Kufa Medical Journal | Vol. 20, No. 2, 2024

Original article | DOI: https://doi.org/10.36330/kmj.v20i2.17321

p-ISSN: 1993-517X

e-ISSN: 2709-4464

Evaluation of Some Haematological Inflammatory Parameters in Type 2 Diabetes Mellitus and its Relationship with Glycemic Control and Disease Complications

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ABSTRACT

Background*:** *Haematological inflammatory indices is a cheap, available and practical laboratory markers reflect the inflammatory process.* ***purpose*: to investigate the association between some haematolgical indices and diabetes control and complications in Iraqi diabetic patients.* ***Methods****: In a case-control study, 78 patients with a documented history of type 2 diabetes mellitus (T2DM) were recruited and matched in regard to age and sex with 57 non diabetic volunteers. RBS, HbA1c and CBP were analyzed.* ***Results****: diabetic patients had higher but non-significant increments in platelets, absolute neutrophil count, absolute lymphocyte count, Neutrophil Lymphocyte ratio (NLR), and Platelets Lymphocyte ratio (PLR) in comparison to controls. The mean platelets count was significant higher in patients with poor glycemic control in compared to patients with good glycemic control, (269.3 ± 16.53 vs. 206.33 ± 20.26) respectively, (P <0.001) while the NLR and PLR not associated with glycemic control. The studied hematological indices were associated but with no statistical significant with diabetic complications (P< 0.05).* ***Conclusion****: hematological parameters not associated with diabetes control or complications in Iraqi patients.*

Keywords: Complications, Haematological Parameters, Glycemic Control, T2DM.

Article Information

Received: August 18, 2024; Revised: November 27, 2024; Online December, 2024

INTRODUCTION

Type 2 diabetes mellitus is a chronic disease characterized by many metabolic and inflammatory changes that may lead to malfunction in erythrocytes, leukocytes, and platelets (1).The hematological alterations in diabetes can be attributed to many reasons, such as the generation of reactive oxygen species (ROS) and the development of advanced glycation end products(AGEs) due to prolonged hyperglycemia. An increase in reactive oxygen species (ROS) production can lead to oxidative stress, which can damage tissues and change blood chemistry by making red blood cells not work properly, platelets become too active, and endothelial cells not work properly (2). In diabetic individuals, alterations in blood chemistry can cause problems which include anemia and hypercoagulability, which in turn can increase the risk of cardiovascular disease (CVD). Additionally, diabetic patients are more likely to experience vascular problems due to

insulin resistance, which speeds up the onset of these problems and is linked to endothelial dysfunction, elevated inflammatory markers, and PLT hyperactivity (3).

Neutrophils are gaining recognition for their involvement in the development of diabetes, recent research in animal models has shown that neutrophils have the potential to infiltrate the pancreas of NOD mice at a young age. It has been shown that therapy with an anti-Ly6G antibody, which can effectively hinder the activities of neutrophils, may effectively prevent the development of insulitis and diabetes (4). Subsequent research revealed that CXCR2-expressing neutrophils may be recruited from the circulation to the pancreatic islets by pancreatic macrophages and β-cells, which generate the chemokines CXCL1 and CXCL2, suggesting a role of neutrophil activation in the onset and pathogenesis of the disease (5). Also, it has been shown that individuals with diabetes have platelets that are hyper-reactive to sub threshold stimuli and that they undergo fast consumption, which leads to increased thrombopoiesis of more reactive platelets. However, the relationship between metabolic syndrome and platelet function is not as well understood (6).

The NLR is a measure of the equilibrium between neutrophils, which promote inflammation, and lymphocytes, which have anti-inflammatory properties. On the other hand, the PLR indicates the interaction between platelets and lymphocytes. Researchers have looked into the link between NLR, PLR, and a number of disorders. Elevated values of NLR and PLR were able to predict the outcomes of cardiovascular disease, cancer, and chronic inflammatory disorders including diabetes (7). There are no many studies have done to evaluate the heamatological indices especially NLR and PLR as laboratory diagnostic indicators for monitoring diabetes and its accompanying complications; Understanding the possible link between NLR, PLR, and diabetic complications could give doctors useful information for figuring out who is at risk, finding issues early, and keeping them under control. In addition, targeted screening and treatment approaches may be developed if the underlying mechanisms connecting these ratios with the pathophysiology of diabetes can be explained (8), hence the present study come to investigate the possible link between some haematolgical indices and diabetes control and complications in Iraqi diabetic patients.

SPECIMENS' COLLECTION AND METHODS

A case-control study was involving a total of 135 individuals. The patient's group of 78 individuals diagnosed with Type 2 Diabetes Mellitus (T2DM) who are chronic visitors to the Specialist Centre for Diseases of Endocrine and Diabetes in Babylon. The patients ranged in age from 35 to 90 years. There were 37 females and 41 males. The control group consists of 57 randomly selected non-diabetic volunteers, with a mean age of 57.37 ± 9.16 years old, they match the patient group in regard to age, sex residence, and BMI. All controls were examined for fasting blood sugar and HbA1c to exclude diabetes.

Patients with complications were divided into either macrovascular (cardiovascular) or microvascular complications, including neuropathy, retinopathy, and nephropathy. The diagnosis of each complication depended on a physical examination by a specialist physician, relevant investigations, and medical reports. Patients with HbA1c ≥ 7 regarded as poor glycemic control, while those with HbA1c < 7 regarded as good glycemic control. Patients with a BMI ≥ 30 are classified as obese, and those <30 are classified as non-obese, according to the WHO classification. A volume of 4 ml were collected, 2 ml in gel tubes and 2 ml in tubes with anticoagulant (EDTA tubes) to measure RBS, HbA1c, and Complete blood count indices.

Approval of the Ethical Committee

The research was approved by the ethics committee at the University of Kufa's Faculty of

Medicine. All participants freely agreed to participate (informed consent), and the study also received authorization from the Institutional Review Board for Endocrine and Diabetes in Babylon.

Statistical analysis

Data analysis was performed using IBM SPSS Statistics version 26. Independent t-tests were employed to compare group means, while ANOVA tests were used to assess differences among the three study groups. Categorical variables were analyzed using bar graphs to describe frequency and mean values. Statistical significance was determined using a p-value of ≤ 0.001 and ≤ 0.05.

RESULTS

The mean of neutrophil count in patients with T2DM was slightly higher than the mean of neutrophil count in healthy control subjects with no significant difference, 5.06 ± 1.29 versus 4.63 ± 1.01 respectively, (P=0.23). Also the mean of lymphocyte count in patients with T2DM was non-significantly differ than the mean of neutrophil count in healthy control subject, 2.48 ± 0.87 versus 2.39 ± 0.61 respectively, (P=0.52).the mean of platelets count in patients with T2DM was a little higher than the mean of platelets count in healthy control subject, 266.87 ± 92.1 versus 260.33 ± 85.05 respectively, (P=0.68). Also the mean of neutrophil lymphocyte ratio in patients with T2DM was higher than the mean of neutrophil lymphocyte ratio in healthy control subject, 2.16 ± 0.11 versus 1.93 ±0.10 respectively, (P=0.15). Furthermore, the mean of platelet lymphocyte ratio in patients with T2DM was non-significantly higher than the mean of platelet lymphocyte ratio in healthy control subjects, 115.52 ± 26.8 versus 109.54 ± 24.25 respectively, (P=0.45). However, all the above differences were statistically not significant (p>0.05).

Table 2 showed that platelets count not affected by age groups, the mean of platelets count was significantly higher in female patients in compared to male patients (290.84 ± 17.37 vs 245.34 ± 14.17) respectively, (P = 0.04). But, the mean of platelets count was non-significantly associated with family history, smoking and duration of, (P> 0.05). Obese patients show higher levels of platelets count than non-obese patients (286.42± 16.39 vs. 248.30 ± 20.58) with no statistical difference p=0.9.

The current findings indicate that the average platelet count was significantly greater in patients with poor glycemic control compared to individuals with good glycemic control (269.3 ± 16.53 vs. 206.33 ± 20.26) respectively, (P <0.001), figure (1).A comparative analysis of platelet counts based on complications has been conducted, and the findings have been presented in a table (3). The present results show the mean of platelets count was higher in those patients suffer from cardiovascular and neuropathy in comparison to those who did not suffer from such complications but with no statistical difference, (P> 0.05). While the mean platelets count was higher in patients who didn't complain from retinopathy and nephropathy but again with no statistical differences p values were 0.2 & 0.5 respectively.

Figure 2 revealed that diabetic patients with poor control had high NLR than those with good control with no significant differences. Figure (3) reveal that diabetic patients with poor control had a non-significant increment in NLR than those with good control (116.23 vs. 96.33, p=0.7). Table (4) show that the mean of NLR was non-significant differences according to all characteristics, (P> 0.05). However, NLR was higher in obese patients than non-obese (2.38 ±

10.113 vs. 1.93 ± 0.51) with a significant difference p = 0Table (5) shows the mean of NLR was non-significant differences according to all complications, (P> 0.05). Table (6) shows the mean of PLR was non-significant differences according to all studied characteristics, (P> 0.05)**.**

Table (7) showed that the mean of PLR was higher in patients with cardiovascular and neuropathic complications but with no significant differences, (P> 0.05). on the other hand, those patients with no retinopathy and nephropathy show a little increase in PLR than those with such complications, but the associated increase was without statistical difference (p values 0.1 & 0.56 correspondingly.

Table (1): Hematological parameters in patients with T2DM and controls.

	Cases –control comparison		p-value
	Patient *n* = 78	Healthy control *n* = 58	
Neutrophil count (*103)			
Mean± SD	**5.06 ± 1.29**	**4.63 ± 1.01**	**0.23 † NS**
Range	**1.80 -14.90**	**1.10-11.50**	
lymphocyte count (*103)			
Mean ± SD	**2.48 ± 0.87**	**2.39 ± 0.61**	**0.52 † NS**
Range	**0.90 -4.50**	**1.20-4.00**	
Platelets counts			
Mean ± SD	**266.87 ± 92.1**	**260.33 ± 85.05**	**0.68 † NS**
Range	**96.00 -527.00**	**20.20-468.00**	
Neutrophil Lymphocyte ratio			
Mean ± SD	**2.16 ± 0.11**	**1.93 ±0.10**	**0.15 † NS**
Range	**0.80 -6.60**	**0.64-6.30**	
Platelet Lymphocyte ratio			
Mean ± SD	**115.52 ± 26.8**	**109.54 ± 24.25**	**0.45 † NS**
Range	**46.60 -273.60**	**10.60-270.00**	

n represents the number of cases, SD stands for standard deviation, † denotes an independent samples t-test, A refers to a one-way ANOVA test, and NS represents non-significance at P < 0.05.

Table (2): The mean of platelets count according to some characteristics.

Characteristics		N	Mean ± SD	*p*
Age groups	< 50 years	10	260.5 ± 20.91	0.64 A NS
	50-59 years	22	283.86 ± 24.48	
	≥ 60 years	46	260.13 ± 23.19	
Sex	Male	41	245.34 ± 14.17	0.04 † S
	Female	37	290.84 ± 17.37	
Family History	Positive	56	267.33± 13.57	0.94 † NS
	Negative	22	265.88 ± 20.35	
Smoking	Positive	21	267.14 ± 24.56	0.98 † NS
	Negative	57	266.73 ± 12.76	
Duration of disease	< 10 years	28	269.89 ±19.30	0.83 † NS
	≥ 10 years	50	265.08 ± 17.04	
BMI	None obese	40	248.30 ± 20.58	0.09 † NS
	Obese	38	286.42± 16.39	

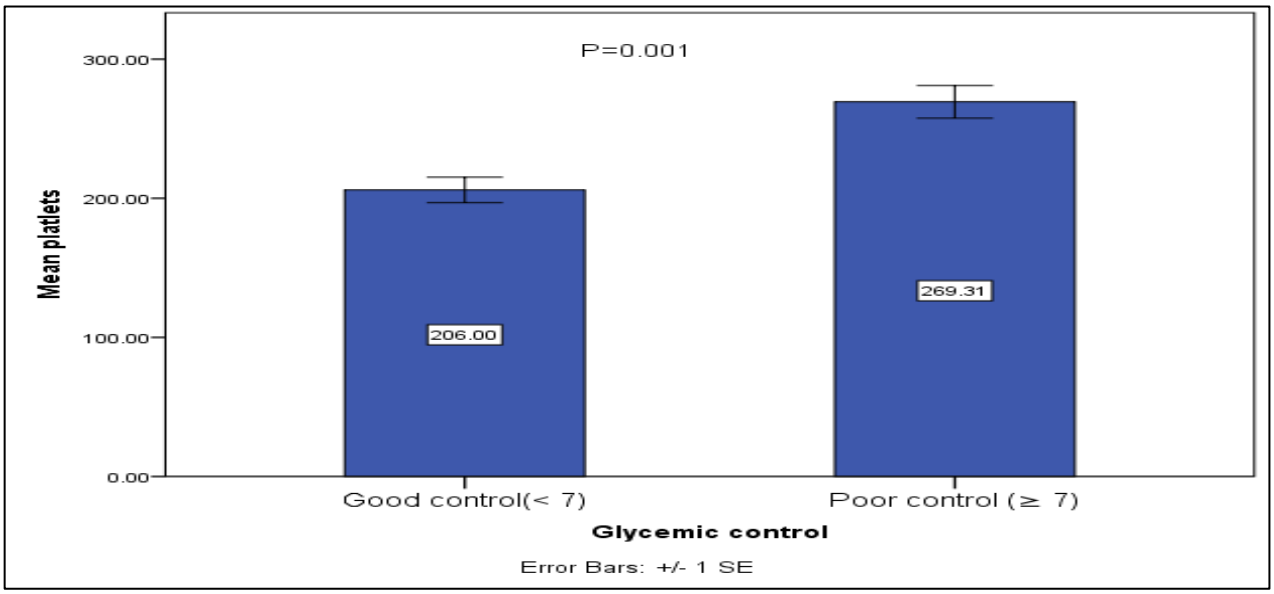

Figure (1): Mean platelets count according to glycemic control.

Table (3): The mean of platelets count according to the complications.

Characteristics		N	Mean ± SD	*P*
CVD	Present	46	268.67 ± 14.66	0.84 NS
	Absent	22	264.15 ± 18.08	
Neuropathy	Present	32	268.18 ± 18.67	0.92 NS
	Absent	46	265.95 ± 14.52	
Retinopathy	Present	13	240.0 ± 31.38	0.29 NS
	Absent	65	272.24 ± 12.06	
Nephropathy	Present	5	237.40 ± 42.02	0.49 NS
	Absent	73	268.89 ± 11.78	

Table (4): The mean of NLR according to some characteristics.

Characteristics		N	Mean ± SD	*P*
Age groups	< 50 years	10	2.39 ± 0.49	0.54 NS
	50-59 years	22	1.99 ± 0.18	
	≥ 60 years	46	2.2 ± 0.13	
Sex	Male	41	2.17 ± 0.18	0.98 NS
	Female	37	2.16 ± 0.12	
Family History	Positive	56	2.16± 0.12	0.94 NS
	Negative	22	2.18 ± 0.23	
Smoking	Positive	21	2.19 ± 0.30	0.91 NS
	Negative	57	2.16 ± 0.15	
Duration of disease	< 10 years	28	2.25 ±0.22	0.52 NS
	≥ 10 years	50	2.11 ± 0.17	
BMI	None obese	40	1.93 ± 0.51	0.05 S
	Obese	38	2.38 ± 0.11	

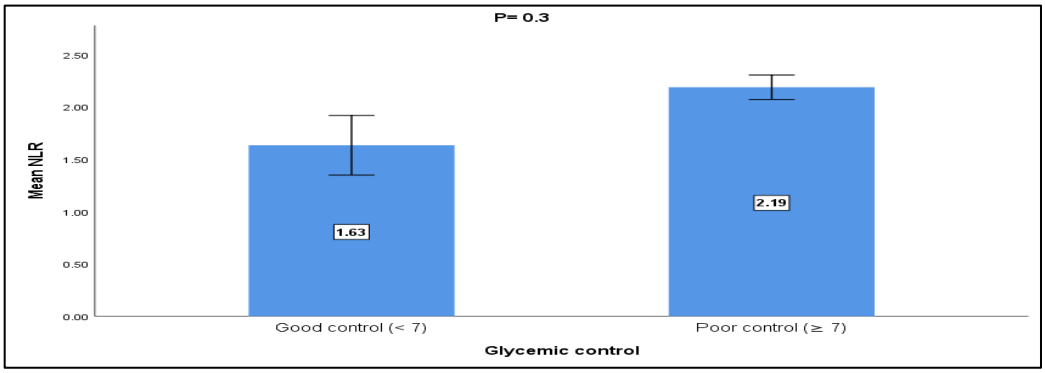

Figure 2: Mean NLR according to glycemic control.

Table (5): The mean of NLR according to the complications.

Characteristics		N	Mean ± SD	*P*
Macro vascular complications				
CVD	**Present**	**46**	**2.33 ± 0.21**	**0.08**
	Absent	**22**	**1.92 ± 0.15**	**NS**
Micro vascular complications				
Neuropathy	**Present**	**32**	**1.98 ± 0.18**	**0.17**
	Absent	**46**	**2.29 ± 0.14**	**NS**
Retinopathy	**Present**	**13**	**2.33 ± 0.31**	**0.29**
	Absent	**65**	**2.05 ± 0.11**	**NS**
Nephropathy	**Present**	**5**	**2.04 ± 0.30**	**0.77**
	Absent	**73**	**2.17 ± 0.18**	**NS**

Table (6): the means of PLR according to some characteristics

Characteristics		N	Mean ± SD	*P*
Age groups	**< 50 years**	**10**	**116.28 ± 15.16**	**0.96 A NS**
	50-59 years	**22**	**113.21 ± 7.76**	
	≥ 60 years	**46**	**116.46 ± 7.61**	
Sex	**Male**	**41**	**107.91 ± 6.85**	**0.13 † NS**
	Female	**37**	**123.96 ± 8.06**	

Characteristics		N	Mean ± SD	*P*
Family History	Positive	56	112.20± 9.98	0.32 † NS
	Negative	22	123.97 ± 10.89	
Smoking	Positive	21	99.93 ± 9.58	0.06 † NS
	Negative	57	121.46 ±6.20	
Duration of disease	< 10 years	28	113.55 ±8.10	0.74 † NS
	≥ 15 years	50	116.83 ± 9.24	
	Oral	49	115.60± 6.84	
	Both	8	97.92 ±7.21	
BMI	None obese	40	114.60 ± 8.79	0.91 † NS
	Obese	38	116.48 ± 7.62	

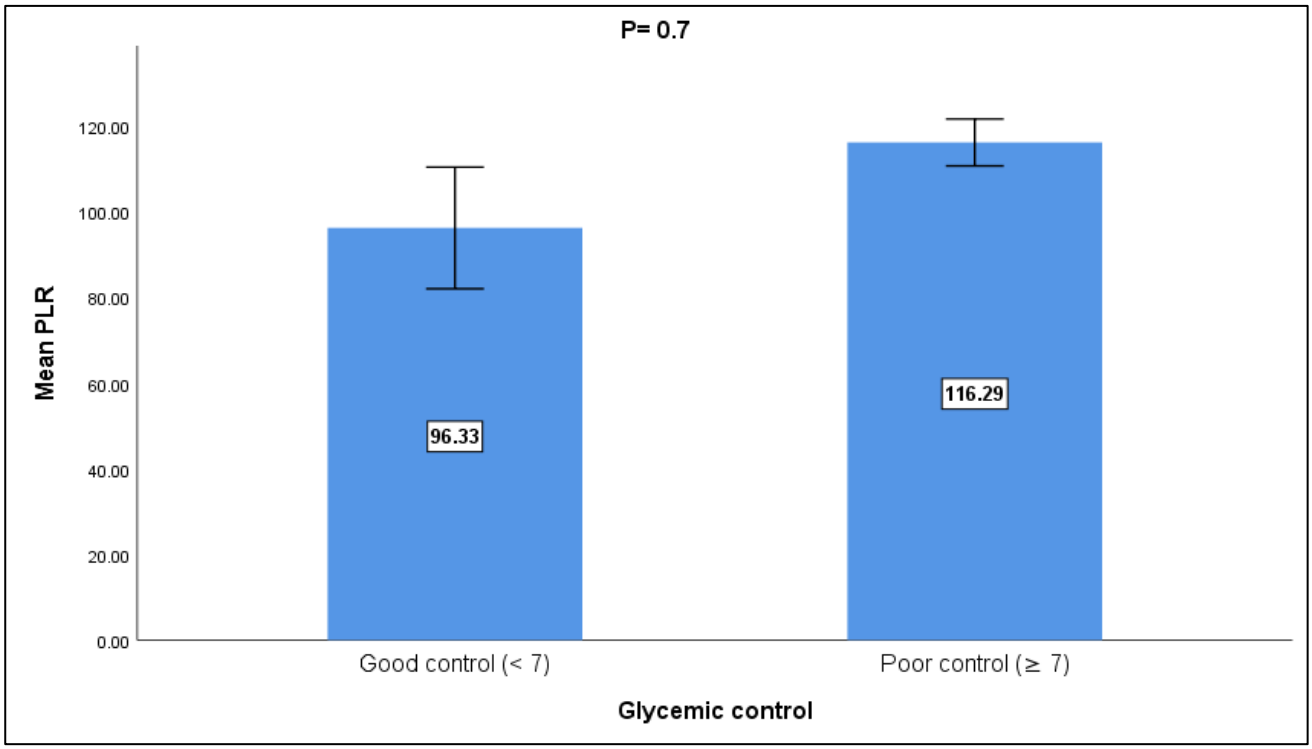

Figure 3: mean PLR according to glycemic control.

Table (7): The means of PLR according to the complications

Characteristics		N	Mean ± SD	*P*
Macro vascular complications				
CVD	**Present**	**46**	**118.78 ± 9.64**	**0.46 † NS**
	Absent	**22**	**110.84 ± 7.34**	
Micro vascular complications				
Neuropathy	**Present**	**32**	**116.93 ± 7.75**	**0.82 † NS**
	Absent	**46**	**114.54 ± 7.32**	
Retinopathy	**Present**	**13**	**131.32 ± 13.54**	**0.10 † NS**
	Absent	**65**	**115.94 ± 9.42**	
Nephropathy	**Present**	**5**	**104.52 ± 14.54**	**0.59 † NS**
	Absent	**73**	**116.76 ± 8.60**	

DISCUSSION

The present study analyzed some haematological parameters in diabetic patients and controls to shed light on the feasibility of using these parameters as indicators for diabetic control and predict complications. The results show that diabetic patients had higher but non-significant increments in platelets, absolute neutrophil count, absolute lymphocyte count, NLR and PLR in comparison to controls ($P > 0.05$). Many studies compared the above haematological indices in both diabetic and non-diabetic persons, and the results were conflicting and controversial among studies. In regard to platelet count Al Salhen & Mahmoud (9), also found no difference in platelet count between patients and controls, while Olana et al. (10) reported that diabetic patients had a higher platelet count. The increase in platelet count was a contributing factor in the action of neutrophils, which release stimulants such as S100A8 and A9, which activate thrombopoietin production from hepatocytes. This, in turn, leads to bone marrow being motivated to recruit more platelets (11).

Moreover, there is a data indicating that platelets derived from individuals with T2DM exhibit heightened responsiveness and baseline activation in comparison to those without the condition (12). Researchers conclude that the platelets of diabetic patients are bigger in size and contain very dense granules; In addition, they exhibit increased enzyme secretion compared to those without the condition, resulting in higher levels of prothrombotic factors such as thromboxane A2, platelet factor 4, serotonin, and P-selectin. These reasons mutually lead to a high propensity to thrombosis and atherosclerosis in diabetics (13). In regard to neutrophils and lymphocytes, Dik also reported non-significantly higher counts in

diabetics than non-diabetics(14) , in contrast to what was submitted by Arkew et al. who found a significantly higher neutrophil and lymphocyte count in diabetics(15). Neutrophils and lymphocytes are essential players in the inflammatory response, and as T2DM is documented to have an underling inflammatory mechanism, it's not strange to find a high level of WBC differential count due to stimulation of WBC maturation and differentiation by pro-inflammatory cytokines (16).

The study results showed non-significant increments in these indices between cases and controls; this goes with the studies of Al Salhen & Mahmoud, (9), Kizigul et al. (17), and Dik (14), while Olana et al. (10) reported a significant difference in regard to NLR but non-significant difference in PLR (p =0.02 vs. 0.67, respectively).

Calculation of NLR and PLR is based on subdivision of neutrophil numbers over lymphocyte numbers and division of platelet numbers over lymphocyte numbers, respectively, and because the previous (neutrophil, lymphocyte, and platelet) parameters were not significantly increased in patients, this could affect the results of ratios to be not significant. The current research tries to examine the links between platelet count, neutrophil-to-lymphocyte ratio (NLR), and platelet-to-lymphocyte ratio (PLR) and certain patient characteristics: Platelet count; Females exhibited a substantially greater platelet count compared to males ($p<0.045$). However, no significant correlations were found between platelet count and age, family history, smoking, or duration of illness.

The findings are consistent with the study conducted by Yun & Eun Kyeong(18), which observed a progressive rise in platelet count in women diagnosed with new-onset diabetes. Researchers attributed this high platelet activity to the supposition that claim women by insulin resistant more than men (19).

The study showed an increase in platelet count in obese people compared with non-obese people, but without statistical significance, and these results agree with what was found by Nada et al. (20) and Biadgo et al. (21) and disagree with the Nigerian study as platelet count and MPV were statistically correlated with high BMI. Such findings may be due to the fact that obesity is an aggravating factor for systemic inflammation that enhances platelet activation and the production of cytokine stimulation (22). Regarding NLR and PLR, the study showed no statistical significance in regard to age, sex, or duration of disease. The result agrees with Dascalu et al. (8) who reported no statistical significance between different diabetic patients with retinopathy with regard to age, sex, and other clinical characteristics.

The study showed no association between obesity and NLR and PLR, and the results agree with Jaaban et al. (13) and Yazaki et al. (23) while Yilmaz et al. (24) established high NLR in obese patients and assumed this ratio as a predictor for diabetes. Obesity is associated with subclinical inflammation because inflammatory cells infiltrate the adipose tissues, and the combined secretory action of adipocytes and inflammatory cells yields copious pro-inflammatory cytokines in the area of the adipose tissues, resulting in an increase in white blood cells and other inflammatory reactants (25).

In regard to the association of Hematological Parameters with Glycemic Control, the study find that, patients who have poor glycemic control have a greater platelet count than those who have good glycemic control ($p=0.001$), The results go with what detected by Kizigul et al. (17) while Nada (20) reported a negative correlation between platelet count and poor glycemic control. Also, NLR and PLR seem to be higher in those patients with poor glycemic control in comparison to those with good glycemic control but with p value > 0.05. The results are consistent with Dik (14), who reported such a non-significant association between HbA1c and hemological ratios. Results also agree with Prakash et al. (26) who found no

statistical difference between HbA1c levels and the haematological indices, while Nagabhushan & Geetha, (27) in a study with a larger sample size showed similar results but with a significant difference.

Persistent hyperglycemia in poor control patients leads to shortening the survival of lymphocytes and oxidative DNA damage, in addition to the low production of IL-2 that affects the number of lymphocytes and causes elevation in the NLR (28). The studied haematological parameters showed an increase in patients with different diabetic complications, but with no statistical significance. These results seem to agree and disagree with other studies that link the haematological parameter with complications and try to customize these simply measured and cost-effective indices as markers for predicting diabetic complications:

Some researchers demonstrated a link between NLR and coronary artery disease (29). The association between cardiovascular and haematological indicators may be linked to the development of endothelial dysfunction and hypertension in diabetes mellitus (2). The study conducted by Olana et al. (10) demonstrates a correlation between retinopathy and nephropathy but no such correlation with neuropathy. In contrast, a study found a positive link between neuropathy and both NLR and PLR(30). Neuropathy is caused by the effects of high blood sugar levels and the presence of TNF-α, these effects include the formation of small blood vessel lesions, increased blood vessel permeability, swelling, increased blood clotting, and then nerve damage. All of these events contribute to the development of neuropathy.

Zeng et al. (31) discovered no correlation between the severity of retinopathy and NLR, which contrasts with the findings of Dascalu et al. (8) who suggest that NLR may serve as a useful diagnostic tool for classifying diabetic patients with retinopathy.

The differences and controversy between the previous studies and the present study could be attributed to different numbers of patients, different study designs, and study participant heterogeneity; as some studies deal with patients with one type of complication while others, like the current study, may have had several types of complications to gather, and this may affect CBC analysis. Additionally, NLR and PLR are affected by heritable and non-heritable factors like sex, age, seasons, life habits, and co-existing illnesses, e.g., acute infection, haematological, and autoimmune disease; however, the current study excludes such conditions. Furthermore, technical approaches, including blood collection and handling, can affect CBC test results (32).

CONCLUSIONS

There were no statistically significant differences in hematological indices between individuals with diabetes and those without. Additionally, the studied hematological parameters were not associated with disease control or complications

Funding

There has been no receipt of funds.

Conflict of Interest

The authors declare no conflict of interest.

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