Original Article

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Hematological Variables (NLR, PLR, MLR, MPR, and RPR) as Predictive Markers for Glucose Levels in Patients of Type 2 Diabetes Mellitus

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ABSTRACT

Objective: This study explores the association between hematological ratios (NLR, PLR, MLR, MPR, and RPR) and HbA1c in T2DM patients.

Methodology: This cross-sectional study was conducted at HIT-hospital Taxila from December 2022 to December 2023. One hundred T2DM patients aged ≥ 35 years from HIT Hospital-Taxila were included. They were divided into two groups (Group-I: HbA1c ≤ 7%, Group- II: HbA1c > 7%). BSF, BSR and HbA1c were analyzed. Hematological parameters were used to calculate the ratios. Statistical analysis was performed using SPSS version 29.

Results: The group with higher HbA1c levels had significantly elevated levels of TC, MPV, PLR, NLR, and MLR. A strong positive correlation of HBA1C with NLR and PLR indicates that uncontrolled diabetes has a strong association with these markers. Stepwise linear regression analysis showed that Model III has better predictive power with a good adjusted R square and significant p-value.

Conclusion: Hematological parameters, especially NLR and PLR correlate well with glycemic control in T2DM and can serve as reliable predictive markers for uncontrolled diabetes. Regular monitoring of these variables may aid in affordable diagnosis and better management of T2DM.

Key Words: Type 2 Diabetes Mellitus, HbA1c, Hematological Variables, Glycemic control.

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Introduction

The prevalence of type 2 diabetes mellitus (T2DM) is growing with changes in lifestyle and the fast expansion of the global economy. According to statistics of 2021, the estimated worldwide prevalence of T2DM among individuals aged 20–79 years was at 10.5% (536.6 million people), with predictions that over 1.31 billion people, in both genders, could be affected by the disease by 2050.[1] In India, it is projected that the figure will be upturned to 69.9 million by 2025.[2] An article from The News states that Pakistan holds the 3rd position globally in diabetes prevalence, following China and India.[3]

Plasma glycated hemoglobin (HbA1c) is an obliging marker used to diagnose and monitor disease and indicate the average blood glucose status of the last three months.[4] HbA1c levels are not affected by other factors like diet, stress or exercise and are used for long-term blood glucose monitoring. [5]

In recent years, low-grade inflammation has been found to play a vital role in the development of T2DM[6], depicted by high levels of a hematological marker, neutrophil-to-lymphocyte ratio (NLR) in T2DM patients.[7] NLR imitating the general inflammatory state of the body compared to distinct biomarkers, is easy to detect and budget friendly.[8] It had been demonstrated in addition to the HbA1c level, the NLR index could be

used as a marker for assessing glycemic control in T2DM patients.[9] The study validated that the NLR value also increases as the HbA1c level deteriorates. However, the association between NLR and T2DM remained unclear due to the small sample sizes in these studies.

Other than NLR, hematological indices in complete blood count (CBC), are designated predictors of chronic inflammation. CBC is a low-price, routine test that delivers significant results. It can be helpful for early diagnosis and treatment of diabetes. Therefore, regular evaluation of hematological parameters plays a vital role in assessing the disease progression and improving the quality of life. [10]

Hematological variations amongst diabetics can lead to long-term complications.[10] With a higher value of HbA1c, a rise in mean platelet volume (MPV) and red cell distribution width (RDW) had been perceived in diabetic patients. Hence raised MPV and RDW scores can be helpful biomarkers to predict diabetes complications, rather than assessing HbA1c levels. [11]

Most recent studies have proved a strong association of hematological parameters with many chronic inflammatory disorders including diabetes and its micro and macrovascular complications, coronary artery disease and metabolic diseases. [10, 11] Regarding T2DM, a positive relationship is found between elevated levels of NLR and PLR (platelet-lymphocyte ratio) with microalbuminuria.[12]

Hematological indices are economical and routinely offer inflammatory markers that can help in the early diagnosis and management of T2DM cost-effectively. However, to our knowledge, there is a paucity of data regarding the association between these parameters and T2DM across different groups in our setting. Data indicating the association between hematological parameters, glucose markers and micro and macrovascular complications of T2DM is still lacking. Therefore, the present study was designed to determine the association of hematological parameters including NLR, PLR, MLR (monocyte-to-lymphocyte ratio), MPR (monocyte-to-platelet ratio), and RPR (RWD-to-platelets ratio) with glucose markers including BSF (blood sugar fasting), BSR (blood sugar random) and HbA1c in patients with T2DM. We also assessed the role of hematological biomarkers as predictive indicators of glucose status in patients with T2DM.

Methodology

This cross-sectional study was conducted at HIT-hospital Taxila from December 2022 to December 2023. After obtaining the Institutional Review Board approval, letter no: HITEC-IRB-28-2022, one hundred diagnosed T2DM patients; male & female with ≥ 35 years of age were included through non-probability convenience sampling. Exclusion criteria include patients with active infectious diseases, hematological disorders, malignant hypertension, tumors, immunodeficiency diseases, liver disorders, and inflammatory conditions such as rheumatoid arthritis, inflammatory bowel diseases and pregnancy.

After taking the informed consent, BSF, BSR, HbA1c, total cholesterol and triglyceride levels were analyzed. Hematological parameters, WBC, neutrophil count, lymphocyte count, hemoglobin (Hb), hematocrit (HCT), RDW, platelet count, and MPV levels were estimated. The NLR was determined by dividing the total number of neutrophils by the number of lymphocytes, while the PLR was calculated by dividing the number of platelets by the number of lymphocytes. MLR, MPR, and RPR were calculated as the division of MPV by lymphocyte count, MPV by platelets, and RDW by platelets, respectively. The patients were categorized into two groups: Group-I (good glycemic control, HbA1c ≤ 7%) and Group-II (poor glycemic control, HbA1c > 7%). The total calculated sample was 100 patients, with 50 in each group. The sample size was calculated with open epi software using 80% power of the study and a 95% confidence interval. The anticipated NLR level in group 1 is 2.21 ± 1.1 and in group 2 is 2.86 ± 1.2.[13]

Statistical Analysis was performed using SPPSS version 29. Kolmogorov-Smirnov test was applied to assess the normal distribution of data. The numerical data was measured as median and interquartile range (IQR). Mann-Whitney U test was used to compare the groups. Spearmen correlation was applied to determine the association of hematological variables with glucose markers. Logistic linear regression was used to assess the predictive ability of hematological variables for HbA1c. P-value < 0.05 was considered statistically significant.

Results

Out of 100 patients, 46 were male and 54 were female. Their median age was 52(44.25-57) years. Their median HbA1c level was 6.9(6.3-8.5). In group 1, there were 28(52.8%) males and 25(47.2%) females. In group II,

males and females were 18(38.3%) and 29(61.7%) respectively. The group with higher HbA1c levels had significantly elevated levels of TC, MPV, PLR, NLR, and MLR (Table I).

A significant positive but weak correlation was found between TC and PLR. It indicates that as total cholesterol increases, PLR increases as well. A significant positive but weak correlation of BSR with NLR, MPR, and MLR suggests that higher BSR levels may be associated with higher ratios. There is a strong positive correlation of HBA1C with NLR and PLR indicate that uncontrolled diabetes has more strong association with these markers. MLR also showed significant but weaker correlations with HBA1C (Table II).

Model II indicates that NLR is a strong predictor of HbA1c, with a high R, adjusted R square and statistical significance. Considering collinearity, the presence of the lowest VIF and highest tolerance proves this model best. In Model III after the addition of PLR, although VIF increases it is still within safe limits which shows that Model III also has better predictive power with a good adjusted R square and significant p-value. In Model IV, the addition of MPR, although increases the adjusted R square and shows a significant p-value, the presence of multicollinearity indicated by High VIF and low tolerance proves this model not to be the best. Adding RPR and MLR does not appear to contribute significantly to Models V & VI (Table III)**.**

Table I: Demographic and biochemical characteristics of groups. (n=100)

Variables	HBA1C < 7% Median (IQR) (n=53)	HBA1C > 7% Median (IQR) (n=47)	p-value
Age (years)	51 (42-58)	52 (50-57)	0.47
Blood Pressure Systolic (mm Hg)	130 (120-150)	140 (130-150)	0.31
Blood Pressure Diastolic (mm Hg)	80 (70-90)	80 (80-90)	0.44
Duration of DM (years)	5 (2 - 10)	5 (3-10)	0.12
Total Cholesterol (mmol/L)	4.6 (3.6-5.7)	5.2(4.8-6)	0.001
Triglyceride (mmol/L)	2.1 (1.4-2.7)	2.3(2-3)	0.13
Red Blood cells ($\times 10^{12}$/L)	4.8 (4.3-5.1)	4.8(4.5-5.1)	0.46
Hemoglobin (g/dL)	13.1 (11.4-14.2)	13.2(12.5-14.2)	0.59
Hematocrit (%)	41 (36-43)	40(38-43)	0.67
MCV(fL)	86 (81-90)	84.5(81.6-89)	0.36
MCH(pg)	28.3(25.9-29.5)	27.8(26-29.2)	0.63
MCHC(g/dL)	32.7(31.4-33.6)	32.8(32-33.4)	0.84
RDW-SD(fL)	30(14.1-44.6)	28(14-42)	0.72
Platelets ($\times 10^9$/L)	194(166-260)	216(189-255)	0.11
MPV(fL)	11.5 (10.7-12.4)	12.8(10.8-13.8)	0.005
ESR mm/at 1st hr	30(19-40)	30(24-55)	0.19
TLC ($\times 10^9$/L)	8.2(6.9-9.4)	8.0(6.2-9.4)	0.35
Neutrophils ($\times 10^9$/L)	4.6 (3.7-5.3)	4.8(3.7-6.2)	0.07
Lymphocytes ($\times 10^9$/L)	2.9 (2.6-3.6)	2.1(1.72-2.51)	0.01
Monocytes ($\times 10^9$/L)	0.4(0.33-0.50)	0.37(0.31-0.50)	0.71
Eosinophils ($\times 10^9$/L)	0.28(0.21-0.35)	0.27(0.20-0.32)	0.22
NLR	1.43 (1.11-1.83)	2.1(1.71-3.20)	0.01
PLR	71.98(48.7- 86.1)	106.1(84.8-129.6)	0.01
RPR	0.14(0.08-0.20)	0.12(0.08-0.19)	0.56
MPR	0.06(0.05-0.07)	0.06(0.05-0.07)	0.71
MLR	0.15(0.10-0.17)	0.18(0.16-0.24)	0.01
Blood Sugar Fasting (mmol/L)	7 (6.3- 8.8)	9.4(7.1-12.2)	0.01
Blood Sugar Random (mmol/L)	9.3(8.8-13.5)	13.5(11.4-19.2)	0.01
HbA1c (%)	6.3(6.2-6.7)	8.6(7.6-10.6)	0.01

Table II: Correlation analysis of NLR, PLR, RPR, MPR and MLR and demographic and biochemical parameters.

Variables	NLR		PLR		RPR		MPR		MLR	
	r	p-value	r	p-value	r	p-value	r	p-value	r	p-value
Age (years)	-0.03	0.78	-0.06	0.53	0.22	0.03	0.21	0.03	0.10	0.32
Blood Pressure Systolic (mm Hg)	0.06	0.55	0.01	0.89	0.04	0.70	0.11	0.30	0.15	0.13
Blood Pressure Diastolic (mm Hg)	0.02	0.86	0.06	0.55	0.06	0.53	-0.02	0.83	0.16	0.12
Duration of Diabetes Mellitus (years)	0.05	0.61	0.08	0.42	0.13	0.20	0.08	0.46	0.06	0.53
Total Cholesterol (mmol/L)	0.17	0.08	0.22	0.02	0.001	0.99	-0.08	0.45	-0.03	0.81
Triglyceride (mmol/L)	0.09	0.39	0.07	0.50	0.02	0.86	0.09	0.36	0.09	0.36
Blood Sugar Fasting (mmol/L)	0.17	0.09	0.03	0.78	0.04	0.673	0.322	0.001	0.18	0.08
Blood Sugar Random (mmol/L)	0.32	0.00	0.19	0.06	-0.03	0.74	0.23	0.02	0.22	0.03
HbA1c (%)	0.60	0.00	0.55	0.00	0.06	0.53	0.08	0.43	0.4	0.00

Table III: Predictive ability of hematological ratios for Diabetes Mellitus keeping HbA1c as dependent variable.

Models	Collinearity		R	R square	Adjusted R Square	R Square change	p-value
	Tolerance	VIF					
Model I							
TC	1.00	1.00	0.135	0.018	0.008	0.18	0.182
Model II							
TC	0.99	1.02	0.787	0.620	0.612	0.601	0.000
NLR	0.99	1.02					
Model III							
TC	0.94	1.07	0.799	0.639	0.628	0.020	0.026
NLR	0.73	1.388					
PLR	0.69	1.45					
Model IV							
TC	0.91	1.10	0.810	0.655	0.641	0.016	0.037
NLR	0.32	3.15					
PLR	0.32	3.15					
MPR	0.38	2.63					
Model V							
TC	0.91	1.10	0.813	0.661	0.642	0.005	0.237
NLR	0.32	3.15					
PLR	0.32	3.15					
MPR	0.26	3.84					
RPR	0.46	2.19					
Model VI							
TC	0.91	1.11	0.814	0.663	0.641	0.003	0.399
NLR	0.28	3.62					
PLR	0.31	3.19					
MPR	0.26	3.84					
RPR	0.45	2.19					
MLR	0.61	1.63					

Discussion

T2DM is the most prevalent type of disease in adults. [14] It poses a major health and financial burden on countries worldwide, with healthcare costs exceeding 966 billion US dollars in 2021. That year, it was responsible for 6.7 million deaths globally. [15]

Chronicity, poor glycemic control, and dyslipidemia are well-known risk factors for diabetic complications. [11] Long-term hyperglycemia with uncontrolled disease may impair many tissues, most particularly the renal, retinal, peripheral nerves, or vascular tissue damage. [16] On the other hand, strictly controlled glucose levels support to prevention of diabetic common complications. [17] Therefore this study was designed to explore the relationship between glycemic indices and routinely used hematological markers in T2DM to predict the glycemic control in these patients.

The association between NLR and the risk of T2DM has been explored in the present study, showing significantly higher NLR levels in T2DM patients. [7] This parameter had been established specifically as a composite biomarker reflecting the systemic inflammatory state in diabetes. [8] Thus health care professionals may pay attention to the dynamics of this marker and its increasing levels be considered as a warning sign of worsening of the disease in addition to HbA1c values.

Likewise, other data confirms that the NLR ratio increases as the HbA1c level gets uncontrolled so can be used as a noble marker for evaluating glycemic control in T2DM. [9]

As described earlier, the inflammatory process in T2DM can be determined with the help of certain unique hematological markers which can be easily measured to predict the disease progression. [18] The role of platelets has been described in disease advancement to recruit leukocytes by releasing pro-inflammatory cytokines. [19] The increase in PLR value in our study participants of T2DM most likely displays the inflammatory burden of the advanced disease.

Furthermore, another complete blood count (CBC) derived parameter, MLR was explored in our study in addition to NLR and PLR. Our data established the higher index of MLR in patients with higher HbA1c levels. This is in accordance with the aforementioned results where cases with poorly controlled diabetes mellitus showed a positive relationship with inflammatory markers, that is, NLR and MLR. [14,20] A higher HbA1c level (>7%) had been established to be

associated with a high score of NLR, MLR and PLR in diabetic patients suggesting their usefulness in discriminating controlled and uncontrolled diabetes. [14,20] Moreover, these are reasonably priced and easily available markers for early detection of diabetes complications in addition to HbA1c percentages. [14]

Micro and macrovascular pathologies, such as heart disease, and cerebrovascular and peripheral vascular disease are the common associations with diabetes; Suvarna R investigated the significance of routine hematological parameters in relation to these complications. [21] Our data showed raised values of NLR and PLR which are recently proven to be closely associated with T2DM and its microvascular complications. [13, 18] Hematological-derived indices of inflammation and thrombosis are clinically important in the development of diabetic complications. [21] These variables provide a thorough reflection of glycemic control and changeable routine activities which strongly predict the onset of upcoming complications. In future, strict monitoring of these indicators in T2DM may impact the disease prognosis and support to avert future complications.[21] The present study validated the significant correlation of MLR with uncontrolled DM. High MLR value is found in individuals with DM complicated with cardiovascular disease. This valuable finding signifies that keeping a low MLR, a handy biomarker, may facilitate healthcare professionals to evaluate a patient's inflammatory status and risk of complications. [22]

The hematological markers are easy to analyze as they are low-priced and can be readily studied in all laboratory settings. This study supports the initial diagnosis and management of diabetes-associated complications in a cost-effective way by finding out the possible association between hematological indices, glycemic markers and microvascular complications of T2DM. Altered NLR value is found to be present in patients with diabetic complications including diabetic nephropathy [23]. Healthcare professionals should deliberate on the dynamics of these indicators in diabetes and consider them as predictive factors in advanced disease. [12]

Previous discoveries revealed that higher MLR and PLR values were linked to the growing risk of insulin resistance.[14] Thus, insulin insulin-resistant patient population can be predicted by identifying individuals with higher MLR and PLR values in T2DM. [20] Findings of the present study are in line with these researches, however, we did not analyze insulin resistance but can be recommended for further research.

Our study verdicts indicate the scope of framing a tailor-made approach for the management of diabetes and its common complications. HbA1c and some specific hematological indices of inflammation are clinically significant in the progression of T2DM. [21]

Conclusion

This analysis articulates the role of hematological parameters in T2DM management. Patients with uncontrolled T2DM may have substantial shifts in certain hematological values including NLR and PLR ratios. Regular testing of these parameters can help in early and affordable diagnosis and managing diabetes and its related complications. [24]

These variables can be utilized as a forthright tool to track the disease progression in addition to HbA1c levels. The markers can offer an in-depth reflection of glycemic control influencing the prognosis of the disease. Therefore, regular monitoring of hematological variables in T2DM may be used to prevent disease progression and the onset of upcoming complications to benefit the patients.

Limitations & future research: This single-centered study had a relatively smaller sample size with T2DM complications. Yet, our study exhibited the standing of hematology-derived inflammatory markers, which validated the shift of the CBC. To get more data it is suggested further that more T2DM studies could be piloted together with other centres in future.

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Abbreviations: "MCV, Mean corpuscular volume; MCH, Mean corpuscular hemoglobin; MCHC, Mean corpuscular hemoglobin concentration, RDW-SD, Red cell distribution width standard deviation; MPV, Mean platelet volume; ESR, Erythrocyte sedimentation rate; TLC, Total leukocyte count; NLR, Neutrophil lymphocyte ratio; PLR, Platelet lymphocyte ratio; MLR, MPV lymphocyte ratio, MPR, MPV platelet ratio; RPR, RDW platelet ratio."