Original Article

MEAN PLATELET VOLUME TO LYMPHOCYTE RATIO AS AN EARLY INDICATOR OF DIABETIC NEPHROPATHY

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ABSTRACT

Objective: To predict the risk of diabetic nephropathy in patients with type 2 Diabetes Mellitus using Mean platelet volume to lymphocyte ratio (MPVLR) and comparison with diabetics without nephropathy.

Material and Methods: This Cross-sectional study was conducted at Chughtai Institute of Pathology, in Lahore, Pakistan from July to December 2021. 100 Patients with type 2 Diabetes mellitus were included. Two groups were made based on the urinary microalbumin/creatinine ratio: diabetic nephropathy and non-nephropathy group. MPVLR derived by dividing MPV to total lymphocyte count.

Results: There were a total of 100 subjects. Mean age of patients of group A was 45.99±13.42 years while mean age of patients of group B was 41.87±14.65 years and p-value 0.105. 75.2% patients of group A were female while 82.1% patients of group B were female (p-value 0.185). The MPVLR of group A was 45.51±8.32 while of group B was 70.33±13.40 (p-value 0.001). The best cut-off value for MPVLR when compared with those of group B indicated a P value that is evident and in relation to that given in literature proving the hypothesis.

Conclusion: The MPVLR is an easily calculated and efficient index and higher values indicate inflammation. It may be considered an independent and reliable predictor of diabetic nephropathy. We suggest, it can be a useful complement to standard tests in labeling diabetic nephropathy.

Key Words: HBA1C, Diabetic nephropathy, Platelet indices, Mean platelet volume to lymphocyte ratio

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INTRODUCTION

One of the primary contributors to the strain on the healthcare system is diabetes mellitus. According to research from the World Diabetes Federation, there will be 439 million diabetics over the age of twenty in 2030, up from 285 million in 2010. Thus, one of the most significant medical issues soon will be target organ problems owing to diabetes, particularly micro and macro vascular abnormalities. It has a connection to mild inflammatory responses [4]. Activation of innate immune and the inflammatory response plays a key role in the development and remodeling of diabetes. In addition to insulin resistance and hyperglycemia, several inflammatory chemicals, chemokines, and pro-inflammatory cytokines, such as Interleukin-1, play an integral role in the development of microvascular complications of diabetes, including nephropathy [1].

HbA1c, which is a measure of glycosylated hemoglobin, shows glycemic management. The control and outcome of the disease are worse with the higher HbA1C level [4]. The inflammatory background is exaggerated by hyperglycemia, which leads to the development of diabetic complications. Leucocytes and activated platelets have a part in the development of these complications during the course of the disease [6]. These indicators have been linked to inflammatory disorders, according to research [4]. Hence, a routine complete blood count contributes to the prediction of illness development and problems [5].

One such indicator is mean platelet volume (MPV), which measures platelet activation and an increase in size of response to an inflammatory stimulus. It exhibits a high inflammatory burden on the body and is a well-known marker of both pro-inflammatory and pro-thrombotic situations [2,6]. In patients with microvascular and macrovascular problems, MPV is an independent predictor of mortality, illness progression, and hospitalization [5]. Instead of changes in platelet count, changes in mean platelet volume appear to be more important for haemostasis [3]. Serial complete blood counts can help forecast the progression and complications of microvascular and macrovascular diseases by measuring platelet activation markers such mean

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platelet volume (MPV), platelet- lymphocyte ratio (PLR), and mean platelet volume to lymphocyte ratio (MPVLR) p [5].

Due to chronic inflammation and endothelial dysfunction, a rise in the ratio of mean platelet volume (MPV) to absolute lymphocyte count (ALC) is linked to an increase in microalbuminuria [1].

MATERIAL AND METHODS

After receiving approval from the institute's institutional review board,this study was carried out. A cross- sectional investigation was conducted at Chughtai Institute of pathology, on 100 patients. Using a lottery system, participants with type 2 diabetes mellitus (T2DM) considered by getting {HbA1C >6.5%} were separated into two groups and included in the study. Patients in group (A) had nephropathy due to diabetes, but those in group (B) did not. Cutoff vale for establishing diabetic nephropathy was considered as ACR > 3.5mg/mmole. Group (A) patients had HbA1C > 6.5% and ACR < 3.5mg/mmole while HbA1C and ACR of group (B) patients were >6.5% and >3.5mg/mmole, respectively. Patients with Chronic kidney disease because of any other cause and patients on dialysis for end stage renal disease were excluded from this study. Their genders and ages were recorded. Absolute lymphocyte count (ALC), mean platelet count (MPV), glycosylated haemoglobin level (HbA1C), and albumin/creatinine ratio in spot urine (ACR) were recorded. For MPV and ALC Sysmex XN-9000 analyzer was used. MPV was divided by ALC to obtain MPVLR, which was also noted. The patients were split into groups with and without renal microvascular dysfunction based on urine albumin/creatinine ratio.

The IBM Statistics 25.0 (SPSS) statistics package tool was used to statistically analyze the data. Statistics were presented using descriptive analysis, with mean, standard deviation, and median (IQR). Kolmogorov- Smirnov tests were used to assess whether continuous variables' normal distribution was correct. The Mann- Whitney U-test was used to compare the medians of non-normally distributed data for the various groups. The means of the normally distributed data were evaluated using the t-test. To predict diabetic nephropathy, receiver-operating characteristic (ROC) curve analyses were done on MPVLR (MPV for comparison) cut-off values, area under the curve (AUC), sensitivity, and specificity. Correlation analysis conducted by Pearson correlation test. Statistical significance was accepted as $p < 0.05$.

RESULTS

The data collected when analyzed showed co-relation to the literature and proved the initial hypothesis.

There was a total of 100 subjects. Mean age of patients included in this project was 55.22±12.28 years. Similarly, mean values of HbA1C, ACR, MPV, ALC and MPVLR were 9.74±8.2, 282.9±630, 10.63±1.55, 2.80±0.972 and 4.41±2.47 respectively. There was no statistical difference between the 2 groups as far age factor is concerned (p-value 0.105). (Table-I).

The MPVLR of group A, when compared with group B was evident with a positive predictive Value of P as shown in table (Table-II). There was a significant difference in the ACR and MPVLR among the two study groups i.e, diabetics with nephropathy and diabetics without nephropathy ($p < 0.05$).

However, no significant difference was observed in the mean values of MPV and ALC between the two groups ($p > 0.05$).

An ROC curve analysis was used to determine platelet activity parameters (MPVLR and MPV) in determining diabetic nephropathy (Figure 1). The best cut-off value for MPVLR was “3.75” (AUC 0.82, $p<0.01$) and for MPV was “9.95” (AUC 0.59).

According to ROC analysis, MPVLR predicted diabetic nephropathy with 76% sensitivity and 80% specificity. MPVLR is more sensitive and specific than MPV (which is 68% sensitive and 42% specific), in predicting diabetic nephropathy.

Table-I: Mean values along-with standard deviation of study variables.

	N	Mean	Std Deviation
Age	100	55.22	12.288
HbA1C (%)	100	9.74	8.210
ACR	100	282.97	630.360
MPV	100	10.63	1.557
ALC	100	2.80	.972
MPVLR	100	4.41	2.472

Table-II: Independent sample T-Test showing p-value between study groups.

Study variables	P-value
ACR	<0.001
MPV	0.854
ALC	0.079
MPVLR	0.002

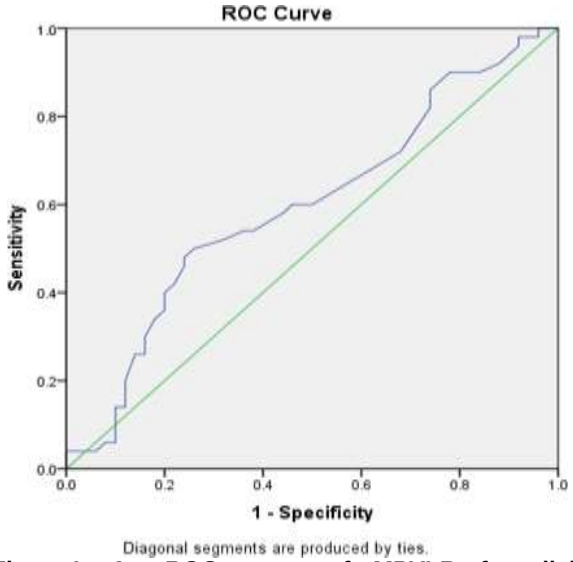

Figure-I: An ROC curve of MPVLR for diabetic nephropathy.

DISCUSSION

A complete inflammatory response is mostly mediated by lymphocytes, and a decreased lymphocyte count may result in increased inflammatory damage. According to reports, MPVLR displays inflammatory pathway activation. As these mediators promote megakaryocytic proliferation in the bone marrow and cause a relative rise in platelet count (thrombocytosis), an increase in platelet count implies underlying inflammation [6]. Yet, compared to platelet count, platelet size and volume rise more accurately depict platelet activity [2,3]. MPVLR, which was determined using MPV rather than the Platelet count in Platelet lymphocyte ratio (PLR), was a more distinct indicator of platelet activity than PLR [1,3]. Recent researches show that, poor prognosis has been observed to be predicted by elevated MPVLR levels at the time of admission in diabetic people with myocardial infarction [1,2]. Podocyte destruction appears in chronic renal failure at a reasonably young stage. According to reports, podocyte destruction is the likely cause of this proteinuria in diabetic nephropathy [2]. In diabetic people with nephropathy, inflammatory cytokines and acute phase reactants are markedly increased [3].

Experimental and clinical trials claimed that inflammation was a key component in the process of diabetic nephropathy [1,2]. According to a study, excessive inflammatory mediator production helps in worsening of diabetic nephropathy [2].

The association of Neutrophil-to-Lymphocyte ratio (NLR) and Platelet-to-lymphocyte (PLR) ration as the determinants of inflammation has been evident in the literature although recent studies have also demonstrated the relation of diabetic nephropathy, NLR, and PLR as inflammatory markers with thickness of epicardial adipose tissues. Akbas and fellows empirically concluded that calculation of Hematology parameters as NLR and PLR are used to predict nephropathy [11].

Similarly, the correlation of inflammation and Mean Platelet volume has also been elaborated in the study conducted by wolkite university [12]. They concluded that there is a significant difference in the MPV between Diabetics and Healthy Controls. It is quite evident that MPV can be taken as a good hematological marker for differentiation between Diabetes Mellitus-metabolic syndrome comorbidity from healthy controls.

Archana (*et al*) [13] also found an increased MPV and PDW in the high risk patients i.e. diabetics with microvascular complications. This states that an increased MPV and PDW can be considered as early biomarkers for detection of imminent complication. They established that an increase in platelet indices were more highlighted in microvascular complications as compared to the macrovascular complications of Diabetes Mellitus.

Increase in platelet volume indices and platelet size show activation of platelets and it contributes to the pro-thrombotic and hypercoagulable state in diabetes mellitus. Because larger platelets are more activated hemostatically, therefore it probably increases a risk of developing diabetic vascular complications. Similarly, Shilpi and Potekar [14] suggested that these activated Platelets with large size could be easily highlighted during any routine hematological analysis as MPV, PDW and P-LCR. Hence, these biomarkers were useful in risk prediction and as prognosis indicator of vascular complications in diabetes.

In healthy individuals, the increased platelet count, via feedback inhibition, leads to decrease in Thrombopoietin production from the liver and in

response causes platelet release from bone marrow megakaryocytes, to maintain constant peripheral platelet count.

However, in patients with ongoing inflammation, there is an increase in concentration of proinflammatory cytokines, especially IL-6. It can lead to increased platelet release. This is associated with the stimulation of thrombopoietin generation by IL-6 and with a direct effect of this cytokine on megakaryocytes. This IL-6 causes an increase in the ploidy and number of megakaryocytic nuclei and increases cytoplasm volume, which in return produces large number of bloods platelets. Platelets with altered morphology, metabolism, and function were found in diabetic patients and high platelet reactivity is the prime cause for increase in risk and worse outcome in the diabetics. Aleksenndra and colleagues [15] reported that there was an elevation in MPV in diabetics and subjects with an impaired fasting glucose level as compared to non-diabetics.

Increased MPV and the number of glycoprotein receptors on platelets of diabetes patients indicate that the process of thrombopoiesis is modified in these patients and this may occur at the beginning of diabetes, when no overt complications and symptoms are noticed.

Mahta Abbasi and others [16] suggested that inflammation has been reported in the pathogenesis of Gestational diabetes Mellitus (GDM). The inflammatory milieu in GDM suggests that two cytokines were increased, being interleukin-6 (IL-6) and tumor necrosis factor-α (TNF- α). An increase in platelet indices (MPV, PCT, PLR) on a routine CBC in second trimester may predict inflammation on the background of diabetes mellitus.

Scientists discovered that the pathophysiology of diabetes and associated microvascular consequences, including diabetic nephropathy, involves ongoing, low- grade inflammation and immune cell activation [2,3]. In addition, Lim *et al*. hypothesized that decreasing inflammation in diabetic nephropathy would represent a feasible therapeutic approach for the illness's management [5].

As MPVLR was considerably greater in patients with diabetic nephropathy than in diabetics without nephropathy, the present study confirmed the relationship between diabetic nephropathy and MPVLR as has been previously reported in the literature.

CONCLUSION

Higher values of the MPVLR, an efficient and simple to calculate index, suggest inflammation. It could be regarded as a valid and independent predictor of diabetic nephropathy in diabetic patients. We contend that it may serve as a helpful addition to established parameters for identifying diabetic nephropathy.

LIMITATIONS

This is a single center study and data are based on the history and lab investigations of the patients, as the patients were not followed up**.**

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CONFLICT OF INTEREST

None

AUTHOR CONTRIBUTION

Ashja Saleem: Article writing, Data collection, Literature search, Statistical analysis.
Nimrah Ishaque: Data collection, Literature search
Ayisha Imran: Drafted the study design and proof reading.
Nauman Aslam Malik Overall supervision of the study.
Muhammad Furqan Sharif: Literature search, Statistical analysis

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