ORIGINAL ARTICLE ASIAN JOURNAL OF MEDICAL SCIENCES

The correlation of neutrophil-lymphocyte ratio and platelet–lymphocyte ratio with nephropathy in patients of type 2 diabetes mellitus-a hospital-based study from South India

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Submission: 12-05-2025 Revision: 04-06-2025 Publication: 01-07-2025

ABSTRACT

Background: Diabetes is a group of metabolic diseases characterized by hyperglycemia due to defects in insulin secretion, action, or both. Diabetic nephropathy is among the serious complications of diabetes. Albuminuria is used as a biomarker for diabetic nephropathy. There is evidence of inflammation leading to the development and progression of diabetic nephropathy. White blood cell count, platelet counts have been used as markers of inflammation. **Aims and Objectives:** This study aims to determine a correlation between neutrophil-lymphocyte ratio (NLR), platelet lymphocyte ratio (PLR), and diabetic nephropathy. **Materials and Methods:** This cross-sectional analytical study was done among 99 individuals availing of the Medical College Hospital services for 18 months. They were classified into three groups of thirty-three participants each, based on the urine albumin–creatinine ratio. The three groups were the normoalbuminuria, microalbuminuria, and macroalbuminuria groups. The NLR and PLR was calculated and compared among the three groups. **Results:** The mean NLR in diabetic patients with macroalbuminuria (2.68) was significantly higher than patients with normoalbuminuria (1.46) and microalbuminuria (1.80) (P = 0.001). The mean PLR was also higher in diabetic patients with macroalbuminuria (156.80) when compared to patients with normoalbuminuria (90.94) and microalbuminuria (119.03) (P = 0.001). **Conclusions:** Increased NLR and PLR levels are associated with diabetic nephropathy. A higher NLR and PLR value can indicate the progression of diabetic nephropathy due to worsening estimated glomerular filtration rate. NLR and PLR can be used as a simple prognostic marker for Diabetic Nephropathy.

Key words: Neutrophil–lymphocyte ratio; Platelet–lymphocyte ratio; Diabetic nephropathy; Type 2 diabetes mellitus

Access this article online

Website: https://ajmsjournal.info/index.php/AJMS/index

DOI: 10.71152/ajms.v16i7.4615

E-ISSN: 2091-0576

P-ISSN: 2467-9100

INTRODUCTION

Diabetes mellitus (DM) is one of the most common metabolic diseases seen all over the world. According to the American Diabetes Association (ADA), diabetes is defined as a group of metabolic diseases characterized by hyperglycemia due to defects in insulin secretion, action, or both.[1] As per the International Diabetes Federation the prevalence of diabetes in India among adults is 8.3%.[2]

Diabetic Nephropathy or Diabetic Kidney Disease (DKD) is one of the serious complications of diabetes and is one of the most common reasons for chronic kidney disease. It is characterized by the presence of pathological

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amounts of urine albumin excretion, diabetic glomerular lesions, and loss of glomerular filtration rate in diabetics.[3] Currently, albuminuria is used as a biomarker for diabetic nephropathy, but its role in determining the early stage of Diabetic nephropathy is limited because renal injury precedes urinary albumin secretion.[3]

Inflammatory cytokines such as interleukin-1, interleukin-6, interleukin 8, and tumor necrosis factor-alpha contribute to the pathogenesis of diabetic nephropathy but due to the high cost and difficulty in determining their assay, they are not routinely used in clinical practice.[4] Total and differential white blood cell count is a sensitive indicator of inflammation which can be easily determined in the laboratory. Ischemic injury and thrombus formation can be associated with an increase in the number of neutrophils.[5] Platelets are involved in atherosclerosis through secreting pro-inflammatory cytokines and binding to endothelial cells thereby causing increased inflammation in patients with higher platelets.[6]

Aims and objectives

This study aims to determine a correlation between neutrophil–ymphocyte ratio (NLR) and platelet–lymphocyte ratio (PLR) and diabetic nephropathy and whether they can be used as predictors for the early detection of Diabetic Nephropathy in patients with Type 2 DM so as to prevent or delay complications such as End stage renal disease.

MATERIALS AND METHODS

This was a cross-sectional, analytical hospital-based study conducted for a period of 18 months from May 2022 to March 2024. The study was initiated after obtaining ethical clearance from the institutional ethical committee (FMMCIEC/CCM/541/2022). A simple random sampling method was used. Written informed consent was taken from each patient fulfilling the selection criteria and was willing to be enrolled in the study. Participants received a patient information sheet explaining the study. Sample size was calculated according to the following formula

$$n=2(Z\alpha+Z\beta)^2/(x1-x2)^2$$

Z_α=1.96 at 95% CI

$Z\beta$=1.281 at 90% power

X1=98.34±27.15 and X2=143.6±35.95[7]

e=allowable error 5%

Sample size (n)=99. Each group containing 33 patients.

Ninety-nine patients with type 2 DM were classified into three groups of 33 patients in each group based on urine albumin–creatinine ratio (UACR): Group 1-Type 2 DM patient with normoalbuminuria (UACR <30 mg/g), Group 2-Type 2 DM patients with microalbuminuria (UACR 30–300 mg/g), Group 3-Type 2 DM patients with macroalbuminuria (UACR >300 mg/g).[8]

Inclusion criteria

(1) Known type II diabetes patients, (2) Newly detected Type II diabetes patients-fasting blood sugar ≥126 mg/dL and hemoglobin A1C- ≥ 6.5% as per ADA guidelines[1], (3) Age 18–70 years of age.

Exclusion criteria

(1) Known cases of malignancy, sepsis, thromboembolic disorder, coronary artery disease, stroke, peripheral vascular disease, chronic liver disease, (2) Immunodeficient conditions such as HIV, leukopenia, patients on immunomodulators, corticosteroids or chemotherapy, (3) Febrile illness such as dengue, malaria, leptospirosis, (4) Patients having any source of bacterial infection including urinary tract infections.

Demographic details were obtained followed by a detailed clinical examination. Urine samples for urine albumin and urine creatinine were taken for albumin-creatinine (UACR) estimation.

Samples for complete blood counts were processed using a Beckman Coulter LH 750 analyzer. Blood samples for renal function tests were also collected. NLR and PLR were calculated. Statistical analysis was done using SPSS software version 21 and was interpreted as frequency, percentage, mean, standard deviation, and analysis of variance test.

RESULTS

Among the 99 participants, the maximum number of participants were within the age group of 61–70 years of age with a mean age of 63 years. Out of the 44 patients in this age group, 31 patients showed the presence of albuminuria. The mean age among the macroalbuminuria group was higher 65.67 compared to other groups (Figure 1). There were 36 females (36.4%) and 63 males (63.6%) involved in the study.

The mean total leukocyte count (TLC) in the macroalbuminuria group (8153.64/μL) was higher than the mean TLC in the normoalbuminuria (7285.76/μL) and microalbuminuria (7369.09/μL) groups. This observation was not significant P=0.071. The mean absolute neutrophil count (ANC) was higher in patients with macroalbuminuria (5117.12/μL) and microalbuminuria (4093.36/μL) than in patients with normoalbuminuria (3733.48/μL). There was an increasing trend in mean ANC with worsening

albuminuria. The P=0.001, indicating a statistically significant correlation. The mean value of absolute lymphocyte count was significantly lower (P=0.001) in patients with macroalbuminuria (1977.10/μL) than with patients having microalbuminuria (2296.36/μL) and normoalbuminuria (2676/μL).

As shown in Table 1, the mean NLR value in our study was found to be significantly higher among patients with macroalbuminuria (2.68) and microalbuminuria (1.80) than with patients with normoalbuminuria (1.46). It was also seen that the mean PLR value was significantly higher among patients with macroalbuminuria (156.80) and microalbuminuria (119.0) than in patients with normoalbuminuria (90.94), as depicted in Table 2.

Patients with macroalbuminuria had a significantly lower mean estimated glomerular filtration rate (eGFR) (73.13 mL/min/1.73 m^2) than in patients with microalbuminuria (84.65 mL/min/1.73 m^2) and normoalbuminuria (87.76 mL/min/1.73 m^2). Table 3 shows that this observation was statistically significant.

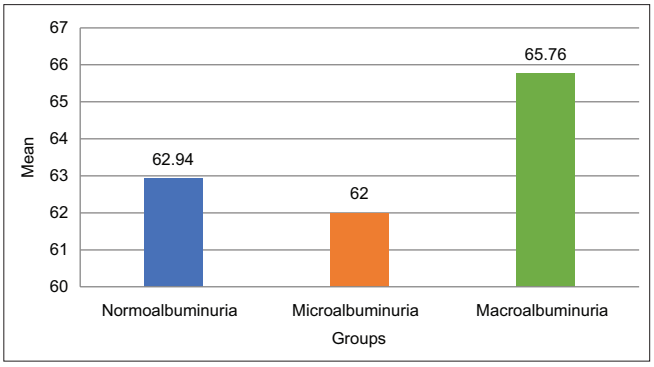

Figure 1: Comparison of the mean age with albuminuria

DISCUSSION

The purpose of this study was to determine the correlation of NLR and PLR with diabetic nephropathy in patients with type 2 DM. Microalbuminuria can be used in the diagnosis and in predicting the progression of diabetic nephropathy.[3] Our results illustrate that the patients with macroalbuminuria and microalbuminuria had a higher NLR and PLR when compared to patients with normoalbuminuria.

In our study, it was found that majority of the patients were within the age group of 61–70 years. Among the individual groups, 51.5% of participants between 61 and 70 years had albuminuria. Our study was in correlation with a study done in Brazil by Nunes Filho et al.,[9] which showed that participants in an older age group had a higher risk of developing proteinuria. As age increases the probability of developing kidney diseases is higher. As eGFR decrease is a part of the aging process of the kidneys, which causes a progressive loss of nephrons as age advances, in addition to alterations on the glomerular basement membrane permeability.[9]

The TLC and the ANC in our study were higher in diabetic patients with albuminuria when compared to diabetic patients with normoalbuminuria. This is comparable

Table 1: Comparison of the mean NLR among the groups

Groups	n	Minimum	Maximum	Mean	Standard deviation	ANOVA P-value
Normoalbuminuria	33	0.7	2.5	1.46	0.47	0.001*
Microalbuminuria	33	1.1	3.0	1.80	0.44	
Macroalbuminuria	33	1.5	4.8	2.68	0.71	

*Significant. NLR: Neutrophil–lymphocyte ratio, ANOVA: Analysis of variance

Table 2: Comparison of the mean PLR among the groups

Groups	n	Minimum	Maximum	Mean PLR	Standard deviation	ANOVA P-value
Normoalbuminuria	33	59.04	138.80	90.94	16.39	0.001*
Microalbuminuria	33	52.46	193.56	119.03	27.51	
Macroalbuminuria	33	101.41	383.82	156.80	55.67	

*Significant. ANOVA: Analysis of variance, PLR: Platelet–lymphocyte ratio

Table 3: Comparison of the mean eGFR among the groups

Groups	n	Minimum	Maximum	Mean eGFR (mL/min/1.73 m^2)	S.D	ANOVA P-value
Normoalbuminuria	33	47.82	116.77	87.76	17.93	0.006*
Microalbuminuria	33	42.88	119.84	84.65	17.94	
Macroalbuminuria	33	36.34	112.26	73.13	20.59	

*Significant. ANOVA: Analysis of variance, eGFR: Estimated glomerular filtration rate

with studies done by Gupta et al.,[10] and Khandare et al.[11] White blood cell counts and their subtypes are considered markers of inflammation, where neutrophilia and relative lymphocytopenia are independent markers of many diseases, including complications of diabetes such as diabetic nephropathy.

Our study also showed significant lymphocytopenia with worsening albuminuria which is in accordance with other studies.[12,13]

Wan et al.,[14] reported that an increased prevalence of cardiovascular and cerebrovascular diseases along with DKD can be observed in diabetic adults with higher NLR levels. A study done by Huang et al.,[15] had shown that NLR values of diabetic patients with DN were significantly higher than the NLR values of diabetic patients without DN and healthy controls and hence concluded that high NLR values are a predictor of early DKD. Our study showed a positive correlation between NLR and albuminuria, this is in line with the published results of other studies that showed a parallel increase in NLR with increasing albuminuria.[4,11,16] Ciray et al.,[17] reported that NLR was inversely related to eGFR, suggesting that there was an association of NLR with a progressive decline in renal function.

PLR is considered to be a predictor of diabetic microvascular complications.[18] The results of our study are in accord with those of a study done by Jaaban et al.,[7] in which PLR had a positive correlation with albuminuria levels and a negative correlation with eGFR. Similar findings were noted in other studies suggesting that PLR could also be used as a parameter to identify early DKD.[19]

Our study could help clinicians in remote areas with insufficient resources to come to an early diagnosis of DKD using cost-effective tests such as NLR and PLR in patients with Type 2 DM and hence take necessary measures to delay End stage renal disease.

Limitations of the study

This study is a small-scale, single-center study. The study provides some evidence that DKD is associated with inflammatory markers, but the specific mechanism still needs more research. A multicentric study with a larger sample size could be done for further association of NLR and PLR with DN.

CONCLUSION

Increased NLR and PLR levels are associated with diabetic nephropathy. A higher NLR and PLR value could indicate the progression of DKD due to its inverse relationship with eGFR. NLR and PLR could be used as a simple and effective prognostic marker for diabetic nephropathy in patients with type 2 DM.

ACKNOWLEDGMENT

We acknowledge the contribution of all the patients who willingly participated in the study.

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Authors' Contributions:
AM- Definition of intellectual content, literature survey, preparation of study protocol, implementation of the study protocol, data collection, data analysis, statistical analysis, interpretation and prepared the first draft of manuscript; **VJP**- Concept, design of the study, preparation of study protocol, literature survey, manuscript preparation, editing, manuscript revision and submission of article and coordination.

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Source of Support: Nil, **Conflicts of Interest:** None declared.