Research Article

Association of Hematological Inflammatory Indices with Glycemic Control in Type 2 Diabetes Mellitus- A Cross-sectional study

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Article Info

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Keywords

Diabetes mellitus, Inflammation, Neutrophil Lymphocyte Ratio, Inflammatory indices, Glycemic control

Abstract

Introduction: Type 2 Diabetes Mellitus (T2DM) is a significant global health concern characterized by chronic low-grade inflammation, contributing to various complications. While Glycated Hemoglobin (HbA1c) is a primary tool for assessing glycemic control, hematological inflammatory indices derived from routine Complete Blood Count (CBC) are emerging as promising, low-cost indicators of systemic inflammation. This study aimed to investigate the association between these indices and glycemic control in T2DM patients.

Methodology: This comparative cross-sectional study included 750 individuals, equally categorized into non-diabetic, well-controlled T2DM (HbA1c < 7%), and poorly controlled T2DM (HbA1c ≥ 7%) groups. HbA1c, and eleven hematological inflammatory indices like NLR, MLR, SII, SIRI, etc, were calculated and compared between the groups using JASP software followed by correlation, Receiver Operating Characteristic (ROC) curves, and binary logistic regression.

Results: NLR, SII, SIRI, and AISI consistently showed a rising trend with poorer glycemic control, correlated moderately with HbA1c, and demonstrated moderate predictive performance for uncontrolled diabetes (AUC > 0.6). Subgroup analysis also revealed higher NLR in poorly controlled diabetics and regression analysis proved NLR as an independent predictor of poor glycemic control (adjusted odds ratio = 4.73, $p < 0.001$).

Conclusion: This study demonstrates that hematological inflammatory indices, particularly NLR, SII, SIRI, and AISI, are significantly elevated in patients with poorly controlled T2DM, reflecting a state of chronic systemic inflammation. Among these, NLR shows the strongest and independent association with poor glycemic status, highlighting its potential as a low-cost, accessible adjunct marker for monitoring glycemic control and systemic inflammation in T2DM.

Introduction

Diabetes mellitus (DM) is a chronic metabolic disorder characterized by persistent hyperglycemia resulting from insulin deficiency, resistance, or both, and has emerged as a major global health issue [1]. In 2015, the global prevalence of diabetes among adults aged 20–79 years was 8.8%, projected to rise to 10.4% by 2040. According to the International Diabetes Federation, by 2019 approximately 463 million adults, and by 2021 over 536.6 million adults had diabetes, with projections indicating a rise to 783.2 million by 2045, most being Type 2 Diabetes Mellitus (T2DM) [2]. Prolonged hyperglycemia contributes to serious complications such as cardiovascular disease, nephropathy, neuropathy and retinopathy [1].

Chronic low-grade inflammation plays a central role in the pathogenesis and progression of T2DM and its complications [3]. Hyperglycemia activates immune responses, disrupts insulin signaling, and promotes inflammatory cascades, with immune cells like macrophages contributing significantly to these processes [4,5]. Monitoring glycemic control is essential to reduce the risk of complications, typically assessed using HbA1c, fasting plasma glucose, or oral glucose tolerance tests [6]. While HbA1c remains the standard for long-term glycemic control, it has limitations including interference from hemoglobin variants and its inability to reflect acute glucose fluctuations [6–8].

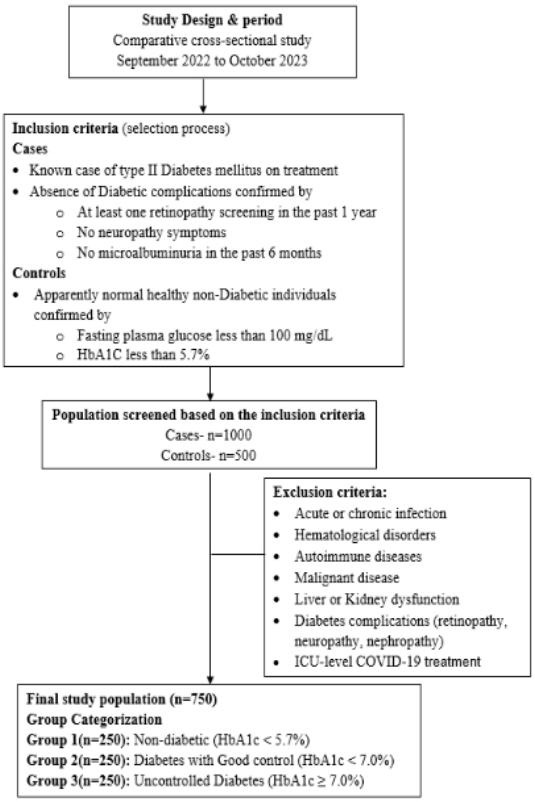
Complete blood count (CBC) derived parameters and indices, calculated from routine hematological tests, particularly white blood cells and platelets are being increasingly investigated as low-cost and easily accessible indicators of systemic inflammation in conditions like malignancy, cardiovascular diseases, autoimmune diseases, metabolic syndrome etc [9]. Some of these indices include the Neutrophil-to-Lymphocyte Ratio (NLR), Platelet-to-Lymphocyte Ratio (PLR), and Monocyte-to-Lymphocyte Ratio (MLR), and composite indices such as the Systemic Immune-Inflammation Index (SII), Systemic Inflammatory Response Index (SIRI). These indices integrate various white blood cell subgroups and platelets, potentially offering a more stable reflection of the body's inflammatory status compared to individual cell counts [9,10]. Several studies have explored the association of these indices with diabetes and its complications. Elevated levels of NLR, PLR, and MLR have been observed in patients with T2DM compared to non-diabetic individuals [11]. NLR has also been associated with microvascular complications like diabetic nephropathy and retinopathy. PLR has been found to be significantly higher in patients with diabetic nephropathy. SII, PLR and SIRI levels were higher in T2DM patients with diabetic retinopathy (DR) compared to those without it, and were identified as independent risk factors for diagnosis and prediction of advanced DR [12]. These findings highlight the potential utility of these hematological inflammatory indices in the assessment of inflammation and its association with glycemic control and complications in T2DM, although their specific relationships and clinical utility warrant further investigation, especially in diverse populations.

This study aims to investigate the association between hematological inflammatory indices and glycemic control in Type 2 Diabetes mellitus patients. Inflammatory indices include Neutrophil-to-Lymphocyte Ratio (NLR), Monocyte-to-Lymphocyte Ratio (MLR), Platelet-to-Monocyte Ratio (PMR), Platelet-to-Lymphocyte Ratio (PLR), Basophil-to-Lymphocyte Ratio (BLR), Eosinophil-to-Lymphocyte Ratio (ELR), Lymphocyte-to-Monocyte Ratio (LMR), and White Cell-to-Platelet Ratio (WPR) and composite indices like Systemic Immune-Inflammation Index (SII), Systemic Inflammatory Response Index (SIRI), and Aggregate Index of Systemic Inflammation (AISI). The objective was to compare these hematological inflammatory indices among groups of individuals with normal glucose tolerance (non-diabetic controls), patients with well-controlled Type 2 Diabetes Mellitus (HbA1c < 7%), and patients with poorly controlled Type 2 Diabetes Mellitus (HbA1c ≥ 7%).

Materials and Methods

This comparative cross-sectional study was retrospectively conducted in the Department of Biochemistry at Sri Ramachandra Medical College and Research Institute, Chennai, Tamil Nadu, India. The study protocol is represented in Figure 1.

Figure 1: Flow chart illustrating the methodology of the study population selection.



The clinical and demographic details were collected from the patient records. The following biochemical and hematological analyses were performed in the central laboratory

- Fasting Blood Sugar (FBS) and Post-Prandial Blood Sugar (PPBS) were measured by Hexokinase method using the Roche Cobas c702 automated chemistry analyzer (Roche Diagnostics GmbH, Mannheim, Germany).
- HbA1c was measured using cation-exchange high-performance liquid chromatography (HPLC) on the Tosoh G8 Analyzer (Tosoh Bioscience, Tokyo, Japan).
- Complete Blood Count (CBC) parameters including total leukocyte count, neutrophils, lymphocytes, monocytes, eosinophils, basophils, and platelets were analyzed using the Sysmex XN-1000 automated hematology analyzer (Sysmex Corporation, Kobe, Japan).

Further the following inflammatory indices were calculated from CBC parameters to evaluate the systemic inflammatory status and its association with glycemic control.

Table 1: Inflammatory indices included in the study along with its calculation formulas.

S.No	Inflammatory indices	Calculation formula
1	Neutrophil Lymphocyte ratio (NLR)	Neutrophil / Lymphocyte
2	Monocyte Lymphocyte ratio (MLR)	Monocyte / Lymphocyte
3	Platelet Lymphocyte ratio (PLR)	Platelet / Lymphocyte
4	Platelet Monocyte ratio (PMR)	Platelet / Monocyte
5	Lymphocyte Monocyte ratio (LMR)	Lymphocyte / Monocyte
6	Eosinophil Lymphocyte ratio (ELR)	Eosinophil / Lymphocyte
7	Basophil Lymphocyte ratio (BLR)	Basophil / Lymphocyte
8	White blood cell Platelet ratio (WPR)	White Blood Cell Count / Platelet Count
9	Systemic Immune-Inflammation Index (SII)	(Platelet × Neutrophil) / Lymphocyte
10	Systemic Inflammatory Response Index (SIRI)	(Neutrophil × Monocyte) / Lymphocyte
11	Aggregate Index of Systemic Inflammation (AISI)	(Neutrophil × Platelet × Monocyte) / Lymphocyte

Statistical Analysis

All statistical analyses were conducted using JASP (Version 0.19, JASP team (2024) JASP (version0.19), University of Amsterdam) and Microsoft Excel. The distribution of continuous variables was assessed using the Shapiro-Wilk test. Data were presented as median with interquartile range [IQR], Kruskal-Wallis test and Dunn's post-hoc test was used to compare hematological and inflammatory parameters across the three groups and Chi-square test was employed for categorical variables. Spearman's correlation was used to assess the strength and direction of association between glycemic parameters and inflammatory indices. For subgroup analysis comparison Mann-Whitney U test or Welch's t-test was used based on the equality of variances. Receiver Operating Characteristic (ROC) curve analysis was performed to evaluate the predictive ability of inflammatory indices for poor glycemic control. In addition, Linear regression was used to assess the direct relationship between NLR and HbA1c. Further, Binary logistic regression was performed to evaluate the predictive value of NLR for poor glycemic control (HbA1c > 7%), both in unadjusted and adjusted models. The adjusted model accounted for age, FBS, PPBS, total WBC count, eosinophils, basophils, and platelets, based on prior correlation analysis. All statistical tests were two-tailed, and significance was defined as a p-value < 0.05.

Results

The final study population of 750 individuals was evenly distributed across three groups based on glycemic control: Group 1 (non-diabetic, HbA1c < 5.7%), Group 2 (well-controlled diabetics, HbA1c < 7%), and Group 3 (poorly controlled diabetics, HbA1c ≥ 7%). The median age significantly increased across the groups ($p < 0.001$), while the proportion of females decreased progressively from 89.6% in Group 1 to 62.4% in Group 3 ($p < 0.001$). Glycemic parameters, including fasting blood sugar (FBS), postprandial blood sugar (PPBS), glycated hemoglobin (HbA1c), and estimated average glucose (EAG), increased significantly from Group 1 through Group 3, indicating worsening glycemic control across the groups as shown in Table 2.

In our study Table 2, the Hematological parameters demonstrated significant difference between the groups. Total WBC count, neutrophils, basophils and platelets increased significantly across the groups while eosinophils, lymphocytes and monocytes showed no statistically significant differences. In post hoc analysis as shown in Table 2, total count and neutrophils were significantly elevated in Group 3 compared to Groups 1 and 2 ($p < 0.001$).

Table 2: Comparison of demographic and hematological parameters between 3 groups in the study conducted from September 2022 to October 2023.

Variables	Group 1 Median [IQR] n=250	Group 2 Median [IQR] n=250	Group 3 Median [IQR] n=250	Overall p-Value
Age (years)	29 [24-37]	40 [30-49.7]	47 [37-56]	<0.0001*#§
Sex (females)	224 (89.6%)	203 (81.2%)	156 (62.4%)	<0.0001
FBS (mg/dL)	92 [86-99]	98 [91-105]	139 [110-194]	<0.0001*#§
PPBS (mg/dL)	107.5 [93-125.7]	121 [101-144.7]	220.5 [152-305]	<0.0001*#§
HbA1c (%)	5.3 [5.1-5.5]	6 [5.8-6.2]	8.6 [7.2-9.9]	<0.0001*#§
eAG (mg/dL)	105 [100-111]	126 [120-131]	175 [146-226]	<0.0001*#§
Total WBC count (cells/µL)	7900 [6770-9395]	8000 [6615-9572]	8920 [7377.5-11097.5]	<0.0001#§
Eosinophils (cells/µL)	197.9 [110.2-311.4]	221.2 [126.4-356.5]	225.5 [137.4-384.2]	0.052
Basophils (cells/µL)	34 [23.1-45.1]	37.4 [21.4-53]	39.5 [26.2-53.6]	0.021#
Neutrophils (cells/µL)	4655.3 [3753.7-5843]	4709.2 [3601.8-5817.2]	5590.4 [4535-7097.7]	<0.0001#§
Lymphocytes (cells/µL)	2317.3 [1964-2806]	2416.9 [1981-2836]	2262.6 [1848-2787.8]	0.131
Monocytes (cells/µL)	447.1 [317.5-565.8]	390 [298-524]	419 [311.6-575.9]	0.161
Platelets (lakhs/µL)	2.84 [2.46-3.35]	3.09 [2.60-3.58]	3.08 [2.51-3.63]	0.002*#

FBS: Fasting blood sugar; PPBS: Postprandial blood sugar: HbA1c: Glycated Hemoglobin; eAG: Estimated average glucose; WBC: White blood cells; ; p-Value <0.01 Highly significant; p-Value <0.05 statistically significant

Post-hoc analysis: *Significant difference between group 1 and group 2; #Significant difference between group 1 and group 3; §Significant difference between group 2 and group 3

Table 3: Comparison of Hematological Inflammatory indices between three groups in the study conducted from September 2022 to October 2023.

Variables	Group 1 Median [IQR] (n=250)	Group 2 Median [IQR] (n=250)	Group 3 Median [IQR] (n=250)	Overall p-Value
NLR	2.05 [1.5-2.5]	1.95 [1.5-2.42]	2.25 [1.8-3.2]	<0.0001#§
MLR	0.19 [0.14-0.25]	0.17 [0.13-0.23]	0.19 [0.13-0.27]	0.006*§
ELR	0.08 [0.05-0.13]	0.09 [0.05-0.15]	0.1 [0.06-0.16]	0.026#
PLR	121.7 [98.4-149.1]	130.5 [99.9-160.8]	131.9 [105.8-165.3]	0.019#
PMR	633.6 [470.3-914.1]	790.9 [570.8-1039.3]	740.8 [493.6-1041.8]	0.001*#
LMR	5.23 [3.93-7.36]	5.96 [4.32-7.90]	5.31 [3.63-7.42]	0.006*§
BLR	0.014 [0.01-0.02]	0.016 [0.009-0.021]	0.017 [0.012-0.024]	0.002#§
SII	564.1 [411.5-765.8]	591.1 [437.9-788.1]	727 [559.7-1040.2]	<0.0001#§
SIRI	885.1 [533.5-1280.6]	776.8 [546.9-1104.6]	1065 [708.8-1608.9]	<0.0001*#§
WPR	0.027 [0.023-0.034]	0.026 [0.021-0.032]	0.029 [0.024-0.036]	<0.0001*§
AISI	2440.9 [1530.3-3762.5]	2312.3 [1498.9-3611.3]	3211 [2049.3-5071.8]	<0.0001#§

NLR: Neutrophil lymphocyte ratio; MLR: Monocyte lymphocyte ratio; ELR: Eosinophil lymphocyte ratio; PLR: Platelet lymphocyte ratio; PMR: Platelet monocyte ratio; LMR:Lymphocyte monocyte ratio; BLR: Basophil lymphocyte ratio: SII: Systemic Immune-Inflammation index; SIRI: Systemic inflammatory response index; WPR: WBC platelet ratio; AISI: Aggregate index of systemic inflammation; p-Value <0.01 Highly significant; p-Value <0.05 statistically significant

Post-hoc analysis: * Significant difference between group 1 and group 2; #Significant difference between group 1 and group 3; §Significant difference between group 2 and group 3

In Table 3, all the calculated hematological inflammatory indices were significantly elevated across the groups (all p<0.05). However, in post hoc analysis, NLR, BLR, SII, SIRI and AISI showed a rising trend with poor glycemic control and significantly elevated levels were observed in Group 3 compared to Groups 1 and 2 (all $p < 0.001$).

Spearman's correlation analysis in Table 4, demonstrated that HbA1c had a moderate positive correlation with NLR ($r = 0.168$, $p < 0.001$), BLR ($r=0.118$, $p <0.001$) SII ($r = 0.233$, $p < 0.001$), SIRI ($r = 0.115$, $p = 0.002$) and AISI ($r = 0.157$, $p < 0.001$). ELR, PLR, and PMR had weaker correlations with glycemic markers, while MLR, LMR and WPR did not correlate with HbA1c. Based on the correlation analysis, NLR was selected for regression analysis to determine its predictive value for poor glycemic control.

Table 4: Spearman correlation analysis between glycemic profile and inflammatory indices included in the study conducted from September 2022 to October 2023.

Variable		Age	FBS	PPBS	HbA1c	eAG
FBS	r-value p-value	0.521 <0.001**	-	-	-	-
PPBS	r-value p-value	0.499 <0.001**	0.717 <0.001**	-	-	-
HbA1c	r-value p-value	0.478 <0.001**	0.578 <0.001**	0.622 <0.001**	-	-
eAG	r-value p-value	0.600 <0.001**	0.742 <0.001**	0.745 <0.001**	0.799 <0.001**	-
NLR	r-value p-value	-0.144 <0.001**	-0.105 <0.001**	-0.003 0.942	0.168 <0.001**	-0.106 0.004*
MLR	r-value p-value	-0.023 0.538	0.036 0.327	-0.018 0.626	-0.009 0.809	-0.164 <0.001**
ELR	r-value p-value	0.209 <0.001**	0.115 0.002*	0.081 0.027*	0.081 0.027*	0.09 0.014*
PLR	r-value p-value	-0.03 0.416	-0.066 0.073	-0.098 0.007**	0.099 0.007**	-0.045 0.218
PMR	r-value p-value	-0.015 0.676	-0.069 0.058	-0.047 0.202	0.099 0.007**	0.118 0.001**
LMR	r-value p-value	0.02 0.579	-0.036 0.33	0.019 0.602	0.01 0.776	0.165 <0.001**
BLR	r-value p-value	0.119 0.001**	0.072 0.048*	0.085 0.020*	0.118 0.001**	0.039 0.286
SII	r-value p-value	-0.153 <0.001**	-0.064 0.081	0.012 0.744	0.233 <0.001**	-0.017 0.645
SIRI	r-value p-value	-0.11 0.002**	0.004 0.910	0.039 0.287	0.115 0.002**	-0.114 0.002**
WPR	r-value p-value	-0.047 0.199	-0.013 0.717	0.097 0.008**	0.05 0.171	-0.041 0.262
AISI	r-value p-value	-0.12 <0.001**	0.020 0.587	0.042 0.246	0.157 <0.001**	-0.051 0.160

FBS: Fasting blood sugar; PPBS: Postprandial blood sugar: HbA1c: Glycated Hemoglobin; eAG: Estimated average glucose; NLR: Neutrophil lymphocyte ratio; MLR: Monocyte lymphocyte ratio; ELR: Eosinophil lymphocyte ratio; PLR: Platelet lymphocyte ratio; PMR: Platelet monocyte ratio; LMR: Lymphocyte monocyte ratio; BLR: Basophil lymphocyte ratio: SII: Systemic Immune-Inflammation index; SIRI: Systemic inflammatory response index; WPR: WBC platelet ratio; AISI: Aggregate index of systemic inflammation;**p-Value <0.01 Highly significant; * p-Value <0.05 statistically significant

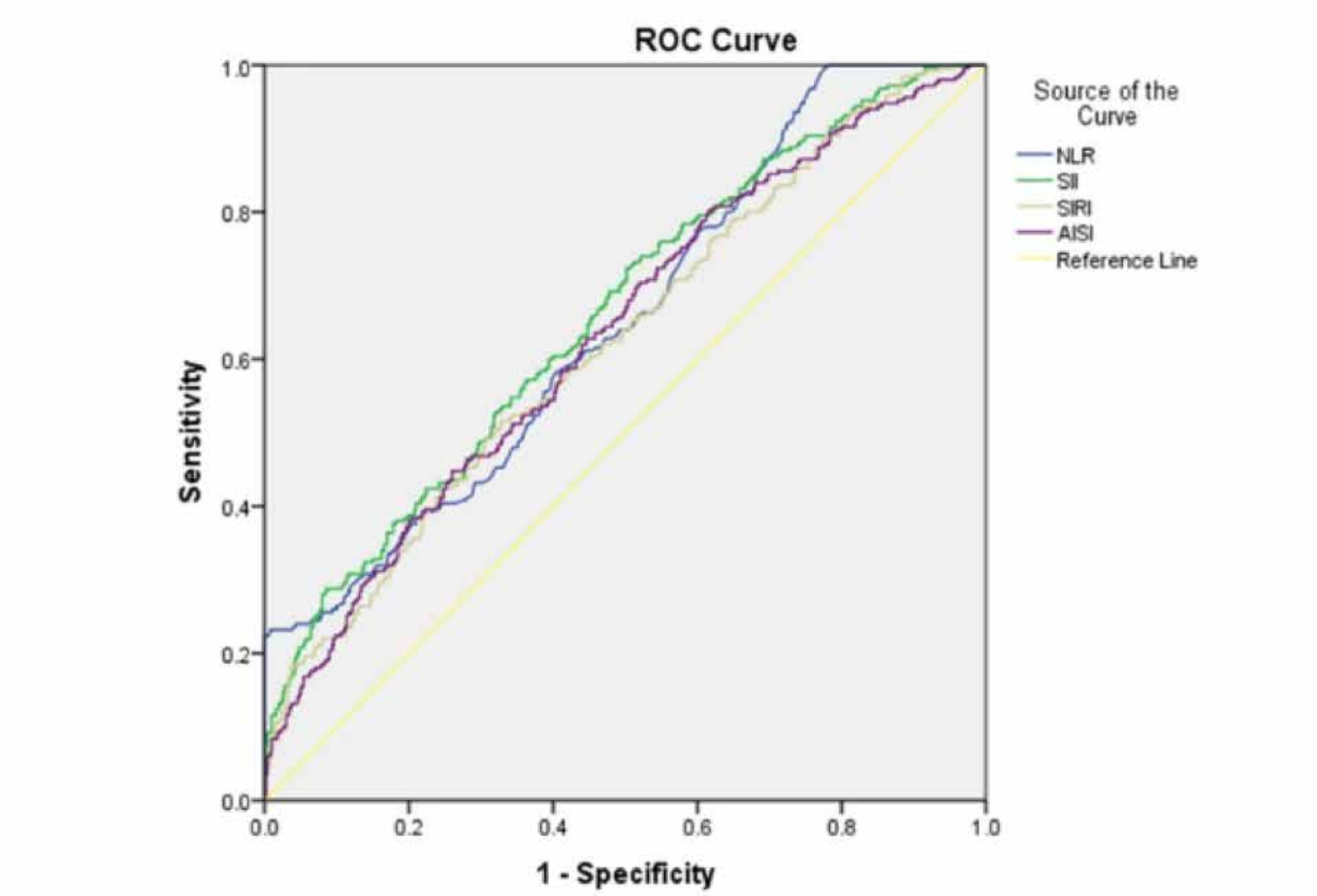
A subgroup analysis (Supplementary Table 1) was conducted within the uncontrolled diabetes group (Group 3) by stratifying individuals based on the severity of the uncontrolled diabetes into sub-group 1 (HbA1c < 8%) and sub-group 2 (HbA1c ≥ 8%). On comparison of the study parameters between the groups, apart from age and glycemic parameters in the study only Neutrophils and NLR showed statistically significant elevation between the groups. Individuals with poor glycemic control had higher NLR values (2.32 [1.89–4.23]) compared to those with moderately controlled diabetes (median 2.19 [1.79–2.98], p = 0.009).

Further Receiver operating characteristic (ROC) curve analysis was performed for all inflammatory indices as shown in Figure 2. The results revealed that only four indices (NLR, SII, SIRI, AISI) had moderate predictive performance. NLR with an optimal cutoff of 1.855 and AUC = 0.651, yielded the highest sensitivity of 76.4% and specificity of 41.0% (p < 0.001) compared to other indices such as SII (AUC = 0.659), SIRI (AUC = 0.625), and AISI (AUC = 0.632).

Out of the four indices that had moderate predictive performance in the ROC analysis, the outcome of logistic regression analysis revealed that only NLR demonstrated statistically significant association with poor glycemic control. In the unadjusted model, elevated NLR was associated with increased odds of uncontrolled diabetes (odds ratio = 2.1, 95% CI: 1.75–2.52, p < 0.001). This association remained strong in

the adjusted model, where NLR was controlled for age, FBS, PPBS, total WBC count, eosinophils, basophils, and platelets, yielding an adjusted odds ratio of 4.73 (95% CI: 3.36–6.65, p < 0.001) (Supplementary Figure 1 and Table 5).

Figure 2: Receiver operating characteristics (ROC) curve analysis of Inflammatory indices for predicting uncontrolled diabetes.



Variable	AUC	Cutoff	Sensitivity	Specificity	p-Value
NLR	0.651	1.8550	76.4%	41.0%	<0.001
SII	0.659	648.06	60.4%	60.0%	<0.001
SIRI	0.625	1030.45	51.6%	67.2%	<0.001
AISI	0.632	2578.06	62.8%	55.4%	<0.001

NLR: Neutrophil lymphocyte ratio; SII: Systemic Immune-Inflammation index; SIRI: Systemic inflammatory response index; AISI: Aggregate index of systemic inflammation; **p-Value <0.01 Highly significant; *p-Value <0.05 statistically significant

Table 5 : Regression analysis for NLR as an independent predictor of uncontrolled diabetes.

Regression model	Variables	Beta coefficient	Odds Ratio	95% CI (odds ratio)	p-value
Linear regression	NLR and HbA1c	0.46	NA	0.35-0.56*	<0.001
Logistic regression (unadjusted)	NLR and HbA1c > 7%	0.74	2.1	1.75-2.52	<0.001
Logistic regression (adjusted)#	NLR and HbA1c > 7%	1.55	4.73	3.36-6.65	<0.001

*The 95% confidence interval in linear regression corresponds to the beta coefficient; #The model was adjusted for Age, Fasting blood sugar, postprandial blood sugar, Total WBC, Eosinophils, Basophils, and Platelets. p-Value <0.01 is considered Highly significant.

Discussion

Diabetes mellitus (DM) is a chronic metabolic disorder marked by sustained hyperglycemia and chronic low-grade inflammation, driving a wide array of vascular complications including cardiovascular disease, diabetic nephropathy, retinopathy, and neuropathy leading to the morbidity and mortality [13]. Among the demographic profiles in Table 2, a significant age gradient was observed, increasing from 29 years [24–37] in Group 1 (non-diabetic) to 40 years [30–49.7] in Group 2 (controlled diabetics), and further to 47 years [37–56] in Group 3 (uncontrolled diabetics) ($p < 0.01$). Further, all glycemic parameters showed statistically significant differences among the groups. HbA1c increased significantly from 5.3% [5.1–5.5] to 8.6% [7.2–9.9] ($9p < 0.01$).

White blood cells (leukocytes) serve as indicators of systemic inflammation and studies have shown elevated total WBC counts in individuals with T2DM compared to non-diabetic controls [9]. In our study table 2, total WBC count increased significantly from 7900 cells/µL [6770–9395] to 8920 cells/µL [7377.5–11097.5] ($p < 0.01$), while neutrophils increased from 4655.3 cells/µL [3753.7–5843] to 5590.4 cells/µL [4535–7097.7] ($p < 0.0001$) and Basophils were significantly higher in Group 3 compared to Group 1 ($p = 0.021$). The lymphocytes, monocytes and eosinophils did not differ significantly across groups (all $p>0.05$).

The mechanistic basis for the leukocyte alterations in T2DM lies in the metabolic disturbances triggered by persistent hyperglycemia [14]. Hyperglycemia induced excessive ROS production and the accumulation of AGEs, stimulates NF-κB and JNK pathways, promoting the transcription of pro-inflammatory genes. Simultaneously, chemokines such as monocyte chemoattractant protein-1 (MCP-1) increase the recruitment of monocytes and other immune cells to sites of tissue injury while IL-6 influences leukocyte production and differentiation contributing to insulin resistance and erythropoietic suppression [15]. Importantly, this chronic inflammatory state linked development of insulin resistance is due to serine phosphorylation of insulin receptor substrate proteins that impairs downstream insulin signaling, exacerbating hyperglycemia and establishing a vicious cycle. WBCs and their inflammatory products are directly implicated in this process. Additionally, in tissues such as the kidneys and retina, leukocyte infiltration contributes to fibrosis, neovascularization, and capillary dropout, all of which are hallmarks of diabetic nephropathy and retinopathy [14-16]. Despite these findings, no single WBC parameter has shown promising outcomes in assessing glycemic control. The Inflammatory indices calculated based on the WBC parameters have shown significant results in conditions like COVID-19, cardiovascular diseases, while the studies of these indices in DM were mostly focused on its vascular complications. In our study, nearly five inflammatory indices from WBC parameters (NLR, MLR, ELR, LMR, BLR), three indices using platelets and WBC (PLR, PMR, WPR) and three composite indices (SII, SIRI, AISI) were compared based on glycemic control in diabetic patients, along with healthy non-diabetic controls. In our study, NLR values were significantly elevated in Group 3 (2.25 [1.8–3.2]) compared to Group 1 (2.05 [1.5–2.5]) and Group 2 (1.95 [1.5–2.42]) with an overall $p < 0.01$. Similar upward trends were observed in SII (564.1 [411.5–765.8] to 727 [559.7–1040.2]; $p < 0.01$), SIRI (885.1 [533.5–1280.6] to 1065 [708.8–1608.9]; $p < 0.01$), and AISI (2440.9 [1530.3–3762.5] to 3211 [2049.3–5071.8]; $p < 0.01$). Statistically significant differences without any particular trend were also found in MLR ($p = 0.006$), ELR ($p = 0.026$), LMR ($p = 0.006$), BLR ($p = 0.002$). These findings were confirmed in the correlation analysis, all the indices correlated with HbA1c all $p<0.05$ except for MLR and LMR. However, in the ROC analysis shown in Figure 2, revealed that only NLR, SII, SIRI, AISI had a moderate predictive performance for uncontrolled diabetes (AUC >0.600). Despite these findings, only NLR and neutrophils exhibited significant difference between the moderate and poorly controlled diabetes patients in the subgroup analysis (all $p<0.05$).

In support of our findings, numerous studies have highlighted the role of the neutrophil-to-lymphocyte ratio (NLR) as a cost-effective reliable indicator of inflammation and its association with diabetic complications [17]. Demirtas et al., Akbas et al., and Li et al., reported significantly elevated NLR levels in diabetic patients with nephropathy or albuminuria [17-19]. While Demirtas et al. found no significant difference in NLR between patients with HbA1c <7% and ≥7%, Prakash et al. observed higher NLR in uncontrolled diabetics (HbA1c >7%) compared to those with better control, despite weak correlation

with HbA1c [17,20]. Mertoglu & Gunay and Yilmaz et al. demonstrated a stepwise rise in NLR from normoglycemic individuals to those with prediabetes and diabetes, with Yilmaz et al. also linking elevated NLR to glucose levels during OGTT in morbidly obese individuals, supporting its role in early disease detection [21,22]. In the context of insulin resistance severity, both Zhang & Liu et al., observed significantly elevated NLR with a positive correlation to HOMA-IR and fasting blood glucose, identifying NLR as an early marker of metabolic dysfunction [23]. Song et al., Verdoia et al. (2015), and Aygun et al.(2015), reported higher NLR levels as independent predictors of diabetic patients with obstructive coronary artery disease (CAD) and peripheral arterial disease (PAD) [24-26]. In diabetic retinopathy (DR), Deng et al. (2025), showed a progressive rise in NLR from 2.19 in No DR to 2.82 in PDR, [10]. Additionally, Lee et al. (2012), demonstrated the long-term predictive utility of NLR in T2DM patients with acute myocardial infarction [27]. Interestingly, a study reported no significant differences in NLR between well and poorly controlled diabetics, likely due to the influence of anti-inflammatory drugs such as aspirin and metformin [11]. In our study, similar to the published literature regression analysis confirmed NLR as an independent predictor of poor glycemic control: linear regression showed a $\beta = 0.46$ (95% CI: 0.35–0.56, $p < 0.001$), and adjusted logistic regression yielded an increased odds ratio of 4.73 (95% CI: 3.36–6.65, $p < 0.001$) from an odds ratio of 2.1 in unadjusted models. Taken together, these findings consolidate NLR's value as a practical, accessible, and low-cost inflammatory marker that reflects systemic inflammation, metabolic stress, and the presence or progression of diabetic complications.

The findings in our study, pertaining to other indices with moderate predictive performance such as SII, SIRI and AISI also align with a growing body of literature. Chen et al. (2024), demonstrated that higher SII quartiles were positively associated with diabetes risk, with BMI and waist circumference acting as partial mediators [28]. Deng et al. (2025), showed that SII was significantly higher across advancing stages of diabetic retinopathy, with a notable linear trend and diagnostic value (AUC > 0.6) [10]. Similarly, Song et al. (2024), reported elevated SII, SIRI, and AISI in T2DM patients with peripheral arterial disease (PAD) with confirmed moderate discriminative ability (all AUC > 0.600) [24]. Wang et al. (2023), and other studies have linked elevated SII and SIRI with increased mortality and risk of diabetic complications including nephropathy, foot infections, hepatic steatosis, and cardiovascular disease [12,29,30]. These findings collectively validate our results and reinforce the role of SII, SIRI, and AISI in detecting worsening glycemic status despite no difference in the subgroup analysis.

In our study, platelet counts significantly increased from 2.84 lakhs/μL [2.46–3.35] in group 1 to 3.09 [2.60–3.58] in group 2, with no significant difference between groups 2 and 3. Among the platelet-related indices, WPR and PLR showed a rising trend, whereas PMR exhibited a biphasic response i.e. elevated in group 2 and subsequently reduced in group 3. Notably, only PLR and PMR correlated positively with HbA1c ($r = 0.099$; $p < 0.007$). Several studies have emphasized the clinical significance of PLR in diabetes. Akdogan et al. (2016), reported significantly higher PLR in diabetic patients and demonstrated strong correlations with HbA1c, disease duration, and atherogenic index [31]. Zhang and Liu. (2024), showed a stepwise increase in insulin resistance across higher PLR tertiles, supporting its role as a marker of chronic inflammation in DM [23]. Deng et al. (2025), observed progressively rising PLR with increasing stages of diabetic retinopathy, although it was not found to be an independent risk factor [10]. Mertoglu and Gunay. (2017), reported a biphasic PLR pattern i.e. lower PLR in prediabetics and newly diagnosed patients, and higher in known diabetics, which mirrors our findings with PMR [21]. PLR was also shown to be associated with diabetic nephropathy and microalbuminuria [17,18]. Additionally, Gao et al. (2024), and Si et al.(2024), linked elevated PLR with DR progression and increased cardiovascular mortality [32,33]. Mechanistically, hyperglycemia-induced platelet activation via oxidative stress and thromboxane A2 promotes inflammation through the release of mediators like Platelet factor 4 (PF4), CD40 ligand (CD40L), and Interleukin-1 beta (IL-1β) contributing to vascular damage [30,34]. Platelet-leukocyte aggregates drive vascular inflammation and endothelial dysfunction, contributing to diabetic macrovascular complications rather than glycemic control.

Other indices like LMR, ELR, and BLR were novel in our study due to the lack of existing literature in diabetes. MLR and LMR showed no correlation with HbA1c, despite differences in comparative analysis, while ELR and BLR exhibited weak to moderate correlation but lacked predictive value in ROC analysis (AUC < 0.5). Lymphopenia is a known marker of chronic inflammation in diabetes, whereas monocyte elevation is gradual and more related to vascular complications than short-term glycemic changes, aligning with the lack of correlation between MLR, LMR and HbA1c in our study. Supporting this, Prakash et al. (2020), found no significant MLR difference between controlled and uncontrolled diabetics (0.2 vs. 0.24; $p > 0.05$), nor any correlation with HbA1c [20]. Zhang & Liu. (2024), reported an MLR–IR association, but no variation across MLR tertiles, limiting stratification [23]. Deng et al. (2025), also observed elevated MLR in PDR, without a linear trend with severity [10]. Ngama et al. (2021), showed no correlation between ELR and HbA1c [35]. BLR findings in our study align with Shen et al. (2024), who found a 2.45-fold increased T2DM risk in the highest BLR quartile, influenced partly by dyslipidemia, potentially explaining the limited discriminative value of BLR in our ROC analysis [36].

The cross-sectional design limits the ability to infer causality between elevated indices and glycemic progression. Lack of data on lipid profiles and co-morbid conditions such as hypertension and Confounding factors such as use of anti-

inflammatory or antiplatelet medications (e.g., aspirin, statins) were not uniformly accounted for, which may influence inflammatory markers. Future longitudinal follow-up studies are required to validate our study findings in development of diabetic complications. Integration of metabolic markers like Homeostatic Model Assessment of Insulin Resistance (HOMA-IR), insulin levels, lipid profile and inflammatory biomarkers can enhance the accuracy and mechanical insight.

Conclusion

This study demonstrates that hematological inflammatory indices derived from routine blood parameters, particularly NLR, SII, SIRI, and AISI are significantly elevated in patients with poor glycemic control, reflecting a state of chronic systemic inflammation in T2DM. Among all indices, NLR showed the strongest and independent association with poor glycemic status, highlighting its potential as a low-cost, accessible adjunct marker for monitoring glycemic control and systemic inflammation in T2DM without complications. While other indices like BLR and PLR also showed significant group-wise differences and correlations with glycemic markers, their predictive performance was less robust, suggesting further evaluation with other confounding factors. Overall, the findings reinforce the utility of inflammatory indices in identifying individuals at risk and tracking metabolic deterioration in diabetes with the novelty of evaluating multiple hematological indices in uncomplicated T2DM. Notably, it is among the first few studies to establish the utility of BLR, ELR, PMR, LMR, and AISI in this context.

Author Contribution

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Writing - review and editing: Kiran S, Karthick E, Sathya Selvarajan, K Sowmya, K.S.Sridharan ; Resources: Kiran S, Karthick E, Sathya Selvarajan, K Sowmya, K.S.Sridharan ; Supervision and final approval: Kiran S, Karthick E, Sathya Selvarajan, K Sowmya, K.S.Sridharan ; Accountability for the research: Kiran S, Karthick E, Sathya Selvarajan, K Sowmya, K.S.Sridharan.

Ethical Approval

The study was conducted in accordance with the ethical principles of the Declaration of Helsinki. Ethical clearance was obtained from the Institutional Ethics Committee (IEC) with reference number CSP/22/SEP/116/486 and waiver of consent was obtained pertaining to the retrospective nature of the study. Confidentiality of the patient data was strictly maintained throughout the study.

Disclosure of Conflict of Interest

The authors declare that there is no conflict of interest concerning this study.

Acknowlegement

The authors like to express sincere gratitude to all participants who contributed to this study and our Institution for providing the necessary facilities. Their invaluable support has been instrumental in the completion of this research.

Funding and data availability

The authors disclose that no external funding was received for the conduct of this study. The data used in this study are available from the corresponding author upon reasonable request, in accordance with institutional policies.

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Supplementary Files

Supplementary Table 1: Subgroup analysis of the Inflammatory indices based on the severity of the uncontrolled diabetes (group 3 HbA1C greater than 7%).

Variable	Group 3 Median [IQR]	Moderate control Median [IQR]	Poor control Median [IQR]	p-value*
Age (years)	47 [37-56]	52 [42-60]	45 [35-52]	<0.001
FBS (mg/dL)	139 [110-194]	124 [108-144]	170 [115-230]	<0.001
PPBS (mg/dL)	220.5 [152-305]	193 [146-231]	280 [174-351]	<0.001
HbA1C (%)	8.6 [7.2-9.9]	7.1 [7.0-7.6]	9.7 [8.9-10.4]	<0.001
EAG (mg/dL)	175 [146-226]	154 [146-169]	220 [186-249]	<0.001
Neutrophils (cells/µL)	5590.4 [4535-7097.7]	5402.7 [4387.5-6724.1]	5717.4 [4758.6-7376.6]	0.016
NLR	2.25 [1.8-3.2]	2.19 [1.79-2.98]	2.32 [1.89-4.23]	0.009

FBS: Fasting blood sugar; PPBS: Postprandial blood sugar: HbA1C: Glycated Hemoglobin; EAG: Estimated average glucose; NLR: Neutrophil lymphocyte ratio; p-Value <0.01 Highly significant; p-Value <0.05 statistically significant

*Comparison was performed using Mann-Whitney U test and Welch test based on the distribution of variance between Moderate control group and Poor control group. Group 3 Data is provided for reference and not used for comparison.

Supplementary Figure 1: Linear regression analysis between NLR and HbA1C in the study.