ORIGINAL ARTICLE

Comparison of Neutrophil-Lymphocyte Ratio between Diabetic Nephropathy and Without Diabetic Nephropathy in Type 2 Diabetes Mellitus at a Tertiary Care Centre

Yadav A[1], Jyoti S[2], Yadav P[3], Rai R[1], Mehta RK[1], Parajuli SB[4], Yadav I[5]

ABSTRACT

Introduction: Type 2 Diabetes mellitus is a kind of systemic disease with serious microvascular and macrovascular complications incorporate diabetic nephropathy. The Neutrophil lymphocyte ratio (NLR) is a simple and cheap laboratory tool used to predict the prognosis of many non-communicable diseases such as diabetic nephropathy. **Aims:** To compare neutrophil-lymphocyte ratio between type 2 diabetes mellitus with diabetic nephropathy and without diabetic nephropathy. **Methods:** An observational cross-sectional study was conducted at teaching hospital, Morang, Nepal. Non probability convenience sampling technique was used to collect data of 226 participants by using clinical and laboratory forms and formats. The data was analysed in SPSS version 21.00. **Results:** Laboratory parameters were compared between two groups. High density lipoprotein (p=0.028) and low density lipoprotein (p<0.01) and glycaemic parameters fasting blood glucose (p=0.028), postprandial blood glucose (p=0.0005) and glycated haemoglobin (p=0.007) were found to be significantly raised in diabetic nephropathy patients as compared to without diabetic nephropathy patient. Renal function tests such as estimated glomerular filtration rate (p<0.01), serum creatinine (p<0.01), urine albumin-to-creatinine ratio (p< 0.01) showed high significant differences between two groups. Blood cell count, platelets (p<0.01) and white blood cell (p<0.01) were found to have statistically significant between patients with diabetic nephropathy and without diabetic nephropathy. Majority of individuals with smoking habit fell in diabetic nephropathy group as compared with individual without diabetic nephropathy. Neutrophil lymphocyte ratio was high in diabetic nephropathy group. **Conclusion:** The neutrophil-lymphocyte ratio was significantly raised in type 2 diabetic patients with diabetic nephropathy. Based on above finding, neutrophil-lymphocyte ratio may be considered as a predictor and a prognostic biomarker of diabetic nephropathy.

Keywords: Diabetes Mellitus type 2, Diabetic Nephropathy, Neutrophil- Lymphocyte Ratio

Authors:

1. Dr. Anil Yadav
2. Dr. Sabita Jyoti
3. Dr. Pratima Yadav
4. Dr. Rabin Rai
5. Dr. Ram Kumar Mehta
6. Dr. Surya Bahadur Parajuli
7. Dr. Indra Yadav

[1]Department of Medicine, Birat Medical College Teaching Hospital, Biratnagar, Morang, Nepal

[2]Department of Community Medicine, Nepalgunj Medical College Teaching Hospital, Nepalgunj, Banke, Nepal

[3]Department of Pediatrics, Nobel Medical College Teaching Hospital, Biratnagar, Morang, Nepal

[4] Department of Community Medicine, Birat Medical College Teaching Hospital, Biratnagar, Morang, Nepal

[5]Department of Obstetrics and Gynaecology, Birat Medical College Teaching Hospital, Biratnagar, Morang, Nepal

Address for Correspondence:

Dr. Anil Yadav
Department of Medicine
Birat Medical College and Teaching Hospital
Biratnagar, Morang, Nepal
Email: cooldewup@gmail.com

INTRODUCTION

Diabetes mellitus (DM) is a systemic disease with serious microvascular and macrovascular complications. Microvascular complications incorporate diabetic nephropathy (DN), diabetic retinopathy, and macrovascular complications include stroke, cardiovascular diseases (CVDs), and peripheral vascular disease.[1] Type 2 diabetes results from body's ineffective use of insulin. Type 2 diabetes accounts for vast majority of people with diabetes around world.[2] DN is a common microangiopathic complication with diabetes and DN is one of most common causes of end-stage renal disease (ESRD).[3] Most of inflammatory markers are related to DN, such as interleukin-1 (IL1), interleukin-6 (IL6), interleukin-8 (IL8), transforming growth factor-beta 1 (TGF-β1), tumor necrosis factor-alpha (TNF-α), and cytokines.[4] Around world, most of investigators have evaluated

value of neutrophil leukocyte ratio (NLR) as markers of DN and these have been identified as novel surrogate markers of DN by them.[5] In South-East Asia (SEA) Region, nearly 71 million are living with diabetes in 2010 and 1 million in SEA Region die from consequences of high blood glucose every year.[6] In 2017, more than 10, 000 individuals died due to T2DM or diabetes-related complications in Nepal.[7] In 2020, prevalence of T2DM in Nepal was 8.5%, higher than that of 8.4% in 2014.[8] NLR has been recently identified as novel biomarker of numerous inflammatory diseases like chronic kidney disease (CKD) and is simple and cheap laboratory tool.[5, 9] Therefore, this study was conducted to evaluate the significance of NLR in between T2DM with DN and T2 DM without DN.

METHODS

An observational cross-sectional study conducted using non probability convenience sampling technique to collect the data. The study was done in tertiary care centre, Morang, Nepal, from December 2021 to December 2022, purposively Birat Medical College was selected as it provides tertiary care facilities and most of the patients are referred here from eastern part of Nepal. The sample size was calculated using prevalence of diabetes kidney disease from a study with 34.4% prevalence[10] so, the intended sample size calculated was (n) = 87 However, keeping in mind the possibilities of dropout and laboratory errors (if any), 10% attrition is added to the sample size.

Thus, total sample size = 95 in each group The criteria for DN were presence of albuminuria (ACR ≥30mg/g) and/or reduced estimated glomerular filtration rate (eGFR) (<60 ml/min//L/1.73 m2) in the absence of signs or symptoms of other primary causes of kidney damage.[10] At first secondary data was collected by the hospital outpatient departments and emergency as well. After selecting the participants, different clinical and laboratory parameters (such as HDL, LDL etc) of both diabetic nephropathy patient and diabetes mellitus patients were tested by laboratory tests and physical check-up. In some patient laboratory retest was done if error was displayed in the testing procedure. Different types of laboratories recording and reporting forms and formats were used to collect the clinical data (information) of the participant.

Ethical clearance was taken from Institutional review committee of Birat Medical College Teaching Hospital (BMCTH) (Reference Number: IRC-PA-178/2078-79). In this study NLR is defined as a way of measuring the inflammation within the body in which NLR was calculated by dividing the neutrophil by the lymphocyte count. Type 2 Diabetic patient attending the department of medicine were included in the study. While the patients with type 1 DM, infections or history of infections in the past 1 month, systemic disorders such as stroke, myocardial infarction, chronic liver disease, blood disorders, autoimmune disorders, malignancy, and poisoning, on anti-inflammatory drugs, systemic or topical steroids, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, uncontrolled blood pressure (BP) (≥160/100 mm Hg), diseases affecting urinary protein excretion as nephrotic syndrome, urolithiasis, renal artery stenosis, dehydration state, and urinary tract infections (UTI), low glomerular filtration rate (GFR) without albuminuria were excluded from study.

The data has been entered in MS-Excel, analysed in SPSS version 21, descriptive analysis such as frequency, percentage mean, etc. were calculated. As well as Pearson correlation were calculated with statistical significance p=0.05 at 95% confident interval.

RESULTS

A total of 226 diabetic patients were taken for the study purpose. Of these, 112 had DN and 114 were not having the DN. Socio demographic variables such as age, sex, occupational status, place of residence, educational status, and average monthly income, duration of disease and body mass index were taken for this study and shown in Table I. In this study, the mean age of the patients of DN and without DN group was 54.41±10.36 years and 52.18±10.59 years, respectively. Both groups have the similar distribution of age (p=0.11). In addition, there was no sex related variability in diabetic neuropathy patients male was 73(65.2%), female was 39(34.8%) and in without DN male was 69(60.5%), female was 45(39.5%. However, there was significant association between the duration of disease among the patient with DN and without DN.

Socio-demographic characteristic	With DN n=112(%)	Without DN n=114(%)	P-Value
Age	54.41 (10.36)	52.18 (10.59)	0.11
Sex			
Male	73 (65.2)	69 (60.5)	0.52
Female	39 (34.8)	45 (39.5)	
Occupation			
Daily wages	20 (17.86)	14 (12.28)	0.43
Salaried service	19 (16.96)	29 (25.44)	
Business	18 (16.07)	14 (12.28)	
Household Chores	37 (33.04)	40 (35.09)	
Retired	18 (16.07)	17 (14.91)	
Place of residence			
Urban	88 (78.57)	91 (79.82)	0.81
Rural	24 (21.43)	23 (20.18)	

Education			
No education	20 (17.86)	18 (15.79)	0.61
Upto Higher Secondary	40 (35.71)	48(42.11)	
Above Higher Secondary	52(46.43)	48(42.11)	
Average Monthly Income			
<26,705.3	34 (30.36)	29 (25.44)	0.6
26,705.3-40,058.01	29 (25.89)	28 (24.56)	
>40,058.01	49 (43.75)	57 (50)	
Duration of Disease(years)	8.17 (6.62)	6.4 (4.83)	0.02
BMI(kg/m2)	25.72 (5.79)	25.66 (4.82)	0.91

DN: Diabetes nephropathy, Statistically significant at 0.05

Table I: Relationship between demographic profile with DN and without DN (n=226)

Association with clinical and laboratory parameters Laboratory parameters such as lipid profile (total cholesterol, TG, HDL, LDL), and glycaemic parameters such as (FBS, PPBS, Hb1Ac) were compared between the two groups. HDL (p=0.028) and LDL (p<0.01) were found to have the significant association between the groups. However, total cholesterol and triglyceride were not associated with DN and without DN groups. All glycaemic parameters (FBS, p=0.028, PPBS, p=0.0005, and HbA1c (p= 0.007) were found to be significantly raised in DN patient group as compared to normal patient group. In relation to eGFR (p<0.01), Serum creatinine (p<0.01), UACR (p< 0.01), blood cell count platelets (p<0.01 and WBC (p<0.01) were found to have statistically significant between the patients with DN and without DN. Smoking was found to be significant between with DN patient and without DN patients (p<0.01). However, intake of alcohol was not found to be significant between the patient groups. DN patients have decreased mean of lymphocyte count and increased mean of neutrophil count as compared to without DN patient. Laboratory parameters such as FBS, HDL, LDL, HbA1c, Hemoglobin, Lymphocyte, Neutrophil, platelets, NLR, DBP, SBP, Total Cholesterol, Triglyceride, UACR, WBC, eGFR, PPBS, HTN, habit of smoking and intake of alcohol intake has been shown in Table II.

Laboratory Parameters	With DN	Without DN	P-Value
Serum creatinine(mg/dL)	1.02 (0.32)	0.88 (0.15)	0.0001
FBS (mg/dL)	148 (55.89)	135.23 (35.13)	0.028
HDL(mg/dL)	43.70 (7.18)	38.08 (7.18)	0.000
LDL(mg/dL)	108.58 (36.04)	105.614 (22.90)	0.45
HbA1c(mmol/mol)	8.02 (1.55)	7.52 (1.15)	0.007
Haemoglobin(gm/dl)	12.69 (1.68)	12.56 (1.33)	0.52
Lymphocyte (cells/cumm)	28.27 (4.50)	32.90 (31.79)	0.000
Neutrophils(cells/cumm)	67.31 (4.37)	63.28 (6.78)	0.000
Platelet (lakhs/cumm)	248167 (9355.66)	211612 (52850.19)	0.0006
NLR	2.44 (0.45)	1.99 (0.48)	0.000
Total Cholesterol(mg/dL)	179.66 (51.63)	175.33 (33.19)	0.45
Triglyceride (mg/dL)	226.85 (12.78)	237 (9.74)	0.49
UACR(mg/g)	417.79 (1126.11)	13.35 (5.88)	0.0002
WBC(cells/cumm)	8081 (167.57)	6840 (1579.97)	0.000
eGFR(mg/min)	56.44 (14.41)	89.39 (16.07)	0.000
Post Prandial Blood Sugar(mg/dL)	246.61 (90.29)	212.28 (50.88)	0.0005

Clinical Parameter	With DN	Without DN	P-Value
Blood pressure(mmHg)			
Diastolic BP	77.58 (8.62)	77.01 (8.51)	0.61
Systolic BP	125.98 (15.50)	123.24 (120.66)	0.16
HTN			
Yes	58.93	42.11	0.01
No	41.07	57.89	
Smoking			
Current Smoker	8.93	2.63	
Past smoker	33.93	21.93	0.008
Non-Smoker	57.14	75.44	
Alcohol			
Consumer	10.71	10.53	
Non-Consumer	69.64	78.07	0.22
Quitted	19.64	11.4	

DN: Diabetes nephropathy, Statistically significant at 0.05

Table II: Association of patients with DN and without DN with clinical and laboratory parameters

Correlation between NLR and other variables

Significant positive correlation was observed between NLR and each of the other variables such as duration of illness (r=0.140, p=0.03), serum creatinine (r=0.1599, p=0.01), HDL (r=0.16, p=0.01), LDL (r=0.1998, p<0.01), HbA1c (r=0.188, p<0.01), UACR (r=0.2345, p<0.001), neutrophil (r=0.58, p<0.001) and WBC (r=0.32, p<0.001). On the other hand, NLR showed a significant negative correlation with eGFR (r=-0.31, p<0.001), total lymphocyte (r=-0.91, p<0.001) which is mentioned in table III and IV.

Variables	Pearson Correlation	P-value
Age (years)	0.1244	0.06
Education	-0.09	0.16
Residence	-0.03	0.6543
Gender	0.005	0.9336
Occupation	-0.02	0.71
Diabetes in first degree relative	-0.09	0.14
Diabetic kidney disease in first degree relative	-0.11	0.09
Hypertension	0.01	0.82
Smoking	-0.11	0.07
Alcohol	0.09	0.14
Duration of T2DM	0.1405	0.03
BMI	-0.0089	0.89

DN: Diabetes nephropathy, Statistically significant at 0.05

Table III: Correlation between NLR and other variables

Variables	Pearson Correlation	P-value
Creatinine	**0.1599**	**0.0161***
HDL	**0.1634**	**0.01***
LDL	**0.1998**	**0.0025***
HbA1c	**0.1884**	**0.004***
FBS	**0.12**	**0.06**
PP	**0.12**	**0.06**
Total Cholesterol	**0.009**	**0.14**
Triglyceride	**0.03**	**0.62**
eGFR	**-0.31**	**0.000**
UACR	**0.2345**	**0.0004**
Haemoglobin	**-0.1**	**0.12**
WBC	**0.32**	**0.000**
Platelets	**0.0687**	**0.3039**
Neutrophils	**0.58**	**0.000**
Lymphocyte	**-0.91**	**0.000**

DN: Diabetes nephropathy, Statistically significant at 0.05

Table IV: Correlation between NLR and other variables

DISCUSSION

Multiple studies have shed light on the significance and importance of inflammatory molecules (such as adipokines, chemokines, adhesion molecules, and cytokines) and endothelial dysfunction in the development of insulin resistance, diabetes, and its numerous consequences over the last decade.[11, 12] Unknown is the precise pathophysiology of DN. However, it is recognized that a series of pathological processes play a significant role in the onset and progression of DN, with glomerular injury serving as an early indicator and the cause of proteinuria, followed by progressive renal damage, fibrosis, inflammation, and finally the loss of functional nephrons.[13] The key finding of this study was that the mean and standard deviation (2.22± 0.52) of NLR for DN and were found to be significantly associated (p<0.001) with patients who were diagnosed with early-stage DN as compared to those without DN. A similar study by Gurmu MZ et al reports the mean NLR value (2.66 ± 0.49) was found significantly higher in diabetic patients with DN compared to the mean NLR (1.65 ± 0.20) in diabetes patients without DN (p < 0.0001). This result has been supported by multiple studies globally.[5,13–15,16]

Increased NLR affects renal function and histologic lesions in patients with T2DM and may be a crucial factor for the progression of DN.[17] Several epidemiological studies have highlighted that NLR is correlated with age, hypertension, smoking which was not similar to our study there which was not significant.[18] We observed no significant correlation between NLR and other variables such as sex, FBS level, and BMI among T2DM patients with and without DN. Laboratory parameters on lipid profile, especially HDL, and LDL were found to be significant predictors for diabetic neuropathy while total cholesterol and triglyceride count was not found to be significantly associated with DN. Systematic review and meta-analysis from 39 studies revealed that higher TG and lower HDL was found (MD = 0.34, 95% CI: 0.20–0.48 for TG; MD = -0.05, 95% CI: -0.08–-0.02, I2 = 81.3% for HDL) than controls.[19] HDL in patients with DN was 43.70 (7.18) and without DN was 38.08 (7.18) p= 0.000 and LDL 108.58 (36.04) in patients with DN was and without DN 105.614 (22.90) with p=0.45. HDL association was found to be in consistent with this study. These findings suggest that changed in lipid profile specially HDL serum levels, may be the risk factor for DN. High-quality randomized controlled trials (RCTs) in the future are needed to better understand the causality between the serum lipid profile and DN.[19] Our study suggest that poor glycaemic control is the predictors of DN and correlated with NLR. These findings has been supported by previous studies that have found correlation between hyperglycaemia and DN.[20]

The most well-known indexes are UACR and eGFR, which reflect glomerular function and are usually used to define staging of chronic kidney disease. Our study findings, reflect mean eGFR was lowered in DN patients as compared to without DN patient (p<0.0001). Another possibility is that individuals with higher eGFRs produce less creatinine, which is a sign of decreased muscle mass and malnutrition, both of which are known to contribute to the pathophysiology of diabetes.[20] UACR mean

value for the patient with DN was 417.79 and without DN was 13.35 with ($p<0.0001$). This finding has been supported by the study conducted by Yang et al.[22]

The peripheral total WBC, monocyte, and neutrophil counts increased in parallel with the advancement of diabetic nephropathy in the study conducted by Chung et al which was found to be coherent with this study findings.[23]

LIMITATIONS

This study still poses some challenges and has limitations. Biomarkers such as interleukin 1, 6, interferon gamma, and tumor necrosis factor alpha were not taken due to high cost. Information on the types of treatment for the DN were also not taken by this study. Also, as this study was conducted small sample the result cannot be generalized conducted. The case control study will give better result as well-established association between several factors.

CONCLUSION

Overall, this study exposed that the NLR was significantly raised in T2DM patients with DN compared without DN. It was evident that NLR showed a significant positive correlation with duration of T2DM, creatinine, HDL, LDL, HbA1c, e-GFR, UACR and WBC. The study also found a strong positive connection between NLR and DN, showing that inflammation and endothelial dysfunction may play a role in the etiology of DN. As a result, NLR could be regarded as a possible predictor and prognostic biomarker of DN in T2DM patients. Based on findings, it can be believed that NLR should be used in clinical practice for the diagnosis and prognosis of DN in Nepalese health facilities. Additional investigation through randomized controlled trial or with a more appropriate study design and a larger sample size could help to add some more values in future research.

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