology of atherosclerosis is well understood. Inflammatory markers like interleukin (IL)-1, IL-6, IL-8, and tumor necrosis factor-α have also been linked to end organ damage in diabetes, in addition to leukocyte count. However, their unavailability in routine clinical practice is made worse by the associated cost and lack of assay standardization. An easy-to-calculate measure of systemic inflammation is the neutrophil-lymphocyte ratio (NLR), which is calculated by dividing the neutrophil count by the lymphocyte count.[9]As the world's diabetes capital and a resource-poor nation with few laboratory facilities, we want affordable and reliable indicators of end organ damage. More significantly, despite a recent report indicating a link between WBC count and albuminuria in type 2 diabetes, there has been limited research on the relationship between WBC count and vascular consequences of diabetes in our population.[10,11] For the purpose of to study the association between inflammatory indicators (neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio) and patients with diabetic nephropathy, a cross-sectional analysis.

MATERIALS AND METHODS

This present cross-sectional study was conducted in the Department of Pathology, World College of Medical Sciences Research and Hospital, Jhajjar collaboration with Department of Medicine and Biochemistry. Total of 96 type-2 diabetes mellitus patients diagnosed according to the ADA criteria during the period from March, 2022 to February, 2023. Patients with a history of infections within the last 1.5 months, pyrexia of unknown cause, parasitic infection, viral infection, tuberculosis, local infection, skin infection, AIDS, patients with known systemic inflammatory disorders, blood disorders, autoimmune disorders, cancer, poisoning, or those taking anti-inflammatory drugs or topical steroids were excluded from the study. Prior approval from the Institutional Ethics Committee was obtained, and all participants gave their informed written consent before being recruited. Every study participant had a thorough medical history taken, and a general and systemic examination was performed to evaluate any problems related to diabetes. Following an overnight fast, venipuncture was used to obtain blood for lipid profile, glucose, HbA1c, and complete blood counts. The results were evaluated using conventional automated procedures. Albumin and creatinine levels were measured in spot pee. The albumin/creatinine ratio in spot urine was used to diagnose proteinuria according to the American Diabetes Association's classification,[12]: no proteinuria: < 30 mg/g creatinine, microalbuminuria: 30 - 299 mg/g creatinine, and macroalbuminuria: ≥ 300 mg/g creatinine. The modification of diet in renal disease (MDRD) equation was utilized to determine the estimated glomerular filtration rate (eGFR), which was used to evaluate renal function. GFR was approximated using a simplified MDRD equation (ml/min/1.73 m2).

Statistical Analysis

Categorical variables are displayed as percentages and frequencies, while continuous variables are displayed as mean±standard deviation. The variable distribution was assessed using the Kolmogorov-Smirnov test. To compare the three research groups, the one-way analysis of variance (ANOVA) test was employed. Pearson's test was used to evaluate correlations. A P value of less than 0.05 was deemed statistically significant. For statistical computations, the Statistical Package for Social Science (SPSS for Windows, version 18.0; SPSS, Inc., Chicago, IL, USA) was utilized.

RESULTS

Ninety-six (96) Participants with type-2 diabetes were included in this cross-sectional study, including 34 patients with nomoalbuminuria who served as controls and 62 patients with nephropathy who had micro or macroalbuminuria. Of them, 46.9% were women and 53.1% were men. Our patients' average age was 49.25 ± 12.26 years, and they had had diabetes for 10.9 ± 2.32 years. The study participants' demographic, anthropometric, and metabolic traits are summarized in Table I. Individuals with macroalbuminuria exhibited higher rates of hypertension and diabetes for noticeably longer periods of time.

Table 1: Shows the comparison of demographic parameters of study participants

Parameter	Normoalbuminuria (n = 34)	Microalbuminuria (n = 32)	Macroalbuminuria (n = 30)	P value
Age (years)	49.42 ± 8.64	48.86 ± 8.72	49.48 ± 8.44	0.16
Male/Female (N)	18/16	17/15	16/14	0.21
BMI (kg/m2)	26.8 ± 6.32	26.6 ± 6.28	26.4 ± 6.27	0.38
Waist circumference (cm)	88.62 ± 10.6	87.8 ±10.42	88.92±10.64	0.16
Blood pressure > 140/90 mmHg (%)	34%	46%	84%	0.01
Duration of diabetes (years)	8.32 ± 2.6	10.2 ± 4.32	14.2 ± 5.64	0.04

Based on their albuminto-creatinine ratio, the patients were divided into three groups: normoalbuminuria (N=34, 35.41%), microalbuminuria (N=32, 33.3%), and macroalbuminuria (N=30, 31.25%). The one-way ANOVA results for the research groups' clinical, laboratory, and demographic variables are summarized in Table 1. The groups did not differ

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significantly in terms of age, BMI, serum albumin, HDL cholesterol, triglycerides, monocyte count, or red blood cell count. FBS ($p<0.01$), HbA1c ($p<0.04$), duration of diabetes ($p<0.04$), blood pressure ($p<0.01$), serum urea ($p<0.04$), serum creatinine ($p<0.02$), GFR ($p<0.01$), total WBC ($p<0.02$), absolute neutrophil count ($p<0.04$), absolute lymphocyte count ($p<0.02$), Hb ($p<0.04$), PLT ($p<0.02$), and inflammatory markers NLR ($p<0.04$) and PLR ($p<0.04$) were all considered to be significant variations among the three groups.

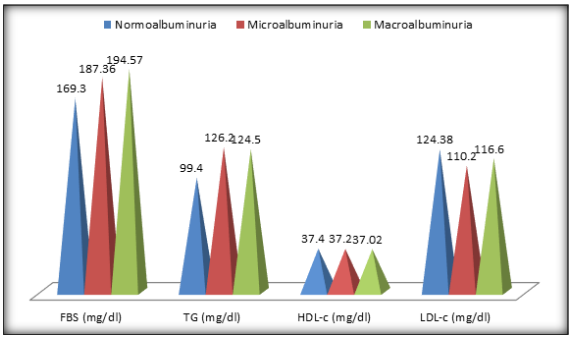

Figure 1: Shows the comparison of biochemical parameters

Table 2: Hematological and Biochemical laboratory parameters of study participants

Parameter	Normoalbuminuria (n = 34)	Microalbuminuria (n = 32)	Macroalbuminuria (n = 30)	P value
FBS mg/dl	169.3±45.32	187.36±48.2	194.57±50.64	0.01
HbA1c (%)	7.86 ± 2.52	8.68 ± 3.46	8.87 ± 3.65	0.04
HDL-cholesterol (mg/dl	37.4 ± 6.2	37.2 ± 6.02	37.02 ± 6.01	0.24
Triglyceride (mg/dl)	99.4 ± 21.4	126.2 ± 24.6	124.5 ± 21.06	0.38
LDL-cholesterol (mg/dl)	124.38 ± 24.5	110.2 ± 35.12	116.6 ± 38.62	0.06
Serum urea (mg/dl)	25.34 ± 6.06	42.46 ± 10.24	44.6 ± 10.26	0.04
Creatinine (mg/dl)	1.09 ± 0.06	1.2 ± 0.08	1.7 ± 0.42	0.02
Serum albumin (g/dl)	3.89 ± 1.02	3.76 ± 1.02	3.68 ± 1.01	0.16
GFR (ml/min/1.73m2)	106.2 ± 16.54	88.32 ± 13.4	71.21 ± 9.72	0.01
CRP (mg/dl)	0.11 ± 0.04	0.42 ± 0.08	1.26 ± 0.21	0.01
WBC ($x10^3$ /µl)	7.38 ± 2.52	8.28 ± 2.58	8.94 ± 2.65	0.02
Absolute Neutrophil count (/µl)	4146.54±146.05	5184.76±156.6	5964.4±1196.8	0.04
Absolute Lymphocyte count (/µl)	2446.31±126.4	2292.4±128.02	1994.26±129.6	0.02
NLR	1.71 ± 0.62	2.4 ± 0.71	3.06 ± 0.39	0.04
Absolute Monocyte count (/µl)	432.2 ± 82.02	461.54 ± 84.21	456.04 ±8405	0.21
RBC (x 10^6 /µl)	4.83 ±1.35	4.85 ±1.42	4.64 ±1.5462	0.32
Hb (g/dl)	13.3 ± 4.02	13.1 ± 4.01	11.8 ± 5.04	0.04
PLT ($x10^3$/µl)	234.56 ± 41.2	258.24 ± 58.4	278.26 ± 59.2	0.02
PLR	96.26 ± 18.6	114.52 ± 30.06	145.26 ± 31.5	0.04
Albumin/creatinine (mg/g)	9.86 ± 2.04	102.56 ± 58.06	532.42 ± 86.24	0.02

Table 3: Shows the pearson's correlation analysis of Neutrophil/Lymphocyte Ratio and Platelet/Lymphocyte Ratio

Parameters	Neutrophil/Lymphocyte Ratio		Platelet/Lymphocyte Ratio	
	r	P-value	r	P-value
Duration of Diabetes	0.62	0.001	0.48	0.001
HbA1c	0.46	0.001	0.24	0.001
Albumin/Creatinine	0.65	0.0001	0.42	0.001
GFR	-0.67	0.001	-0.38	0.000
CRP	0.72	0.0001	0.46	0.001
Hb	-0.26	0.001	-0.32	0.000
NLR	-	-	0.51	0.001
PLR	0.56	0.001	-	-

NLR and the duration of diabetes, HbA1c, GFR, albumin/creatinine ratio, CRP, and PLR were revealed to be significantly correlated by Pearson correlation analysis. Additionally, the Pearson test showed a significant relationship between PLR and HbA1c, GFR, albumin/creatinine ratio, CRP, NLR, and duration of diabetes. [Table 3]

DISCUSSION

The main objective of this research was to examine and assess the predictive usefulness of NLR and PLR for DN in patients with type 2 diabetes. Patients with type 2 diabetes who were split into three groups based on their albumin-to-creatinine ratio made up the sample. The three groups' levels of inflammatory markers (NLR, PLR) and other metrics were contrasted. According to the results, diabetic patients with macroalbuminuria had considerably higher NLR and PLR values than both microalbuminuric and albuminuric patients. The precise etiology of DN, a prevalent serious consequence in diabetic patients, is still unknown.[13]Glomerular injury is thought to be an early indication of DN and occurs before microalbuminuria, despite the fact that microalbuminuria is a powerful marker for DN diagnosis and progression.[14]The formation and progression of DN are known to be influenced by a series of pathological processes, including glomerular injury leading to proteinuria, increasing renal damage, fibrosis, inflammation, and ultimately loss of functional nephrons. Chronic inflammation

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has been shown to be a major factor in the emergence of problems related to diabetes mellitus.[15]Since several inflammatory chemicals, including adipokines, chemokines, adhesion molecules, and cytokines, may play a role in the development of DN, numerous studies have linked DN to chronic inflammation.[16]According to Spranger et al., the risk of type 2 diabetes may be altered by circulating inflammatory cytokines, specifically a joint elevation of IL-1 and IL-6 that raises the risk of type 2 DM.[17]While neutrophilia and relative lymphocytopenia are independent indicators of numerous disorders, including DM complications like DN, white blood cell counts and their subtypes have been widely regarded as indicators of inflammation.[18]Nevertheless, there are biases in DN diagnosis based on WBC, neutrophil, or lymphocyte numbers. A new inflammatory biomarker that reflects both the innate immune response (mediated by neutrophils) and the adaptive immune response (mediated by lymphocytes), NLR is an easily accessible and inexpensive index that is determined by routine blood examination. Its stability is superior and less affected by physiological and pathological conditions. Therefore, it's important to assess the associations between the NLR level and other diabetic problems. NLR has been identified as a predictive marker for a number of cancer types as well as cardiovascular disorders, including heart failure, acute coronary syndromes, and coronary artery disease. Furthermore, NLR is positively associated with both the existence and severity of metabolic syndrome.[19]Numerous recent research have suggested that NLR may be used as a predictor to evaluate the microvascular consequences of diabetes mellitus. According to Wan et al., in people with diabetes, a greater NLR level was linked to a higher prevalence of cardiovascular and cerebrovascular disorders as well as diabetic kidney disease. NLR is an independent predictor of microvascular problems in older diabetic people, according to a study by Oztürk et al.[20] According to Moursy et al., NLR is a reliable and effective measure of inflammation and a key indicator of the existence of microvascular diabetic problems in type 2 diabetic patients in Egypt.[21]According to Ulu et al., NLR is a quick and accurate indicator of retinopathy severity.[22]NLR may serve as a prognostic and predictive marker for sensorineural hearing loss in diabetic patients, according to a different study by Ulu et al.[23]According to a 3-year follow-up study, NLR appears to be crucial in predicting diabetics' declining renal function.[24] Furthermore, our research showed that albuminuria levels and NLR were positively correlated, while GFR and NLR levels were negatively correlated. Kahramn et al. showed that albuminuria, GFR, and NLR levels were strongly correlated in type 2 diabetes patients,[25]which is consistent with our findings. As a result, NLR may be an inflammatory marker of DN. Khandare et al. found a strong correlation between NLR and DN, suggesting that endothelial dysfunction and inflammation may play a role in DN. NLR was therefore taken into consideration in that study as a predictive risk factor and predictor of DN.[26]Huang et al. found that NLR is a good predictor of early-stage diabetic nephropathy and that elevated NLR values were independently connected with DN.[27]PLR is thought to be a possible inflammatory marker in chronic kidney illness,[29]cardiac conditions, and oncologic conditions.[28]Additionally, PLR, similar to NLR, which can be determined by a complete blood count, could be used as an inexpensive way to predict microvascular problems in diabetics.[30] PLR can be a helpful marker for evaluating high-risk diabetic foot and foot ulcers in individuals with type 2 diabetes, according to Mineoka et al.[31] According to our research, PLR shows a negative correlation with GFR and a positive correlation with albuminuria levels. These findings are supported by Abdelaziz et al.'s discovery that NLR and PLR were substantially correlated with DN, suggesting that they might be used as prognostic and predictive risk indicators for DN.[32]Despite albuminuria, the current study found a significant increase in serum creatinine levels, which may be a marker of altered kidney function. In line with our findings of elevated blood pressure, hypertension also plays a role in the onset and development of DN.[33] Additionally, this study demonstrated a positive link between NLR, PLR, and CRP and a negative correlation between NLR, PLR, and hemoglobin. These findings imply that PLR and NLR are useful indicators of systemic inflammation. Significant differences were between the groups in terms of glycemic parameters; all research groups had HbA1c levels above 7%, which may have suggested inadequate glycemic management in patients with type 2 diabetes. It may also be used as a disease monitoring tool when diabetic individuals are being followed up with.

CONCLUSION

These findings suggest that increased NLR and PLR were substantially associated with DN, and that they might be used as a prognostic risk indicator and predictor of DN. The results of our investigation suggest that NLR and PLR could be utilized as indicators of DKD. From CBC, which is almost a standard test, they are simple to compute. Therefore, these could be used as a substitute for other expensive indicators and predictors of DKD and other diabetic microangiopathies in environments with limited resources.

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