ORIGINAL RESEARCH

Use of Neutrophil to Lymphocyte Ratio as A Screening Parameter for Assessment of Glycemic Control: A Cross Sectional Study

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ABSTRACT

Background: Recently, the evaluation of the neutrophil-lymphocyte ratio (NLR) has been proposed as novel, cost-effective, and reliable tools for assessing disease progression and prognostication in various medical conditions. The aim of this study was to examine the association between NLR levels and microalbuminuria levels in diabetic patients, with the objective of determining the utility of NLR in predicting disease progression.

Methods: The study involved the categorization of patients into four groups based on their HbA1c levels- Low (L), Medium (M), High (H), Very High (VH). We conducted an analysis to determine the sensitivity and specificity of NLR values as a screening tool for early nephropathy in each category. Additionally, the utility of NLR as independent markers of glycemic control was assessed using Pearson correlation analysis.

Results: The study findings revealed a significant relationship between NLR, creatinine, urea, and microalbuminuria in Group L patients. Similarly, in Group M, a significant association was observed between NLR and microalbuminuria. However, no such relationship was evident in Group H and VH.

Conclusion: The study's results indicated that NLR levels were not significantly correlated with microalbuminuria levels in diabetic patients. Moreover, the utility of NLR in assessing glycemic control was found to be limited.

Keywords: Glycated Hemoglobin, Creatinine, Albuminuria, Glycemic Control.

Introduction

Diabetes mellitus is a prevalent chronic disease associated with considerable morbidity and mortality. Inadequate glycemic control in diabetic patients can lead to an accelerated onset of microvascular complications, including neuropathy, nephropathy, and retinopathy [1]. A recent comprehensive review highlights that approximately half of diabetic adults exhibit diabetic microvascular complications, while 27% experience macrovascular complications [2].

As a result, there has been significant emphasis on the early detection and effective monitoring of diabetic complications. Research has demonstrated a strong association between acute and chronic inflammatory conditions and suboptimal glycemic control. Chronic inflammation has been identified as a potential underlying mechanism responsible for the development of diabetic complications. Numerous inflammatory markers, including interleukin-1 (IL-1), IL-6, IL-8, transforming growth factor beta-1, tumor necrosis factor-alpha (TNF-α), and cytokines, have been found to be linked to this process [3,4]. The primary constraints are the high costs associated with measuring these markers and the technical complexities involved in their assessment, rendering them less feasible for routine clinical use.

The total white blood cell (TWBC) count serves as a basic yet sensitive indicator of inflammation, offering

a straightforward and routine laboratory assessment [5, 6]. Moreover, the neutrophil-lymphocyte ratio (NLR) and platelet-lymphocyte ratio (PLR) have emerged as novel, cost-effective, and dependable tools for evaluating disease progression and prognostication in various cardiovascular diseases and acute or chronic systemic inflammatory conditions [7]. Consequently, these inflammatory markers are being investigated and proposed not only as alternatives to traditional tests like HbA1c but also as potential indicators for the prediction of diabetic nephropathy (DN).

The current study aims to explore the association between NLR levels and microalbuminuria in diabetic patients, with the objective of assessing the applicability of NLR in predicting disease progression. This research is particularly relevant as the diagnosis of DN relies on the detection of albuminuria. An escalation in urinary albumin excretion signifies the clinical manifestation of DN, starting from microalbuminuria, progressing to macroalbuminuria, and eventually leading to end-stage renal disease [8].

Materials & Methods

In this observational clinical study, 427 diabetic patients attending outpatient services at a tertiary care medical college in central India. The primary aims of the study were to establish correlations between NLR and levels and microalbuminuria in diabetic patients, as well as to assess the utility of NLR as indicator for glycemic control. Exclusion criteria encompassed patients with Type 1 Diabetes Mellitus, recent infections, systemic disorders, uncontrolled blood pressure, conditions affecting urinary protein excretion, and reduced glomerular filtration rate. The researchers categorized the participants into four groups based on their HbA1c levels- Low (L), Medium (M), High (H), Very High (VH) to evaluate NLR sensitivity and specificity as screening tool for early nephropathy.

Group L: HbA1c = 4%–5.6% i.e. Normal glycemic control

Group M: HbA1c = 5.7%–6.4% i.e. Pre-diabetic group

Group H: HbA1c = 6.5–7.0 i.e. Diabetics, moderate glycemic control

Group VH: HbA1c > 7.0, Diabetics, poor glycemic control

Retrospective analysis of patient hematology records was conducted, and statistical analyses, including Pearson correlation, were employed to assess the utility of NLR as independent markers of glycemic control.

Results

A total of 427 diabetic patients were included in this study, and their demographic characteristics are presented in Table 1. Based on their glycated hemoglobin levels, the patients were categorized into four groups: L, M, H, and VH. The details of each group are displayed in Table 2.

Table 1: Demographic summary of study population

Age (Years) (Mean ± SD)	50.57 ± 12.85	
Gender	**n**	**(%)**
Male	235	55.04
Female	192	44.96

Table 2: HbA1c (%) distribution in study population

HbA1c Level	n	(%)
Normal (HbA1c ≤ 5.7)	89	20.84
Pre-diabetic (HbA1c: 5.8 − 6.4)	90	21.08
Diabetics, moderate glycemic control (HbA1c: 6.5 − 7.0)	52	12.18
Diabetics, poor glycemic control (HbA1c > 7.0)	196	45.90

The Pearson correlation analysis was performed to examine the relationship between the Neutrophil-Lymphocyte Ratio (NLR) and various laboratory parameters for each group of patients. For Group L patients, as shown in Table 3, a significant positive correlation was observed between NLR and Serum Creatinine as well as Urea.

Table 3: Correlation of NLR with various parameters in Group L

Variable	r value	P-value
Serum Creatinine	0.3015	<0.05
Random Blood Glucose	-0.1345	0.2518
HbA1c	-0.1273	0.2679
Direct low-density lipoprotein	-0.0313	0.7764
High density lipoprotein	-0.0112	0.9054
Urea	0.4781	<0.05

Estimated GFR	-0.2493	0.0302
Microalbuminuria	0.2276	0.0469
C Reactive Protein	-0.0435	0.7122
Highly sensitive C Reactive Protein	-0.0921	0.4289
Prothrombin Time	0.0505	0.6654
Alkaline Phosphatase	0.1832	0.1126
Gamma Glutamyl Transferase	0.1218	0.2974

In the case of Group M patients, as indicated in Table 4, a significant positive correlation was found between NLR and Microalbuminuria.

Moving on to Group H patients, Table 5 displays the Pearson correlation results, indicating a significant correlation between NLR and HDL (High-Density Lipoprotein) levels, as well as hsCRP (High-Sensitivity C-Reactive Protein).

Table 4: Correlation of NLR with various parameters in Group M

Variable	r value	P-value
Serum Creatinine	-0.0162	0.8785
Random Blood Glucose	-0.1205	0.3018
HbA1c	-0.1694	0.1427
Direct low-density lipoprotein	0.0283	0.8132
High density lipoprotein	-0.1558	0.1723
Urea	-0.0198	0.8537
Estimated GFR	-0.0371	0.7449
Microalbuminuria	0.2553	<0.05
C Reactive Protein	0.1335	0.2406
Highly sensitive C Reactive Protein	0.0489	0.6785
Prothrombin Time	-0.0798	0.4873
Alkaline Phosphatase	-0.0649	0.5668
Gamma Glutamyl Transferase	0.0693	0.5416

Table 5: Correlation of NLR with various parameters in Group H

Variable	r value	P-value
Serum Creatinine	-0.2062	0.1723
Random Blood Glucose	-0.1896	0.2179
HbA1c	-0.1045	0.4987
Direct low-density lipoprotein	0.2287	0.1321
High density lipoprotein	-0.3209	<0.05
Urea	0.0773	0.6191
Estimated GFR	0.1179	0.4459
Microalbuminuria	-0.0711	0.6387
C Reactive Protein	0.0129	0.9382
Highly sensitive C Reactive Protein	0.3376	<0.05
Prothrombin Time	-0.1832	0.2261
Alkaline Phosphatase	-0.2536	0.0938
Gamma Glutamyl Transferase	-0.1132	0.4569

For Group VH patients, the Pearson correlation analysis presented in Table 6 revealed significant correlations between NLR and Serum Creatinine, estimated Glomerular Filtration Rate (eGFR), and Prothrombin Time (PT).

Table 6: Correlation of NLR with various parameters in Group VH

Variable	r value	P-value
Serum Creatinine	0.1614	<0.05
Random Blood Glucose	0.0287	0.7012
HbA1c	0.0099	0.8832
Direct low-density lipoprotein	-0.0524	0.4702
High density lipoprotein	-0.0428	0.5629
Urea	0.1372	0.0595
Estimated GFR	-0.1485	<0.05

Microalbuminuria	0.1338	0.0704
C Reactive Protein	0.0883	0.2217
Highly sensitive C Reactive Protein	-0.0467	0.5215
Prothrombin Time	-0.1869	<0.05
Alkaline Phosphatase	0.0428	0.5636
Gamma Glutamyl Transferase	-0.1204	0.0993

Discussion

In this study, significant associations were observed between NLR and specific laboratory parameters in different patient groups. Among Group L patients, NLR displayed a significant relationship with creatinine, urea, and microalbuminuria. Similarly, in Group M, NLR exhibited a significant correlation with microalbuminuria. However, no such significant relationships were observed in Group H and VH patients.

NLR emerges as a novel marker for chronic inflammation, effectively reflecting the interplay between two key components of the immune system: neutrophils, acting as active nonspecific mediators of inflammation and forming the first line of defense, and lymphocytes, acting as protective or regulatory components of inflammation [9]. Previous research by Goldberg and others has consistently demonstrated the independence of inflammatory markers, such as neutrophilia and relative lymphocytopenia, as predictive markers for various diseases, particularly complications associated with diabetes mellitus, such as DN [10].

Goldberg's findings also indicate that NLR holds potential as a valuable tool for identifying and monitoring diabetic complications and their progression. Kahraman et al. supported this notion, reporting a positive correlation between NLR and C-reactive protein, urea, creatinine, and red cell distribution width in their study [11]. Additionally, Almalki's study involving 416 patients with Type 2 diabetes found NLR to be an independent predictor of albuminuria in this patient population, further emphasizing its relevance in predicting and managing diabetic complications [12].
While previous research has indicated higher NLR values in diabetic patients with poor glycemic control, our study did not establish a significant correlation with HbA1c levels in this context [13, 14]. Although NLR levels were elevated in Group H and Group VH compared to Group L, the statistical analysis did not reveal significant differences, raising doubts about the utility of NLR in assessing glycemic control.

DN remains a major concern, contributing to significant complications and end-stage renal failure in a considerable percentage of patients. Microalbuminuria serves as a robust marker for diagnosing and monitoring DN, with chronic inflammation playing a pivotal role in its pathogenesis [15, 16]. The underlying pathogenesis involves a cascade of pathological events leading to glomerular damage, proteinuria, progressive renal damage, fibrosis, inflammation, and loss of functional nephrons [17, 18]. Furthermore, chronic inflammation has been associated with the development of Type 2 diabetes and its complications, with certain inflammatory cytokines influencing the risk of Type 2 diabetes [19].

Accordingly, our study supports the notion that NLR may serve as predictive and prognostic marker for diabetic nephropathy, in subjects with normal andpre-diabetic conditions, respectively, exhibiting microalbuminuria. However, its utility in assessing glycemic control remains uncertain based on our findings, warranting further investigation and validation studies to establish their broader applications in diabetic patient management and prognosis.

Conclusion

NLR offers cost-effectiveness, easy accessibility, and simplicity, making it a viable test that can be readily conducted in primary to tertiary healthcare centers. These advantages extend beyond assessing chronic or acute inflammation, as they also serve as valuable screening tools for nephropathy cases associated with diverse conditions, including diabetes, hypertension, and chronic kidney disease. Our study demonstrated a significant correlation between NLR levels with urea, creatinine, and microalbumin in both Group L and Group M subjects. Detecting nephropathy at its early stages can lead to a reduction in overall morbidity, the burden of dialysis, and mortality rates. However, the utility of NLR in assessing glycemic control remains uncertain based on our findings.

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