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# Neutrophil-Lymphocyte Ratio as a Prognostic Marker for Inflammatory Status Among Patients with Diabetes Mellitus

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## ABSTRACT

Diabetes mellitus (DM) is a chronic metabolic disorder associated with systemic inflammation and multiple vascular complications. Identifying accessible and cost-effective biomarkers for inflammation can improve the management and prognosis of diabetic patients. **Objectives:** To evaluate the neutrophil to lymphocyte ratio (NLR) as a prognostic marker for inflammatory status in patients with diabetes mellitus. **Methods:** This cross-sectional analytical study included 212 diabetic patients recruited from Liaquat University Hospital, Hyderabad. Data were collected on demographics, clinical history, complications, and comorbidities. Blood samples were analyzed for complete blood count and C-reactive protein (CRP) to calculate NLR. Patients were categorized based on normal (≤3) or raised (>3) NLR. Statistical analysis was performed using SPSS version 21.0, with $p<0.050$ considered significant. **Results:** Of the 212 participants, 52.8% were female and 81.1% had Type 2 diabetes. Raised NLR was observed in 24.1% and elevated CRP in 40.1%. Neuropathy (34.4%) and nephropathy (24.5%) were the most frequent complications. Raised NLR was significantly associated with elevated CRP ($p=0.012$), diabetic nephropathy ($p=0.030$), and diabetic retinopathy ($p=0.040$), while no significant association was observed with gender, duration of diabetes, or hypertension. **Conclusions:** NLR is a cost-effective, readily available marker significantly associated with systemic inflammation and microvascular complications in diabetes. It holds promise for routine inflammatory screening in clinical settings.

## INTRODUCTION

Chronic inflammation is increasingly recognized as a central mechanism in the pathogenesis of type 2 diabetes mellitus (T2DM) and its complications [1, 2]. The neutrophil-to-lymphocyte ratio (NLR), a simple calculation from routine complete blood count (CBC) has emerged as a reliable, cost-effective surrogate marker of systemic inflammatory status [3]. Physiologically, NLR elevation reflects the dual shift in immune response during chronic inflammation. Neutrophilia occurs due to increased bone marrow stimulation by pro-inflammatory cytokines (such as IL-6 and TNF-α), while lymphopenia results from stress-induced cortisol release and apoptosis of lymphocytes, collectively contributing to a raised NLR [4]. Several recent meta-analyses and cohort studies have confirmed NLR's association with poor glycemic control (HbA1c elevations), diabetic nephropathy, retinopathy, and cardiovascular disease outcomes among T2DM patients [5, 6]. Despite its global relevance, the utilization of NLR in Pakistan has only recently begun to be validated through local research. [7] A notable retrospective cohort study at Aga Khan University Hospital in Karachi assessed 130 patients hospitalized with diabetic foot ulcers and found that an NLR greater than 4 was significantly associated with higher ulcer grades, increased rates of major amputation, greater

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postoperative complications (p< 0.001), and elevated in-hospital and 1-year mortality (p=0.008 and p=0.010 respectively). This finding supports the role of NLR as a sensitive and economically feasible prognostic biomarker for severe diabetic complications in Pakistan [8]. Globally, T2DM continues to rise. Data from the International Diabetes Federation indicate that in 2021, there were approximately 537 million adults (20–79 years) with diabetes, the majority type 2, with projections exceeding 700 million by 2045 [9]. Specifically, in South Asia, and Pakistan in particular, prevalence remained high, approximately 17% among adults by 2019, with diabetes ranking among the top causes of morbidity and mortality [10]. Chronic low-grade inflammation in T2DM underpins the vascular complications that contribute heavily to Pakistan's healthcare burden [11]. While cytokine profiling remains the gold standard, its limited feasibility underscores the utility of simpler alternatives. In resource-limited settings like Pakistan, NLR's advantages are efficiency, affordability, and integration into routine diagnostics, making it a highly attractive tool. While advanced inflammatory markers (e.g., serum cytokines IL-6, TNF-α) are costly and not widely available, NLR provides a pragmatic alternative for early risk stratification and monitoring [12].

Diabetes mellitus is increasingly recognized as a chronic inflammatory condition that contributes to the development of microvascular and macrovascular complications. Although several inflammatory biomarkers have been studied, many of them are expensive and not readily available in routine clinical practice, particularly in resource-limited settings. The neutrophil-to-lymphocyte ratio (NLR), derived from a simple complete blood count, has emerged as a potential surrogate marker of systemic inflammation; however, evidence regarding its clinical significance among diabetic patients in Pakistan remains limited. This highlights the need to evaluate the prognostic value of NLR in assessing inflammatory status and related complications in diabetic populations. This study aims to evaluate the prognostic value of the neutrophil-lymphocyte ratio in assessing the inflammatory status of patients with diabetes mellitus, offering a potentially valuable approach to early detection and improved clinical management.

## METHODS

This cross-sectional analytical study was conducted at the Diagnostic and Research Laboratory, Liaquat University of Medical and Health Sciences (LUMHS), Hyderabad, in collaboration with the Department of Medicine at Liaquat University Hospital, Hyderabad. The study spanned six months, from December 2024 to May 2025, after obtaining ethical approval from the Ethical Review Committee of LUMHS, Jamshoro (Ref. No. LUMHS/REC/-545). A total of 212 participants were recruited through non-probability consecutive sampling. The sample size was determined using the WHO OpenEpi calculator, considering a 26.7% prevalence of diabetes mellitus in Pakistan (2022), a 5% margin of error, and a 90% confidence level. The calculation was based on the formula: $n = [DEFF \times Np(1-p)] / [(d^2/Z^2 1-\alpha/2 \times (N-1) + p(1-p))]$ [13]. Patients aged 18 years and above with a confirmed diagnosis of Type 1 or Type 2 diabetes mellitus for at least one year were included. Individuals with recent infections, chronic inflammatory or autoimmune diseases, those on immunosuppressive therapy, or with known malignancies or hematologic disorders affecting neutrophil or lymphocyte counts were excluded. After obtaining informed consent, demographic and clinical data were collected using a structured questionnaire. Blood samples (5 cc) were drawn to assess complete blood counts (CBC) using the Siemens ADVIA 2120i automated hematology analyzer. Neutrophil counts were considered normal between $2.0–7.5 \times 10^9$/L (40–75% of total WBCs), while lymphocyte counts ranged from $1.0–3.5 \times 10^9$/L (20–45%). The neutrophil-to-lymphocyte ratio (NLR) was calculated from complete blood count (CBC) results, and C-reactive protein (CRP) levels were recorded as a supplementary marker of inflammation. NLR values were categorized as normal (1–3) or elevated (>3). Data were analyzed using SPSS version 26.0. Descriptive statistics, including means, standard deviations, and frequencies, were used to summarize patient characteristics. Independent t-tests were applied to compare NLR values across groups. Chi-square test was used to examine associations between NLR status and diabetes duration, and treatment status. All statistical tests were conducted using a 95% confidence interval, and a p-value <0.050 was considered statistically significant.

## RESULTS

The study comprised 212 diabetic patients, with a slight female predominance (52.8%). The majority (81.1%) had Type 2 diabetes, and 53.3% reported a positive family history of diabetes. The mean duration of diabetes was 11.8 ± 8.3 years, indicating a chronic disease course in most participants (Table 1).

**Table 1:** Demographics, Clinical History

| Variables | | Frequency (%) |
|---|---|---|
| Gender | Female | 112 (52.8) |
| | Male | 100 (47.2) |
| Type of Diabetes | Type 2 | 172 (81.1) |
| | Type 1 | 40 (18.9) |
| Family History of DM | Yes | 113 (53.3) |
| | No | 99 (46.7) |
| Duration of Diabetes | | 11.8 ± 8.3 years |

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Regarding inflammatory markers, 24.1% of patients exhibited elevated neutrophil-to-lymphocyte ratio (NLR), while 40.1% had raised C-reactive protein (CRP) levels. This suggests that a notable proportion of diabetic patients may be undergoing active systemic inflammation, even in the absence of overt clinical signs (Figure 1)

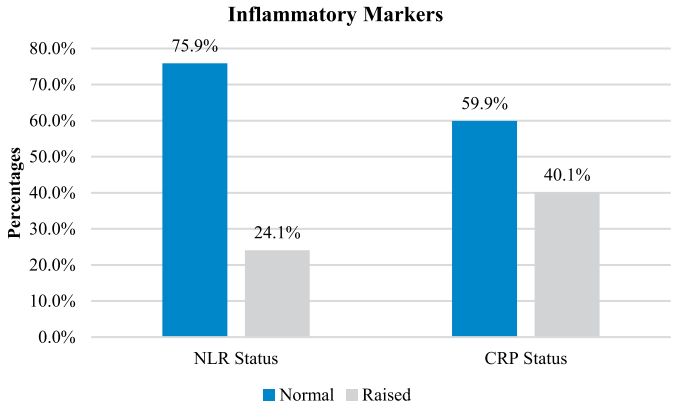


**Figure 1:** Status of Inflammatory Markers

Among complications and comorbidities, neuropathy (34.4%) and nephropathy (24.5%) were the most common microvascular complications, while retinopathy was present in 19.8% of patients. Cardiovascular disease was observed in 20.8%, and nearly half of the participants had hypertension (46.2%) and dyslipidemia (46.2%). Obesity was present in 47.2%, and chronic kidney disease in 11.3%, indicating a high burden of coexisting conditions (Table 2).

**Table 2:** Complications and Comorbidities

| Variables | | Frequency (%) |
|---|---|---|
| Nephropathy | Absent | 160 (75.5) |
| | Present | 52 (24.5) |
| Retinopathy | Absent | 170 (80.2) |
| | Present | 42 (19.8) |
| Neuropathy | Absent | 139 (65.6) |
| | Present | 73 (34.4) |
| Cardiovascular Disease | Absent | 168 (79.2) |
| | Present | 44 (20.8) |
| Hypertension | Absent | 114 (53.8) |
| | Present | 98 (46.2) |
| Dyslipidemia | Absent | 114 (53.8) |
| | Present | 98 (46.2) |
| Obesity | Absent | 112 (52.8) |
| | Present | 100 (47.2) |
| Chronic Kidney Disease | Absent | 188 (88.7) |
| | Present | 24 (11.3) |

Among 212 patients with type 2 diabetes, 161 had normal NLR and 51 had raised NLR. Gender distribution was comparable between the groups, with 48.4% males in the normal NLR group versus 43.1% in the raised NLR group (95% CI: 13.6% to 22.1%, p=0.520). The mean duration of diabetes was longer in the raised NLR group (13.2 ± 6.9 years) compared to the normal NLR group (10.5 ± 7.4 years), though this difference was not statistically significant (95% CI: 1.9 to 7.2 years, p=0.240). Raised CRP was significantly more frequent in patients with elevated NLR (60.8%) than in those with normal NLR (33.5%) (95% CI: 6.4% to 44.6%, p=0.012). Likewise, diabetic nephropathy was more prevalent in patients with raised NLR (41.2% vs. 19.3%) with a significant difference (95% CI: 2.1% to 40.2%, p=0.030). Similarly, diabetic retinopathy occurred in 31.4% of patients with raised NLR compared to 16.1% with normal NLR (95% CI: 1.7% to 28.5%, p=0.040). Hypertension was more frequent among those with raised NLR (64.7% vs. 40.4%); however, this was not statistically significant (95% CI: 2.8% to 37.0%, p=0.260) (Table 3).

**Table 3:** Comparison of Clinical and Laboratory Variables by NLR Status

| Variables | NLR Normal (N=161) N (%) | NLR Raised (N=51) N (%) | 95% CI | p-Value |
|---|---|---|---|---|
| Gender (Male) | 78 (48.4) | 22 (43.1) | 13.6% to 22.1% | 0.520 |
| Duration of Diabetes (years) | 10.5 + 7.4 | 13.2 + 6.9 | 1.9 to 7.2 years | 0.240 |
| Type 2 Diabetes | 129 (80.1) | 43 (84.3) | 9.8% to 17.3% | 0.530 |
| CRP Raised | 54 (33.5) | 31 (60.8) | 6.4% to 44.6% | 0.012* |
| Diabetic Nephropathy | 31 (19.3) | 21 (41.2) | 2.1% to 40.2% | 0.030* |
| Diabetic Retinopathy | 26 (16.1) | 16 (31.4) | 1.7% to 28.5% | 0.040* |
| Hypertension | 65 (40.4) | 33 (64.7) | 2.8% to 37.0% | 0.260 |

*Statistical significance: p<0.050

## DISCUSSION

The findings yielded a notable association between elevated NLR levels and the presence of microvascular complications, particularly diabetic nephropathy and retinopathy. Among the 212 diabetic patients evaluated, 24.1% exhibited elevated NLR values (>3), while 40.1% had increased C-reactive protein (CRP) levels. The significant correlation between raised NLR and CRP underscores the utility of NLR as a surrogate inflammatory marker in diabetic individuals [14]. These findings are consistent with the work of Liu *et al.* (2017), who reported a positive relation in elevated NLR and increased CRP and IL-6 levels among patients with Type 2 DM, emphasizing NLR's potential as a cost-effective and readily available inflammatory indicator [15]. The current study also demonstrated a statistically significant association between raised NLR and diabetic nephropathy. This is in line with the study by Li *et al.* in China, which found that diabetic patients with nephropathy had significantly higher NLR values compared to those without renal involvement [16]. Further supporting this, Tang *et al.* in China concluded that elevated NLR was independently associated not only with the presence but also the severity of diabetic kidney disease, suggesting its relevance in disease stratification [17]. Moreover, our data showed a significant relationship

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between raised NLR and diabetic retinopathy. This observation resonates with a 2023 study-analysis by El-Tawab *et al.,* which affirmed a strong association between high NLR levels and the risk of diabetic retinopathy, particularly its proliferative forms. [18] While hypertension and obesity were prevalent among our participants, no statistically significant association was found between NLR and these comorbidities. These findings partially contrast with a study by Zhang *et al.,* who reported a mild but significant relationship between elevated NLR and hypertension in diabetic patients [19]. However, differences in sample size, population characteristics, and the control of confounding factors could account for this discrepancy. The prevalence of diabetic neuropathy in our study (34.4%) was notably high, but it did not reach statistical significance when associated with raised NLR. This contrasts with results from the study by Rezaei Shahrabi et al., who identified NLR as a potential marker for diabetic peripheral neuropathy severity [20]. However, differences in diagnostic criteria and neuropathy grading may explain these variations. The use of NLR as a prognostic biomarker is advantageous due to its accessibility, cost-effectiveness, and correlation with well-established inflammatory parameters. In contrast, cytokine assays (e.g., IL-6, TNF-α) are not feasible in most routine clinical setups due to cost and technical limitations. This positions NLR as a practical tool for primary screening, particularly in low-resource settings like Pakistan. Our findings support recommendations by the ADA and recent literature advocating for inflammatory profiling in the management of diabetic patients to prevent complications [21]. Integrating NLR into routine assessments may facilitate early identification of patients at risk for vascular complications, enabling timely interventions.

This study was limited by its single-center cross-sectional design, which restricts the ability to establish causal relationships between elevated NLR and diabetic complications. Additionally, the use of consecutive sampling and the absence of longitudinal follow-up may limit the generalizability of the findings. Advanced inflammatory markers and glycemic control indicators such as HbA1c were not extensively analyzed for correlation with NLR. Future multicenter longitudinal studies with larger sample sizes and comprehensive inflammatory profiling are recommended to further validate NLR as a reliable prognostic biomarker in diabetic patients.

## CONCLUSIONS

Elevated NLR showed a significant association with increased CRP levels and microvascular complications, including diabetic nephropathy and retinopathy, highlighting its value as a convenient and cost-effective marker.

## Authors' Contribution

Conceptualization: SN,
Methodology: SN, IDU, SK, SM, AR
Formal analysis: IS,
Writing and Drafting: SN, IDU, SK, SM, IS, AR
Review and Editing: SN, IDU, SK, SM, IS, AR

All authors approved the final manuscript and take responsibility for the integrity of the work

## Conflicts of Interest

All the authors declare no conflict of interest.

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