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Original Research

Neutrophil to Lymphocyte Ratio as a Reliable Biomarker of Diabetic Nephropathy in Type 2 Diabetes

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ABSTRACT-
Background: Inflammation plays a central role in pathogenesis of diabetic nephropathy (DN), a major cause of morbidity and mortality in type 2 diabetes mellitus (T2DM). Neutrophil lymphocyte ratio (NLR) is a novel and easily available inflammatory marker that can be used to predict DN.
Objective : To determine the neutrophil–lymphocyte ratio (NLR) as an inflammatory biomarker among type 2 diabetes mellitus (T2DM) patients with diabetic nephropathy (DN).
Results: The 100 patients of diabetic nephropathy were taken In this study with type 2 diabetes mellitus patients In GNDH GMC Amritsar both from OPD and IPD.
Interestingly these results are found in study:-
1.Increasing age serves as a factor for increasing severity of Diabetic microvascular complications with increasing duration of diabetes as well as diabetic nephropathy.
2.HbA1C levels significantly increased with age ($p < 0.001$), suggesting poorer glycemic control in older patients.
3.Serum urea levels showed significant differences across age groups ($p = 0.005$), reflecting variability in renal function with age.
4.A strong negative correlation established between GFR and urinary ACR.
5.NLR is increases as diabetic nephropathy in type 2 diabetes mellitus prevalence is increases.
6.Presence of increasing grades of renal dysfunction was found to be associated with type DM , implying that greater is the severity of micro vascular complication, greater is the presence of neutrophil-lymphocyte ratio which act as inflammatory marker present in DN.
7.More is the duration of diabetes, more is the severity of micro vascular complication, and more is the prevalence of diabetic nephropathy.
Conclusion :-Over all, the present study assessed NLR in diabetic nephropathy in type 2 diabetes, the data has led us to conclude that NLR values are higher in patients with DN and this difference is statistically significant. NLR is easily available; cost effective and routinely done, hence can be considered as a novel biomarker for DN in patients with type 2 diabetes mellitus.
Keywords: diabetes mellitus, diabetic nephropathy, hyperglycaemia, neutrophil to lymphocyte ratio.

INTRODUCTION

Diabetes mellitus refers to a group of common metabolic disorders that are characterized by hyperglycaemia. It is caused by deficiencies in either the action or secretion of insulin, or both. In society, it significantly increases morbidity and mortality.1 Diabetes has lately reached epidemic proportions, impacting over 460 million people globally. According to estimates, the number of persons with diabetes worldwide will be 9.3% (463 million) in 2019. By 2030, that number will rise to 10.2% (578 million), and by 2045, it will reach 10.9% (700 million), with developing nations in Asia, South America, and Africa experiencing the biggest increases.2 It is (DN), diabetic retinopathy, and diabetic neuropathy, and macrovascular complications, including cardiovascular diseases, stroke, and peripheral vascular diseases.3

Type-1 diabetes affects the pancreas' ability to create insulin, while type-2 diabetes affects the body's insufficient release of insulin or its insufficient production of insulin. Serious microvascular complications such as diabetic nephropathy is unable respond to it proficiently in systemic disease .4

The number of patients with Type 2 Diabetes Mellitus (T2DM) reached around 90% of all DM patients globally. Because post-receptor signal interference occurs, type 2 diabetes is referred to as non-insulin dependent. T2DM process begins with insulin resistance in peripheral cells which induces compensation for pancreatic β cells. When the progression of DM continues to occur, at one point the pancreatic cell is exhausted and unable to compensate for the situation.3

Diabetic retinopathy, diabetic neuropathy, and diabetic nephropathy (DN) are examples of major microvascular problems caused by DM in addition to stroke, cardiovascular diseases (CVDs), and peripheral vascular diseases (macro vascular complications).5

Patients with T2DM who receive a diagnosis after 20 to 25 years are susceptible to consequences including DN.6 Diabetic kidney disease (DN) is a syndrome characterized by pathological amounts of proteinuria, diabetic glomerular lesions, and decreased glomerular filtration rate (GFR) in people with diabetes. Although DN is currently the most frequent cause of chronic kidney disease (CKD), its aetiology is still unknown. Chronic kidney disease and end-stage renal disease (ESRD) are possible outcomes of either type of diabetes. Type2 diabetes, on the other hand, is far more common than type 1 diabetes and is frequently present in ESRD patients.7.

The clinical symptom of diabetic kidney disease (DN) is an increase in urine albumin excretion, which progresses from micro albuminuria to macro albuminuria and ultimately ESRD.8 Currently, albuminuria is used as a biomarker for DN diagnosis. Renal damage frequently occurs prior to urine albumin secretion, so its diagnostic use in early-stage DN is restricted. The mechanism of DN with the activation of Renin Angiotensin Aldosterone System (RAAS), Reactive oxygen species (ROS) and advanced glycation end products (AGEs) 9 are linked to tubulointerstitial renal sclerosis and inflammation in mesangial cells.The kidney's inflammatory process is distinguished by elevated levels of inflammatory cytokines, including TNF-α, NF-κB, and Interleukin 1, 6, and 18 (IL-1, IL-6, and IL-18).which increases in patient with T2DM. However, the measurement of these inflammatory markers is not used in daily clinical practice because of their costs and technical difficulties in application.5

Neutrophil-to-lymphocyte ratio (NLR) has become a novel alternative marker in this regard.9 Neutrophil to lymphocyte ratio (NLR) has been identified as a promising biomarker for systemic inflammatory status across different disease states. NLR is a typical laboratory calculation that is straightforward, economical, and easy to do. It may be useful as a substitute inflammatory marker. It has been suggested that NLR serves as a stand-in marker for inflammation and endothelial dysfunction. Diabetic nephropathy is best identified and managed with early and prompt examination using low-tech diagnostic methods.10

The subtypes, particularly the neutrophils, lymphocytes, and subsequent calculation of neutrophil–lymphocyte ratio (NLR), which is relatively more stable than individual leukocyte parameters, could be altered by various physiological, pathological, and physical factors.11 Many non-communicable diseases, including acute MI, stroke, heart failure, appendicitis, cardiac disorders, cancer, and DN, have prognoses that can be predicted using the NLR, a low-cost, straightforward laboratory test that is being explored as an inflammatory marker.12, 13

NLR represents a combination of two marker and neutrophil which represents the active nonspecific mediator initiating the first line of defence and lymphocyte representing the regulatory and protective component of inflammation.14

Depending on the clinical context, two diagnostic modalities are primarily used to diagnose and monitor diabetic nephropathy: estimating renal damage in terms of albuminuria and evaluating kidney function in terms of estimated glomerular filtration rate (eGFR).15

These techniques are currently applied in practice all over the world as clinical indicators of diabetic nephropathy. These markers also provide information for evaluating the risks of ESRD and CVD in patients with diabetic nephropathy, which helps decide when to employ early therapeutic methods. However, there are a number of disadvantages to diagnosing and monitoring diabetic nephropathy with these markers. Understanding these restrictions and working to find new and improved biomarkers are crucial to the effective treatment of diabetic nephropathy.16

In T2DM patients, there may be a correlation between increased NLR levels and the existence and severity of DN. It is still unclear how useful NLR is in this cohort as a trustworthy biomarker of DN. Adequate screening can detect the development or progression of diabetic nephropathy early, improving the quality of life for people affected and reducing the condition's social burden. Diagnostic tools are essential for prompt and appropriate care of the condition.17

Therefore, the primary objective of this research work is to systematically investigate the utility of NLR as a reliable biomarker of DN in patients with T2DM. This study aims to assess the association between NLR levels and the presence, severity, and progression of DN, as well as to explore potential correlations with other clinical and biochemical markers of renal function and inflammation.

MATERIALS AND METHODS

The present study titled "NEUTROPHIL TO LYMPHOCYTE RATIO AS A RELIABLE BIOMARKER OF DIABETIC NEPHROPATHY IN TYPE 2 DIABETES" was conducted on patients with diagnose of diabetic nephropathy in type-2 diabetes mellitus patients admitted in the department of medicine of Guru Nanak Dev Hospital attached to Govt. Medical College.

This was a cross-sectional study. A total 100 patients of diabetes were enrolled in this study. The patients were examined in their vernacular language about the procedure to be adopted in the study and their informed written consent was taken. A study was conducted after seeking permission from Institutional Ethics Committee, Government Medical College, Amritsar. The study was carried out by taking Written informed consent from the patients. A detailed study, history, clinical examination and laboratory investigation will be performed in patient with diabetes mellitus.

INCLUSION CRITERIA:

Patients diagnosed to have diabetic nephropathy based on clinical features/biochemical investigation and ultrasound, HbA1c, renal function test in OPD and admitted patient in the hospital for management diabetic nephropathy is considered in the study.

EXCLUSION CRITERIA:

- Type 1 diabetes mellitus.
- Gestational diabetes.
- Secondary diabetes.
- Sepsis.
- Diagnosed autoimmune disease
- Diagnosed hypertensive Nephropathy.

Following investigation will be done in hospitalized patient, complete blood count (CBC+) absolute neutrophil count, absolute lymphocyte count, liver function test, blood urea, serum creatinine, USG whole abdomen and viral markers.

RESULTS

The present study was conducted on patients with diagnose of diabetic nephropathy in type-2 diabetes mellitus patients admitted in the department of medicine of Guru Nanak Dev Hospital attached to Govt. Medical College, Amritsar from 1st March 2023 to 28th February 2024. Total 100 study participants were included in the present study.

The mean duration were found among study participants (13.01 +/- 7.45) years Regarding blood glucose and glycaemic control, the mean fasting blood sugar (FBS) was 221.05 mg/dL with a standard deviation of 81.638 mg/dL, spanning from 80 to 432 mg/dL. The mean HbA1C level was 10.984% with a standard deviation of 11.952%, ranging widely from 6.00% to 93.00%. These figures indicate significant variability in glucose levels and long-term glycaemic control among the study population, highlighting potential challenges in managing diabetes or impaired glucose metabolism.

In terms of renal function, the mean serum urea level was 128.55 mg/dL with a standard deviation of 67.82 mg/dL, ranging from 24.00 to 401.00 mg/dL. The mean serum creatinine level was 4.911 mg/dL with a standard deviation of 3.55 mg/dL, ranging from 1.500 to 20.40 mg/dL. The mean glomerular filtration rate (GFR) was 16.30 mL/min/1.73m² with a standard deviation of 9.88 mL/min/1.73m², ranging from 3 to 44 mL/min/1.73m². These renal function parameters indicate a spectrum of kidney health among participants, with notable variations in kidney function and potential implications for renal disease management.

Regarding immune and inflammatory markers, the mean neutrophil percentage was 81.91% with a standard deviation of 10.76%, ranging from 54.00% to 97.00%. The mean lymphocyte percentage was 12.28% with a standard deviation of 8.82%, ranging from 1.60% to 36.10%. The mean neutrophil-to- lymphocyte ratio (NLR) was 12.13 with a standard deviation of 10.96, ranging from 1.57 to 58.75 .

These markers suggest varying levels of systemic inflammation and immune response among participants, highlighting potential implications for overall health and disease susceptibility.

Table1 :-Distribution Of Study Participants According To Their Age

Age (years)	Frequency (years)	Percent (%)
<=40	3	3.0
41-50	11	11.0
51-60	28	28.0
61-70	38	38.0
>70	20	20.0
Total	100	100.0
Mean Age ±S.D : 62.61±10.59		

Table shows distribution of study participants according to their age profile where it was found that approximately two-third of study participants (66%) were aged between 51-70 years, (20%).

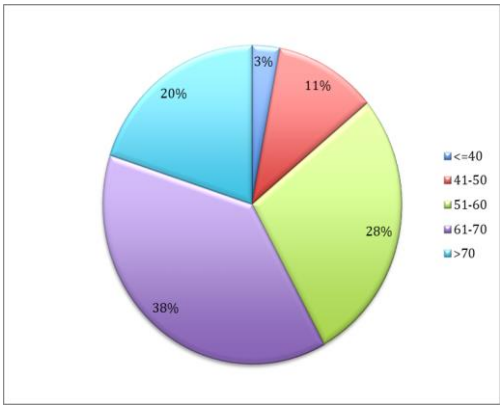

Table 2 : Distribution Of Study Participants According To Their Age

GENDER	Frequency	Percent
Male	44	44.0
Female	56	56.0
Total	100	100.0

(Figures in parenthesis are percentages)

Table shows distribution of study participants according to their socio-demographic profile where it was found that, 56% of study participants were females and 44% males.

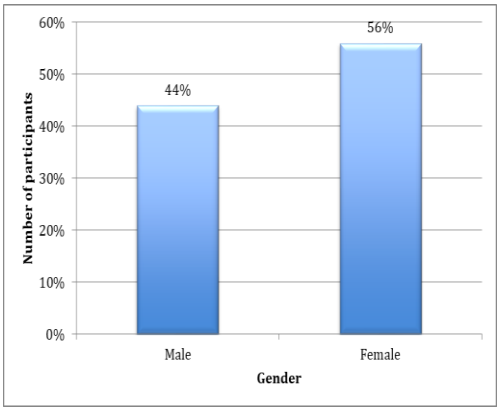

Table 5: Distribution Of Study Participants According To Their Duration Of Diabetes Mellitus By Age Group.

	Age	N	(%) Age	Mean	Std. Deviation	P value
DURATION OF DIABETES MELLITUS	<=40	3	3	5.67	0.577	0.000
	41-50	11	11	7.64	2.335	
	51-60	28	28	10.18	3.742	
	61-70	38	38	13.97	6.495	
	>70	20	20	19.20	10.268	
	Total	100	100	13.01	7.456	

The mean duration of diabetes mellitus increased with age, with the highest mean duration observed in the >70 age group (19.20) and the lowest in the <=40 age group (5.67).Standard deviations also varied across age groups, indicating the dispersion of data points around the mean duration of diabetes mellitus. A significant P value of 0.000 suggests that there are statistically significant differences in the duration of diabetes mellitus among the various age categories. The total mean duration of diabetes mellitus for all participants was calculated at 13.01 years, with a standard deviation of 7.456, reflecting the overall variability in diabetes duration across the entire sample.

Table 19: Correlation Of Nlr With Serum Urea, Serum Creatinine, Gfr And Urinary Acr.

Variable	Pearson Correlation	Significance (2-tailed)
NLR vs. Serum Urea	0.348**	0
NLR vs. Serum Creatinine	0.241*	0.016
NLR vs. GFR	-0.132	0.19
NLR vs. Urinary ACR	0.151	0.183

**. Correlation is significant at the 0.01 level (2-tailed).
*. Correlation is significant at the 0.05 level (2-tailed).
From the provided table, the correlations of NLR (Neutrophil-to-Lymphocyte Ratio) with Serum Urea, Serum Creatinine, GFR (Glomerular Filtration Rate), and Urinary ACR (Albumin-to-Creatinine Ratio) are as follows:

NLR vs. Serum Urea:
Pearson Correlation: 0.348**
Significance (2-tailed): 0.000
Interpretation: There is a significant positive correlation between NLR and Serum Urea at the 0.01 level.
N\LR vs. Serum Creatinine
Pearson Correlation: 0.241*
Significance (2-tailed): 0.016
Interpretation: There is a significant positive correlation between NLR and Serum Creatinine at the 0.05 level.
NLR vs. GFR:
Pearson Correlation: -0.132
Significance (2-tailed): 0.190
Interpretation: There is a negative correlation between NLR and GFR, but it is not statistically significant.
NLR vs. Urinary ACR:
Pearson Correlation: 0.151
Significance (2-tailed): 0.183
Interpretation: There is a positive correlation between NLR and Urinary ACR, but it is not statistically significant.
This table summarizes the correlations between NLR (Neutrophil-to-Lymphocyte Ratio) and Serum Urea, Serum Creatinine, GFR (Glomerular Filtration Rate), and Urinary ACR (Albumin-to-Creatinine Ratio), including the Pearson Correlation coefficients and their significance levels.

TABLE 21: CORRELATION OF GFR WITH URINARY ACR.

GFR Classification	Pearson Correlation	Significance (2-tailed)
G 1 (≥90)	-0.605**	0
G 2 (60-89)	0.581**	0
G 3a (45-59)	0.102	0.311
G 3b (30-44)	-0.049	0.631
G 4 (15-29)	0.171	0.089
G 5 (<15)	-0.218*	0.029

The table shows the correlation coefficients between Urinary GFR (Glomerular Filtration Rate) and Urinary ACR (Albumin-to-Creatinine Ratio) based on different GFR classification ranges. Here is an explanation of the table:
GFR 1 (≥90):
Pearson Correlation: -0.605**
Significance (2-tailed): 0.000
Interpretation: There is a strong negative correlation between Urinary GFR and Urinary ACR for individuals with a GFR of 90 or higher. This negative correlation is statistically significant at the 0.01 level.
GFR 2 (60-89):Pearson Correlation: 0.581**
Significance (2-tailed): 0.000
Interpretation: There is a strong positive correlation between Urinary GFR and Urinary ACR for individuals with a GFR between 60 and 89. This positive correlation is statistically significant at the 0.01 level.
GFR 3a (45-59):
Pearson Correlation: 0.102
Significance (2-tailed): 0.311
Interpretation: There is a weak positive correlation between Urinary GFR and Urinary ACR for individuals with a GFR between 45 and 59. This correlation is not statistically significant.
GFR 3b (30-44):
Pearson Correlation: -0.049
Significance (2-tailed): 0.631
Interpretation: There is a very weak negative correlation between Urinary GFR and Urinary ACR for individuals with a GFR between 30 and 44. This correlation is not statistically significant.
GFR 4 (15-29):
Pearson Correlation: 0.171
Significance (2-tailed): 0.089
Interpretation: There is a positive correlation between Urinary GFR and Urinary ACR for individuals with a GFR between 15 and 29. This correlation is not statistically significant but shows a trend towards a positive relationship.
GFR 5 (<15):
Pearson Correlation: -0.218*
Significance (2-tailed): 0.029
Interpretation: There is a moderate negative correlation between Urinary GFR and Urinary ACR for individuals with a GFR less than 15. This negative correlation is statistically significant at the 0.05 level.

DISCUSSION

Diabetes mellitus is the most grueling problem in today's world. It's a complex complaint characterized by habitual hyperglycemia, metabolic abnormalities and long term micro- and macro vascular complications. Diabetic nephropathy, one of the micro vascular complications of DM, is characterized by patient albuminuria, hypertension and low GFR. Micro albuminuria is set up to be an early marker of DN.33
Albuminuria can lead to some changes in the situations of multitudinous biomarkers in blood rotation, which could be applied to opinion and the threat evaluation of progression of order complaint. Several studies showed that NLR are advanced in cases of diabetes with nephropathy when compared with those without nephropathy. Lymphocytes are essential for seditious response that can drop due to convinced apoptosis and therefore can serve as a marker for DN.34
Neutrophill and lymphocyte count are hence proposed to be implicit labels in individual workup of DN. The present study was done to demonstrate the below proposition and showed that increased NLR values were associated with

DN. The increased NLR values were significantly advanced in cases with DN.35

In our study 100 cases of type 2 diabetes mellitus were Included. The cases were both from OPD and IPD of Medicine Department of Guru Nanak Dev Hospital, Amritsar. These cases were estimated for the diabetes control, presence of nephropathy, clinical and laboratory examinations and these compliances were identified to the presence of Diabetic nephropathy. These cases before registration into the study were explained about the study in conversational language and an informed concurrence was taken for the same. In this study we enrolled 56 ladies, and 44 Males with all cases being Type 2 DM independently.

The mean age of the study participants was 62.61±10.59 years with the majority of the participants within the age ranges of 61-70 years and 51-60 years, constituting 38% and 28% respectively. The gender distribution showed a slight female (56%) predominance over males (44%).

Duration of diabetes mellitus with age

In present study the mean duration of diabetes mellitus increased with age, with the highest mean duration observed in the >70 age group (19.20) and the lowest in the <=40 age group (5.67).Standard deviations also varied across age groups, indicating the dispersion of data points around the mean duration of diabetes mellitus. A significant P value of 0.000 suggests that there are statistically significant differences in the duration of diabetes mellitus among the various age categories. The total mean duration of diabetes mellitus for all participants was calculated at 13.01 years, with a standard deviation of 7.456, reflecting the overall variability in diabetes duration across the entire sample.

Duration of diabetes with various parameters of renal function

There is a moderate positive correlation between Serum Urea and Urinary ACR (r = 0.348). The correlation between Serum Urea and Serum Creatinine is moderate positive (r = 0.241), Serum Urea shows a strong negative correlation with Neutrophil (r = -0.898).

Serum Creatinine has a moderate positive correlation with Urinary ACR (r = 0.241). The correlation between Serum Creatinine and Serum Urea is moderate positive (r = 0.241) There is a strong negative correlation between Serum Creatinine and Neutrophil (r = -0.688).

GFR shows a moderate negative correlation with Urinary ACR (r = -0.132), the correlation between GFR and Serum Urea is moderate negative (r = -0.218), there is a strong negative correlation between GFR and Neutrophil (r = -0.542).

Urinary ACR has a moderate positive correlation with Serum Urea (r = 0.348) The correlation between Urinary ACR and Serum Creatinine is moderate positive (r = 0.241) ,there is a moderate negative correlation between Urinary ACR and GFR (r = -0.132).

These correlations provide insights into how the duration of diabetes mellitus may influence the levels of Serum Urea, Serum Creatinine, GFR, and Urinary ACR, indicating potential relationships between these and also with neutrophil variables in the context of diabetes. Gupta N et al20 in 2018 delved the relationship between the neutrophil/ lymphocyte rate and the presence and inflexibility of diabetic nephropathy (DN) the study concluded that. A positive correlation was detected between NLR, e GFR, ESR and C- reactive protein. A high degree of correlation was determined among albuminuria, glomerular filtration rate and NLR situations. Almalki AH et al23 in 2020 conducted an experimental study involving 416 adult cases with type 2 diabetes mellitus (DM). The end of the study was to probe the relationship between Neutrophil- to- Lymphocyte rate (NLR) and early Diabetic order Disease (DKD), as well as to explore predictors of Albuminuria including NLR as similar to in this present study, Multivariable analysis indicated that the rate of albuminuria was advanced among cases with hypertension, cases with HbA1c> 7 and cases with an NLR score>1.25. In conclusion, NLR was set up to be an independent predictor of albuminuria in cases with type 2 DM.

NLR with various parameters of renal function

The present study shows, the correlations of NLR (Neutrophil-to-Lymphocyte Ratio) with Serum Urea, Serum Creatinine, GFR (Glomerular Filtration Rate), and Urinary ACR (Albumin-to-Creatinine Ratio), There is a significant positive correlation between NLR and Serum Urea at the 0.01 level, There is a significant positive correlation between NLR and Serum Creatinine at the 0.05 level, There is a negative correlation between NLR and GFR, but it is not statistically significant, and also There is a positive correlation between NLR and Urinary ACR, but it is not statistically significant

Above correlation between NLR and various parameter of renal function as urea, creatinine, GFR, and urinary ACR shows that NLR is a potential inflammatory biomarker of diabetic nephropathy in type 2 diabetes mellitus. Kothai G

et al24 in 2020 estimated the predictive capability of NLR in the opinion of diabetic nephropathy among Indian cases. They concluded that NLR is a simple, easily available and cost effective exploration which can be used as a netting tool to descry diabetic nephropathy at an earlier stage. Shahrabi A et al17 in 2023 reviewed the being scientific literature on the part of neutrophil to lymphocyte rate(NLR) in diabetic supplemental neuropathy(DPN) and to perform a meta- analysis on the available data. The study concluded that NLR serves as a distinct marker of inflammation, and its elevation in cases of DPN suggests an vulnerable system imbalance contributing to the development of the complaint. Gurmu MZ et al28 in 2022 conducted a comparative cross-sectional study involving 199 type 2 diabetes mellitus (T2DM) patients, aimed to assess the neutrophil–lymphocyte ratio (NLR) as an inflammatory biomarker among those with diabetic nephropathy (DN). The study utilized various tests including urine albumin testing, fasting blood sugar measurement, and complete blood count analysis, Results revealed that inflammation and endothelial dysfunction may play a role in the pathogenesis of DN, making NLR a potential predictor and prognostic biomarker for this condition.

Conclusion :-

Over all, the present study assessed NLR in diabetic nephropathy in type 2 diabetes, the data has led us to conclude that NLR values are higher in patients with DN and this difference is statistically significant. NLR is easily available; cost effective and routinely done, hence can be considered as a novel biomarker for DN in patients with type 2 diabetes mellitus .

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