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RESEARCH ARTICLE

A STUDY OF THE PLATELET LYMPHOCYTE RATIO AS A PREDICTIVE MARKER OF PREDIABETES AND DIABETES MELLITUS AND ITS CORRELATION WITH HbA1c

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ABSTRACT

Introduction: Diabetes is a multifaceted metabolic disorder affecting the glucose status of the human body. Pathogenesis of type 2 diabetes mellitus is an inflammatory process. Chronic inflammation plays a central role in the development and progression of diabetes, and in the pathogenesis of its complications. The neutrophil-lymphocyte ratio (NLR) and platelet-lymphocyte ratio (PLR) are indicators of subclinical inflammation. This study was planned to find the association of platelet to lymphocyte ratio with diabetes as well as HbA1c in patients with type 2 diabetes mellitus. **Material and Methods:** The study was a hospital based descriptive cross-sectional study. The study population comprised of Prediabetic & Diabetes Mellitus Patients attending General Medicine OPD as well as admitted in these wards after approval from Institutional Ethical Committee and written informed consent was obtained from the participating patients. Similar age and sex matched healthy control were enrolled in the study. The sample size was calculated using open epi info software v. 3.0. Detailed history, examination and a group of tests CBC, DLC, ESR, CRP, Hb1Ac, Urine Routine was done. Calculation of Platelet lymphocyte ratio (PLR) in each study group. **Results:** In our study, 100 diabetic cases and 100 controls were evaluated. Out of 100 subjects, 17 were prediabetic and 83 were diabetics. Majority of study subjects had diabetes between 1-5 years (59%) followed by 6-10 years (19.3%) and 11-15years (12%). 08 (9.6%) subjects were having diabetes since >15 years. ESR, marker of inflammation was found to be raised in diabetic group with a mean value of 26.75±14.54 when compared to control (12.40±4.83) with a p value of <0.001. The PLR was calculated to be 122.43±12.89 in diabetic group and 106.81±10.12 in the control group, e.g., PLR was higher in patients with hyperglycemia and the result was statistically significant (p value <0.001). Mean NLR among diabetic cases was 2.24±0.77, while that in controls was lower (1.24±0.17). This difference was found to be statistically significant (p<0.001). There was moderate positive correlation between HbA1c and PLR (r value = 0.45; p value <0.001) & HbA1c and NLR (r value = 0.36; p value <0.001). There was moderate positive significant correlation between duration of diabetes and PLR (r value = 0.40; p value <0.001) & duration of diabetes and NLR (r value = 0.34; p value <0.001). **Conclusion:** In conclusion, increased PLR were found to be useful predictors of diabetes. As in earlier studies, NLR and PLR were found to be indicators of chronic inflammation in prediabetes and diabetes. A significant finding of this study is that the NLR and PLR values were significantly different between the cases and controls. If this finding is confirmed by future studies with larger series and different patient groups, NLR and PLR values can be used for the diagnosis of diabetes as a simpler and cost-effective alternative to HbA1c. In diabetic patients, NLR and PLR deterioration is associated with uncontrolled glycemic status, thereby increasing the importance of hemogram in during follow up of diabetic patients.

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INTRODUCTION

The prevalence of diabetes is rapidly rising all over the world.[1] The first WHO global report on diabetes published in 2016 demonstrates that the number of adults living with diabetes has almost quadrupled since 1980 to 422 million adults and this is expected to rise to 552 million by 2030. [2,3] Diabetes is a multifaceted metabolic disorder affecting the glucose status of the human body. Impaired glucose tolerance and hyperglycemia are the main clinical and diagnostic features and the result of an absolute or relative insulin deficiency or resistance to its action. It is the commonest metabolic disorder affecting the world population today.[4] Type 2 or maturity-onset diabetes is also linked to metabolic syndrome which comprises elevated triglyceride and uric acid levels, obesity, increased waist circumference with and without hypertension, and impaired fasting glucose.[5] Chronic hyperglycemia associated with diabetes can result in end organ dysfunction and failure which can involve the retina, kidneys, nerves, heart and blood vessels. [6] The clinical relationship between diabetes and atherosclerotic cardiovascular disease are well established, with the risk for cardiovascular disease (CVD) being significantly elevated in patients with diabetes. [7] Pathogenesis of type 2 diabetes mellitus is an inflammatory process.[8] There are many studies in the literature that point to an association between diabetes mellitus and inflammation. Many inflammatory markers are found to be related to DKD, such as I nterleukin-1 (IL1), IL6, IL8, transforming growth factor-beta 1 (TGF-β1), tumor necrosis factor-alpha (TNF-α), and cytokines. High cost, lack of availability, and difficulty in their assay standardization limit their use in routine clinical practice for this purpose.[9,10]Glycosylated hemoglobin (HbA1c) is often used to measure long-term glucose control in diabetic patients and is thought to be a predictor of the evolution of diabetic complications.[11] Elevated HbA1c is now considered as an independent risk factor for the development of diabetic complications in diabetic patients. Maintaining an HbA1c level below 7% significantly reduces the risk of developing diabetic complications as shown by the Diabetes complication and control trial (DCCT).[12]
Pradhan *et al.*[13]suggested that an increase in inflammatory markers such as CRP and interleukin-6 may predict the development of diabetes mellitus. In another study, authors concluded that chronic inflammation in Type 2 DM was associated with mortality risk.[14]Chronic complications from diabetes, in particular, have been linked to the inflammatory status of the patients.[15]Navarro *et al.*[16] showed that albuminuria was closely associated with inflammatory markers, including highly sensitive CRP and tumor necrosis factor-alpha. Total white blood cell (WBC) count is a crude but cheap, readily available, and sensitive indicator of inflammatory status; WBCs are positively associated with inflammation, particularly in cardiovascular diseases.[17] An increase in the number of neutrophils is associated with thrombus formation and ischemic injury.[18]

Research has shown that Platelet-to-lymphocyte ratio (PLR) and Neutrophil-lymphocyte count ratio (NLR) may be considered as novel markers of subclinical inflammation.[19] Leucocyte count and its subtypes are well-known markers of inflammation. Since the physiological response of the leucocytes in circulation against stress precipitates an increase in neutrophil count and decrease in the lymphocyte count, the ratio of these two sub-groups to one another is engaged in the intensive care practice. In various recent studies, Platelet-to-lymphocyte ratio (PLR) has been evaluated for its probable role in the inflammation periods and as prognostic factor of chronic diseases such as pancreatitis, acute coronary syndrome etc. It has been established in previous studies that various inflammatory markers like C-reactive protein (CRP), fibrinogen and leucocyte count increase in stable patients of T2DM and that this increase is associated with the negative results of the disease. The Platelet-to-lymphocyte ratio (PLR) has emerged as an informative marker revealing shifts in platelet and lymphocyte counts due to inflammatory and prothrombotic states. Several large observational studies have demonstrated the value of shifts in PLR in evaluating the severity of systemic inflammation and predicting infections and other comorbidities.

Also, it has been demonstrated as an independent risk factor for a DPN-related pathophysiological process named diabetic microangiopathy, which affects the nutrition supply of neuronal and Schwann cells, causes nerve degeneration, and eventually leads to peripheral neuropathy. [20] Unlike other inflammatory biomarkers e.g., ESR and CRP, the Platelet-lymphocyte ratio (PLR) is derived from routine complete blood count (CBC) tests. It does not need a special request. It is a rapid, easy and cost-effective method. This study was planned to find the association of platelet to lymphocyte ratio with diabetes as well as HbA1c in patients with type 2 diabetes mellitus. This study will not only generate useful information regarding blood glucose regulation and complications arising due to poor control, but it will also help in developing new strategies in the treatment plan and patient education for better control of complications in diabetic patients

MATERIALS AND METHODS

STUDY DESIGN: The study was a hospital based descriptive cross-sectional study.

STUDY AREA: The study was carried out in the department of General medicine and endocrinology, R N T Medical College and attached group of hospitals, Udaipur (Rajasthan).

STUDY PERIOD: The study was carried out over a period of 19 months from June 2021 to December 2022.

STUDY POPULATION: The study population comprised of Prediabetic & Diabetes Mellitus Patients attending General Medicine and endocrinology OPD as well as admitted in these wards after taking informed consent. Similar age and sex matched healthy control were enrolled in the study.

INCLUSION CRITERIA

- Prediabetic and Diabetes Mellitus Patients as well as Normoglycemic subjects were included in study.
- Age > 18 years, who gave written consent.

EXCLUSION CRITERIA

- Severely ill patients with altered sensorium or mental illness
- Patients who have Established source of infection / Sepsis
- Patients who have Allergic reactions
- Patients with Malignancy
- Patients on Drugs such as corticosteroids, lithium, heparin, antiepileptic drugs
- Patients with CVA
- Pregnant Patients
- Patients with Pancytopenia
- Patient who known case of Platelet disorder

STUDY METHOD

The sample size was calculated using open epi info software v. 3.0. The sample size obtained is 196. This sample size was rounded off to 200 subjects for ease of calculation.

Application of Inclusion / Exclusion Criteria

- Normoglycemic - FBS < 100 mg/dl
- Prediabetic - FBS: 100 - 125 mg/dl

PPBS: 140 - 199 mg/dl
HbA1c: 5.7 - 6.4

- Diabetic – FBS: >126

PPBS: ≥ 200
HbA1c: ≥6.5

Detailed history, examination and a group of tests CBC, DLC, ESR, CRP, Hb1Ac, Urine Routine was done. Calculation of Platelet lymphocyte ratio (PLR) in each study group. Then, PLR and NLR were jolted down for all the subjects under the study.
Relevant observation was reported.

OBSERVATIONS AND RESULTS

Present study was a hospital based descriptive cross-sectional study done in 100 Prediabetic & Diabetes Mellitus Patients attending General medicine and endocrinology OPD as well as admitted in these wards after taking informed consent. 100 healthy Control were enrolled in the study. Finding of study are as follows:

Table 1. Age wise distribution of study subjects

Age (in years)	Diabetic group (n=100)		Control group (n=100)	
	No.	%	No.	%
<40 years	2	2.0	2	2.0
40-49 years	60	60.0	74	74.0
50-59 years	24	24.0	14	14.0
≥60 years	14	14.0	10	10.0

Most of the cases in diabetes group (60%) as well as control group (74%) were within the age group of 40-49 years of age followed by 50-59 years.

Table 2. Comparison of Mean age between both group

	Diabetic group (n=100)		Control group (n=100)		P value
	Mean	SD	Mean	SD	
Age in years	50.67	7.69	48.50	7.04	0.04

Mean age of diabetic patients was 50.67±7.69 years while mean age of control group was 48.50±7.04 years. Mean age was significantly higher in diabetics compared to control group.

Table 3. Distribution of study subjects according to prediabetes and diabetes

	Diabetic group (n=100)	
	No.	%
Prediabetes	17	17.0
Diabetes	83	83.0

Out of 100 subjects, 17 were prediabetic and 83 were diabetics.

Table 4. Duration of DM in diabetic patients

Duration of DM	Diabetic group (n=83)	
	No.	%
Upto5 years	49	59.0
6-10 years	16	19.3
11-15 years	10	12.0
>15 years	8	9.6

Majority of study subjects had diabetes between 1-5 years (59%) followed by 6-10 years (19.3%). 8 (9.6%) subjects were having diabetes since >15 years.

Table 5. Comparison of Mean HbA1c between pre-diabetes and diabetes group

	Pre-diabetes		**Diabetes**		
	Mean	**SD**	**Mean**	**SD**	**P value**
HbA1c (%)	5.91	0.30	7.56	0.54	<0.001

Above table shows a comparison of glycosylated hemoglobin among prediabetes and diabetes group.

The mean HbA1C was 5.91±0.30 in prediabetes and 7.56±0.54 in diabetes group and this difference was found to be statistically significant with a p value of less than 0.001.

Table 6. Comparison of Mean ESR between diabetes and control group

	Diabetic group (n=100)		Control group (n=100)		P value
	Mean	SD	Mean	SD	
ESR	26.75	14.54	12.40	4.83	<0.001

The above table shows the mean ESR among study population. ESR, marker of inflammation was found to be raised in diabetic group with a mean value of 26.75±14.54 when compared to control (12.40±4.83) with a p value of <0.001.

Table 7. Comparison of Mean ESR between pre-diabetes and diabetes group

	Pre-diabetes		Diabetes		P value
	Mean	SD	Mean	SD	
ESR	16.53	3.85	29.17	13.39	<0.001

ESR was found to be raised in diabetic group with a mean value of 29.17±13.39 when compared to pre-diabetes group (16.53±3.85) with a p value of <0.001.

Table 8. Comparison of Mean PLR& NLR between diabetes and control group

	Diabetic group (n=100)		**Control group (n=100)**		**P value**
	Mean	**SD**	**Mean**	**SD**	
PLR	122.43	12.89	106.81	10.12	<0.001
NLR	2.24	0.77	1.24	0.17	<0.001

The PLR was calculated to be 122.43±12.89 in diabetic group and 106.81±10.12 in the control group, e.g., PLR was higher in patients with hyperglycemia and the result was statistically significant (p value <0.001). Above table shows that the mean NLR among diabetic cases was 2.24±0.77, while that in controls was lower (1.24±0.17). This difference was found to be statistically significant (p<0.001).

Table 9. Comparison of Mean PLR& NLR between pre-diabetes and diabetes group

	Pre-diabetes		**Diabetes**		
	Mean	**SD**	**Mean**	**SD**	**P value**
PLR	115.03	11.58	123.94	12.68	<0.001
NLR	1.78	0.50	2.33	0.78	<0.001

The mean PLR was 123.4±12.68 in diabetic group and 115.03±11.58 in the pre-diabetes group, e.g., PLR was higher in patients with diabetes group compared to pre-diabetes group and the result was statistically significant (p value <0.001). Above table shows that the mean NLR among diabetic cases was 2.33±0.78, while that in pre-diabetes group was lower (1.78±0.50). This difference was found to be statistically significant (p<0.001).

Table 10. Association of PLR with duration of diabetes mellitus

Duration of DM	**N**	**Mean**	**SD**	**P value**
Upto 5 years	49	120.392	10.272	<0.001
6-10 years	16	124.526	15.927	
11-15 years	10	130.150	7.908	
>15 years	8	136.82	14.311	

Above tables shows association of PLR with duration of diabetes mellitus. As the duration of DM increase mean PLR was also increased. This association was found statistically significant (p value <0.001).

Table 11. Association of NLR with duration of diabetes mellitus

Duration of DM	N	Mean	SD	P value
Upto 5 years	49	1.9403	0.6729	<0.001
6-10 years	16	2.216	0.757	
11-15 years	10	3.233	0.313	
>15 years	8	3.311	0.672	

Above tables shows association of NLR with duration of diabetes mellitus. As the duration of DM increase mean NLR was also increased. This association was found statistically significant (p value <0.001).

Table 12. Correlation of PLR & NLR with HbA1c

	HbA1c	
	r value	p value
PLR	0.457	<0.001
NLR	0.367	<0.001

There was moderate positive correlation between HbA1c and PLR (r value = 0.45; p value <0.001) & HbA1c and NLR (r value = 0.36; p value <0.001).

Table 13. Correlation of PLR & NLR with duration of diabetes

	Duration of diabetes	
	r value	p value
PLR	0.40	<0.001
NLR	0.34	<0.001

There was moderate positive significant correlation between duration of diabetes and PLR (r value = 0.40; p value <0.001) & duration of diabetes and NLR (r value = 0.34; p value <0.001).

Table 14. Correlation of NLR with different parameters

	r value	p value
ESR	0.62	<0.001

There was moderate positive significant correlation between ESR and NLR (r value = 0.62; p value <0.001).

Table 15. Correlation of PLR with different parameters

	r value	p value
ESR	0.56	<0.001

There was moderate positive significant correlation between ESR and PLR (r value = 0.56; p value <0.001).

DISCUSSION

Present study was a hospital based descriptive cross-sectional study done in 100 Prediabetic & Diabetes Mellitus Patients attending General medicine OPD as well as admitted in these wards after taking informed consent. 100 healthy Control were enrolled in the study. The study was aimed to know the role of Platelet Lymphocyte Ratio as Predictive Marker of Prediabetes and Diabetes Mellitus and its correlation with HbA1c. Out of 100 subjects, 17 were prediabetic and 83 were diabetics. Majority of study subjects had diabetes between 1-5 years (59%) followed by 6-10 years (19.3%) and 11-15years (12%). 08 (9.6%) subjects were having diabetes since >15 years. ESR, marker of inflammation was found to be raised in diabetic group with a mean value of 26.75±14.54 when compared to control (12.40±4.83) with a p value of <0.001. In our study, there was moderate positive significant correlation between ESR and NLR (r value = 0.62; p value <0.001) & moderate positive significant correlation between ESR and PLR (r value = 0.56; p value <0.001). In study by Atak B *et al*[21], PLR was significantly and positively correlated with CRP (p=0.003, r=0.30 level. Safak Ozer Balın [22] studied the predictive role of haematological parameters in the diagnosis of osteoarticular brucellosis. The correlation coefficients of the NLR with the ESR and CRP (r) were 0.243 (P = 0.043) and 0.258 (P = 0.031), respectively. Additionally, the correlation coefficients of the PLR with the ESR and CRP (r) were 0.342 (P = 0.004) and 0.334 (P = 0.005), respectively, in accordance with the Spearman analysis. These results were significant. In present study, the mean PLR was calculated to be 122.43±12.89 in diabetic group and 106.81±10.12 in the control group, e.g., PLR was higher in patients with hyperglycaemia and the result was statistically significant (p value <0.001). The mean PLR was 123.4±12.68 in diabetic group and 115.03±11.58 in the pre-diabetes group, e.g., PLR was higher in patients with diabetes group compared to pre-diabetes group and the result was statistically significant (p value <0.001). According to study by Mertoglu C *et al*.[23] PLR was significantly lower in patients with impaired glucose tolerance (90.35±44.34) and newly diagnosed diabetics (86.38±45.24) compared to normoglycemic patients (100.55±48.18) but significantly higher in known case of diabetics (124.45±37.43). PLR significantly decreases in prediabetes and early stages of diabetes but increases in later stages. PLR values may be reliable predictive markers in prediabetes and diabetes mellitus. Finding of our study were also collaborated with study by Atak B *et al*[21] who also reported increased PLR in diabetic group [122 (44-472)] compared to control group [94 (48-170)]. Similarly, in study by Nagabhushan BK *et al*[24], the average PLR in poorly controlled diabetics was 122.3 and, in well-controlled diabetics, it was 105.7. In contrast to our study Dik Y *et al*[25] found that PLR value was 145.9 and 146.7 in diabetic group and healthy group, respectively, and we did not find any significant relationship (p = 0.97). Elevated PLR in patients with type 2 diabetes mellitus may be a reflection of the underlying inflammatory burden of the disease. As HbA1c worsens due to poor diabetes control, underlying chronic low-grade inflammatory status intensifies and thus, inflammatory markers, including PLR, increase. Mean NLR among diabetic cases was 2.24±0.77, while that in controls was lower (1.24±0.17). This difference was found to be statistically significant (p<0.001). There was moderate positive correlation between HbA1c and PLR (r value = 0.45; p value <0.001) & HbA1c and NLR (r value = 0.36; p value <0.001). There was moderate positive significant correlation between duration of diabetes and PLR (r value = 0.40; p value <0.001) & duration of diabetes and NLR (r value = 0.34; p value <0.001). There was moderate positive significant correlation between ESR and NLR (r value = 0.62; p value <0.001.There was moderate positive significant correlation between ESR and PLR (r value = 0.56; p value <0.001.

CONCLUSION

The study entitled "A study of the platelet lymphocyte ratio as a predictive marker of prediabetes and diabetes mellitus and its correlation with HbA1C" was done to understand and know the role of PLR as a marker to predict about diabetes mellitus. In conclusion, increased PLR were found to be useful predictors of diabetes. As in earlier studies, NLR and PLR were found to be indicators of chronic inflammation in prediabetes and diabetes. A significant finding of this study is that the NLR and PLR values were significantly different between the cases and controls. If this finding is confirmed by future studies with larger series and different patient groups, NLR and PLR values can be used for the diagnosis of diabetes as a simpler and cost-effective alternative to HbA1c. In diabetic patients, NLR and PLR deterioration is associated with uncontrolled glycemic status, thereby increasing the importance of hemogram in during follow up of diabetic patients. Moreover, NLR & PLR can be used as a population screening, disease and drug monitoring tool on large scale basis. NLR & PLR can be used as marker of diabetic control in addition to HbA1c in type 2 diabetic subjects.

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