Neutrophil-Lymphocyte and Platelet-Lymphocyte Ratios as a Marker for Diabetes Control and Complications

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Abstract:

Introduction: Hematological changes affecting the red blood cells, white blood cells, platelet function, and the coagulation factors were associated with diabetes mellitus (DM). The neutrophil-to-lymphocyte (N/L) and the platelet-to-lymphocyte (P/L) ratios, were offered as markers of inflammation in cardiac diseases, neoplasms and diabetes-related complications. **Patients and Methods:** A retrospective, cross sectional study of data from 200 patients with type 2 DM who attended the internal medicine clinic in Benha University Hospital. Clinical data were collected, including; age, sex, duration of DM, body mass index (BMI), micro-vascular and macro-vascular complications of DM. Laboratory data were collected in the form of glycosylated hemoglobin (HbA1c), fasting blood glucose (FBG),complete blood count with calculation of the N/L, and P/L ratios. The selected patients were divided into two groups; group I (good glycemic control, HbA1c ≤ 7 %) and group II (bad glycemic control, HbA1c >7). **Results:** Age was statistically insignificant between the two groups (p value of 0.341). HbA1c, BMI, and FBG were significantly higher in group II. A significant higher total leucocyte, neutrophil, and platelet counts in group II were noticed (p = 0.000). There were a significant higher N/L and P/L ratios in uncontrolled diabetics. Linear regression analysis revealed that age, FBG, neutrophil count, P/L and N/L ratios were significant independent parameters associated with HbA1c**. Conclusion:** The present study proposed that N/L& P/L ratios may be independently associated with poor blood glucose regulation in patients with type 2 DM. Furthermore, diabetic complications were associated with higher N/L & P/L ratios.

Key words: Neutrophil-Lymphocyte ratio, and Platelet-Lymphocyte ratio, diabetes control.

Introduction:

Vascular complications of diabetes mellitus (DM) results from various disorders including metabolic, cellular, and blood disturbances [1]. Excessive production of pro-inflammatory adipokines from adipose tissue, resulting in low-grade chronic inflammation, causing insulin resistance (IR) and type 2 DM [2]. Hematological changes affecting the red blood cells (RBCs), white blood cells (WBCs), platelet function, and the coagulation factors are detected to be associated with DM [3].

It is important to add that, high WBC count, one of the chief components of inflammatory process, sharing to atherosclerosis development and cardiovascular diseases (CVD) [4]. Lately, the neutrophil-to-lymphocyte (N/L) and the platelet-to-lymphocyte (P/L) ratios, were offered as markers of inflammation in cardiac diseases, neoplasms and diabetes-related complications [5] & [6].

Moreover, high leucocyte counts have been used as diagnostic and prognostic markers in vascular complication of diabetes [7]. Studies assessing the N/L & P/L ratios in relation to control of diabetes are inconsistent. So, our goal is to evaluate these simple hematological parameters as markers of diabetes control and complications.

Materials and methods:

A retrospective, cross sectional study of data from 200 patients with type 2 DM patients who attended the internal medicine clinic in Benha University Hospital between May to July 2021. Diagnosis of Type 2 DM according to American Diabetes Association (ADA) criteria of 2021 [8] after consent taken from the participants. The study was approved by the Ethics Committee of Benha Faculty of Medicine, Benha University (RC;1-5-2021) .We excluded patients if they were younger than 18 years old or had type 1 diabetes mellitus, subjects with any acute inflammatory conditions, cancer, chronic liver diseases, hematologic diseases, pregnant women, and autoimmune diseases. Clinical data were collected, including; age, sex, duration of DM, body mass index (BMI), complications of diabetes. Microvascular complications represented diabetic nephropathy, neuropathy, and retinopathy. Diabetic retinopathy was diagnosed through fundus examination performed by an ophthalmologist, while albuminuria is defined as urinary albumin excretion ratio is generally defined ≥ 30 mg/g Cr. [9]. Diabetic neuropathy was diagnosed by the presence of one or more of manifestations of peripheral neuropathy, or nerve conduction studies. Macrovascular complications were represented by ischemic

heart disease (IHD), cerebrovascular, and peripheral vascular diseases. IHD was diagnosed by documented history of myocardial infarction, and/or electrocardiographic and echocardiographic evidence of IHD. Stroke presented by documented history of previous stroke requiring. Peripheral vascular disease presented by history of gangrene, or ankle-brachial index < 0.7 with signs of atherosclerosis of arteries of lower limbs at the echo-color Doppler examination [10]. Laboratory data were collected on the same day which included; glycosylated hemoglobin (HbA1c), fasting blood glucose (FBG), complete blood counts. All laboratory parameters were performed in Clinical Pathology department, Benha University Hospital according to the routine methods. The selected patients were divided into two groups; group I (good glycemic control, HbA1c ≤ 7 %) and group II (bad glycemic control, HbA1c > 7). The neutrophil lymphocyte ratio (NLR) was calculated by dividing the total number of neutrophils by the number of lymphocytes, and the platelet lymphocyte ratio (PLR) by dividing the number of platelets by the number of lymphocytes.

Statistical analysis:

The collected data were statistically analyzed using SPSS 22.0 for Windows (SPSS Inc., Chicago, IL, USA) .The normality of distribution for the analyzed variables were tested using Kolmogorov-Smirnov test .The collected quantitative data were summarized in terms of Mean ± Standard Deviation (SD), while qualitative data were presented as number and percentage. Comparisons between the different study groups were carried out using student t-test for mean ± standard deviation of quantitative data, Chi-square ($\chi 2$) to compare (number and percentage) of qualitative data as appropriate. Correlation analysis to determine the association between variables was performed, using Pearson correlation coefficient (r). Significant predictors of HbA1c was determined by multilinear regression analysis. All tests were two sided. The level of significance in this work was ($p \leq 0.05$). While $p \leq 0.001$ was considered highly statistically significant (HS).

Results:

The study population consisted of 200 patients with type 2 DM; 72 patients represented the level of HbA1c ≤ 7 (group I) (24 males, 48 females), and 128 patients with HbA1c > 7 (group II) (40 males, 88 females). Demographic and clinical data were shown in table (1). Macro-vascular and micro-vascular complications of diabetes were significantly higher in group II ($p = 0.014$ and 0.026 respectively), table (2). In terms of hematological parameters, as

shown in table (3), a significant higher total WBCs, neutrophil, and platelet count in the group II were noticed (p = 0.000**). There were a significant higher N/L and P/L ratios in group II than group I (p = 0.000** and 0.025* respectively). Correlation analysis revealed a positive association between HbA1c and both N/L & P/L ratios (figure 1 & 2). Significant higher N/L and P/L ratios were found in the patients with micro- and macro-vascular complications (table 4). Linear regression analysis revealed that age, FBG, neutrophil count, PLR and NLR were significant independent parameters associated with HbA1c (table 5).

Table (1): Demographic & clinical data of the study population.

Variables	Group I (n=72)	Group II (n=128)	Test of significance	P value
Age (Ys)	61.88±7.9	60.50±10.8	0.954	0.341
Duration of DM(Ys)	14.22±10.6	16.63±8.6	-1.731	0.085
BMI(Kg/m2)	35.68±3.7	38.22±5.9	3.25	0.001**
HbA1c (%)	6.17± 0.62	9.49±1.5	-17.28	0.000**
FBG (mg/dl)	102.4±20.35	188.8±70.34	-10.18	0.000**

BMI: body mass index, HbA1c: glycated hemoglobin, FBG: fasting blood glucose.

Table (2): Comparison of diabetic complications between group I and II.

Complications	Group I (n=72)	Group II (n=128)	Chi^2	P value
Macro-angiopathy (IHD, PVD &CVD)				
Yes	8(11.1%)	33(25.8%)	6.08	0.014*
No	64(88.9%)	95(74.2%)		
Micro-angiopathy (DR,DN,DPN)				
Yes	15(20.8%)	46(35.9%)	4.95	0.026*
No	57(79.2%)	82(64.1%)		

(IHD; ischemic heart disease, PVD: peripheral vascular disease, CVD: cardiovascular disease)

(DR: diabetic retinopathy, DN: diabetic nephropathy, DPN: diabetic peripheral neuropathy).

Table (3): hematological parameters in the study population.

Variables	Group I (n=72)	Group II (n=128)	Test of significance	P value.
Total WBCs (x10^3/µL)	6.95 ± 1.91	9.07 ± 2.22	-6.77	0.000**
Neutrophil (x10^3/µL)	4.03 ± 1.08	5.85 ± 1.70	-8.16	0.000**
Lymphocytes (x10^3/µL)	2.17 ± 0.90	2.31 ± 0.82	-1.11	0.265
NLR	2.21 ± 1.1	2.86 ± 1.2	-3.57	0.000**
Hemoglobin (gm/dl)	13.16 ± 1.8	12.13 ± 1.0	5.05	0.000**
MCV (fl)	82.63 ± 16.4	80.86 ± 11.4	0.889	0.375
MCH (pg)	29.46 ± 2.2	26.75 ± 3.7	5.64	0.000**
Platelets x10^5	2.16 ± 0.57	3.19 ± 0.53	-12.67	0.000*
PLR	1.31 ± 1.04	1.58 ± 0.68	-2.25	0.025*

**Highly significant, NLR= Neutrophil lymphocyte ratio, PLR =Platelet lymphocyte ratio, MCV =Mean corpuscular volume, MCH = Mean corpuscular hemoglobin.

Table (4): N/L & P/L ratios in patients with macro- and micro-**vascular diabetic complications.**

	Macro-complications		**t-test**	**P value**
	Yes (32)	**No (168)**		
N/L ratio *(Mean ±SD)*	3.18±1.49	2.60±1.25	2.31	0.02*
P/L ratio *(Mean ±SD)*	174.86±80.90	136.80±98.78	2.05	0.04*
	Micro-complications		t-test	P value
	Yes (40)	No (160)		
N/L ratio *(Mean ±SD)*	3.16±1.37	2.65±1.311	2.18	0.03*
P/L ratio *(Mean ±SD)*	173.73±74.01	138.61±99.55	2.09	0.03*

Table (5): Linear regression analysis of parameters affecting HbA1c levels in patients with Type II DM.

Characteristics	Standardized Coefficients *β*	t	P value	F of the model &p value
Age(y)	-0.114	-2.053	0.041*	
Duration of DM(y)	-0.028	-0.45	0.665	
FBG (mg/dl)	0.526	10.97	0.000**	
BMI (kg/m^2)	0.013	0.34	0.731	**67.8**
WBCs (x10 ^{3}/µL)	-0.880	-1.39	0.165	**(0.000**)**
Neutrophil (x10 ^{3}/µL)	1.428	2.84	0.005**	
Lymphocytes (x10 ^{3}/µL)	0.105	0.41	0.681	
Hb (gm/dl)	0.047	0.88	0.383	
NLR	-0.417	-3.34	0.001**	
PLR	**0.437**	**5.77**	**0.000****	

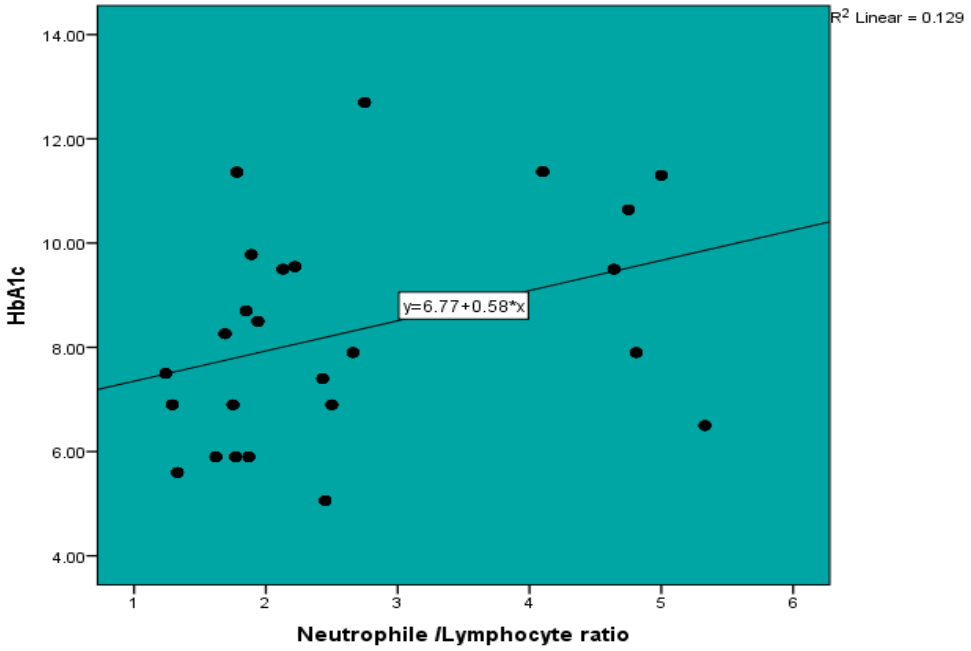

Figure (1): Scatter plot showing positive correlation between NLR and HbA1c in patients with Type II DM.

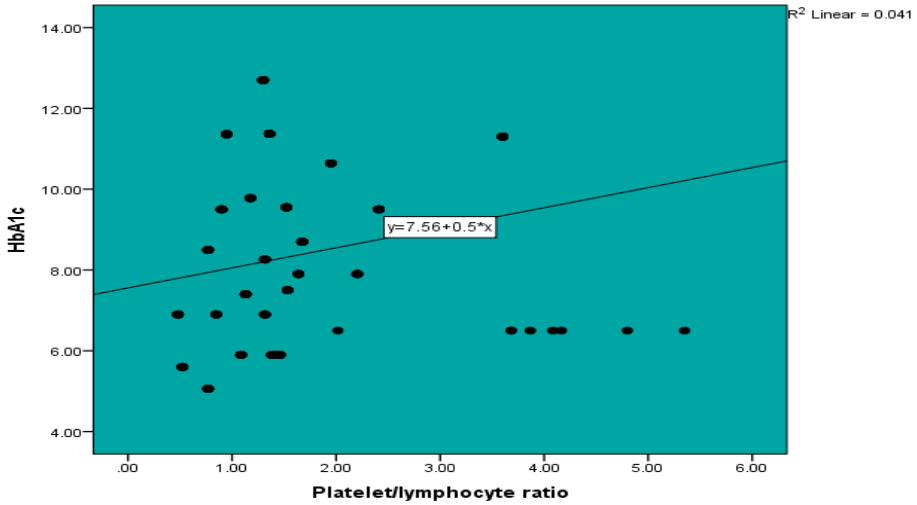

Figure (2): Scatter plot showing positive correlation between PLR and HbA1c in patients with Type II DM.

Discussion:

Many epidemiological studies have highlighted that chronic low grade inflammation is connected to diabetes mellitus [11]. In the current study, total leukocytic and neutrophilic counts were significantly higher in the group with uncontrolled DM. Previous studies showed similar results [7] & [12]. In diabetic patients, plasma cortisol, leptin and insulin are increased, contributing to neutrophilia observed in these patients. In addition, advanced glycation end products (AGEs), oxygen free radicals, and other cytokines may play a role in preparing the

neutrophils [13]. In mice with diabetes, hyperglycemia has been revealed to reduce neutrophils apoptosis, leading to impaired neutrophil clearance and prolonged inflammatory process [14]. In the present study, there was no significant difference in the lymphocytic count between controlled and uncontrolled groups. Similarly, one study stated that, no significant difference in the lymphocyte between controlled and uncontrolled diabetic patients [7]. However, another study found that lymphocytic count was significantly lower in uncontrolled diabetic patients [12]. One study declared that lymphocyte levels are lower in type 1 DM than in healthy individuals [15]. However, we also agree that lymphocyte levels in chronic inflammatory conditions should be increased [16]. In type 2 DM, lower lymphocyte levels were noted due to decreased proliferation [17] as a result of the lower levels of IL-2 receptor expression, the stimulator of lymphocyte proliferations [16] & [18]. In addition, Increased lymphocytes apoptosis has been stated in both rats with and in human being with diabetes [19]. In terms of NLR, it could be a significant marker of systemic inflammation as it is cost effective, readily available and could be measured easily [20]. In the current study, NLR was significantly higher in the uncontrolled group and there was a positive correlation between NLR and HbA1c. Other authors pointed that NLR was significantly higher in patients with higher HbA1c [7] & [12]. One study reported that NLR was correlated with the severity of glucose intolerance [21]. While, another study found no difference between NLR of controlled and uncontrolled diabetic patients [2]. It was mentioned that, higher HbA1c levels were associated to higher levels of inflammatory markers [22]. Beside this, one study demonstrated that patients with positive CRP were found to have elevated HbA1c values [23]. As previously known, elevated CRP levels, an inflammatory biomarker, is a predictor of development of type 2 diabetes and other metabolic syndromes [24].

Our study stated that micro-vascular and macro-vascular complications of diabetes had significantly higher NLR. Similar study found that, diabetic patients with complications had higher NLR than diabetics without complications [25]. Generally, levels of glycated hemoglobin (HbA1c) predict possible diabetic micro- and macrovascular diabetic complications [26] & [27]. Furthermore, NLR is not only an essential marker of systemic inflammation, but also, an indicator of increased risk for cardiovascular events in patients with metabolic syndrome [11] & [28]. Higher NLR is an independent predictor of major adverse cardiac events

(MACEs) in post myocardial infarction of diabetic patients [13]. Likewise, NLR is independently related to endothelial dysfunction and could predict cardiovascular end points independent of other ordinary risk factors in patients with moderate to severe chronic kidney disease (CKD) [29]. In the same way, the NLR of the patients with diabetic retinopathy (DR) [30], and acute limb ischemia [31] was higher than diabetic patients without these complications. Possible explanations of the higher NLR in complicated diabetic patients, firstly, higher levels of glucose stimulate the formation of AGEs which are formed through the non-enzymatic glycation and oxidation of proteins, lipids and nucleic acids [32]. AGEs excess is one of the most important mechanisms involved in the pathophysiology of diabetic vascular complications [33] through generation of reactive oxygen species (ROS) and activate inflammatory signalling cascades [34]. Secondly, it was emphasized that neutrophils in diabetes are activated then producing many inflammatory mediators, contributing to increased levels of oxidative stress, inflammation, necrosis and subsequently complications [13]. Thirdly, chronic hyperglycaemia also increases the release of reactive oxygen species from neutrophils [35]. Platelets and PLR were another marker of inflammation in our study, which were significantly higher in uncontrolled diabetic group. Platelets of diabetic patients are characterized by a greater platelet reactivity [36]. It was demonstrated that more activated platelets circulate in newly diagnosed type 1 DM patients [37]. While, one study showed no difference in PLR between those with HbA1c ≥7% and those with HbA1c <7% [2]. Similarly, another study revealed that there were no differences in platelet count between the controlled diabetic patients compared to that in the controlled group [38]. Our results can be explained by the nation that diabetes is closely related to inflammation. Higher platelet counts may reflect underlying inflammation as several inflammatory mediators stimulate megakaryocytic proliferation [23]. Our study stated that micro-vascular and macro-vascular complications of diabetes had significantly higher P/L ratio. Previous studies have proved that higher platelet and lower lymphocyte counts were linked with adverse cardiovascular outcomes [39]. Platelets can interact with different cell types of inflammatory cells [40]. High platelet counts can be associated with higher degree of antiplatelet drug resistance and greater tendency to form platelet rich thrombi on atherosclerotic plaques, leading to worse outcomes [41].

Conclusion:

The present study proposed that N/L& P/L ratios as markers of inflammation may be associated with poor blood glucose regulation in patients with type 2 DM. Furthermore, diabetic complications were associated with higher N/L & P/L ratios making it a potential marker of diabetic complications.

Limitations of the study:

No other conventional markers of inflammations were studied to clarify the role of these inflammatory markers in glycemic condition of diabetic populations. Future research with prospective design and healthy control subjects could provide more strong evidence on role of N/L & P/L ratios as a predictor of diabetes control and complications.

Abbreviations:

DM (diabetes mellitus).
IR (insulin resistance).
RBCs (red blood cells).
WBCs (white blood cells).
N/L (neutrophil-to-lymphocyte).
P/L (platelet-to-lymphocyte).
FBG (fasting blood glucose).
HbA1c (glycosylated hemoglobin).
ADA (American Diabetes Association).
VPT (Vibration Perception Threshold).
IHD (ischemic heart disease).
NLR (neutrophil lymphocyte ratio).
PLR (platelet lymphocyte ratio).
AGEs (advanced glycation end products).
CKD (chronic kidney disease).
DR (diabetic retinopathy).
ROS (reactive oxygen species).
SD (standard deviation).

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