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Association Between Mean Platelet Volume to Lymphocyte Ratio (MPVLR) and Diabetic Nephropathy Incidence in Type 2 Diabetes Mellitus

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ABSTRACT

Introduction. Diabetic nephropathy is a microvascular complication of uncontrolled diabetes mellitus (DM), with inflammation among its underlying pathogenesis. Inflammation causes fibrosis, increased vascular permeability, and podocytopathy, which lead to albuminuria. Mean Platelet Volume (MPV) measures thrombocyte size, which may mark increased metabolic and enzymatic activity of thrombocytes. An absolute decrease in lymphocytes occurs due to inflammation-induced decrease in apoptosis. MPVLR value can be used to assess low-grade inflammation in diabetic nephropathy in type 2 DM patients. This study aimed to determine the association between MPVLR values and diabetic nephropathy incidence in type 2 DM. **Methods.** This study was a cross-sectional study on type 2 DM patients at the Endocrinology outpatient clinic of Adam Malik Hospital aged ≥ 18 years. Sixty patients met the inclusion criteria. Complete blood count, creatinine, and albumin creatinine ratio (ACR) were performed to determine the incidence of diabetic nephropathy**. Results.** There was a significant difference in age between the diabetic nephropathy and non-nephropathy groups. There were significant differences in absolute lymphocyte count, Hb, HbA1c, and renal parameters such as estimated Glomerular Filtration Rate (eGFR) and creatinine between diabetic nephropathy and non-nephropathy groups. MPVLR showed a significant negative correlation with eGFR and Hb (r = -0.325, p = 0.011), showing that MPVLR increased in line with eGFR and Hb decrease. MPVLR was not significantly associated with diabetic nephropathy incidence based on semiquantitative ACR (p = 0.139). **Conclusion.** MPVLR was not associated with diabetic nephropathy in type 2 DM patients.

1. Introduction

Diabetes mellitus (DM) is currently becoming a dangerously common disease, and its incidence is projected to continue rising in the future. The International Diabetes Federation (IDF) reported that DM prevalence in 2024 had reached 588.7 million cases and is predicted to continue to increase by 45% by 2050, globally.[1] In Indonesia, based on the *Indonesian Health Survey* 2023, the prevalence of DM reached 1.7%.[2]

Uncontrolled hyperglycemia may trigger protein, lipid, and deoxyribonucleic acid (DNA) damage, and the extent of these damages is associated with oxidative stress or reactive oxygen species (ROS) release rates. Oxidative stress may trigger an increase in Angiotensin-II (Ang-II) levels, activation of protein kinase C (PKC), and expression of transforming growth factor (TGF-β), which also stimulates stress as pro-oxidants. Increased oxidative stress and its stimulants may lead to remodelling of the extracellular matrix in the mesangium and trigger fibrosis of the interstitial tubules. These processes lead to the development of diabetic nephropathy in uncontrolled DM.[3]

In chronic kidney disease (CKD) patients, the inflammatory condition can be classified as low-grade. Inflammatory cytokine levels, such as tumor necrosis factor-α (TNF-α) and interleukin (IL), are slightly increased in systemic circulation to regulate the inflammatory response. While persistent, this low-grade inflammation does not show clear clinical manifestations. However, this low-grade persistent inflammation may lead to further renal damage and complications of CKD. Presently, there remains no consensus on the diagnostic gold standard for low-grade systemic inflammation based on traditional inflammatory biomarker increases, such as TNF-α and IL. High costs and technical challenges limit the

use of these inflammatory biomarkers to research only.[4]

Recently, an index called mean platelet volume-to-lymphocyte ratio (MPVLR), which is a ratio of mean platelet volume (MPV) to lymphocytes (LR) in complete blood count, has gained research interest. This ratio can be considered a new indicator for inflammation and a potential diagnostic or prognostic marker.[3] MPV describes the mean volume of platelets, so high MPV means thrombocytes are larger than usual. Larger thrombocytes commonly have higher metabolic and enzymatic activities, and release more substances such as thromboxane-A2 (TXA2), β-thromboglobulin, and adhesion factors.[5]

MPVLR has been used in studies for several diseases, such as acute appendicitis, thoracic aortic aneurysm, contrast-induced nephropathy, and cardiovascular diseases.[4] A prior study linking MPVLR and diabetic nephropathy had been conducted by Kocak et al. (2018) in Turkey, reporting that MPVLR index values were higher in DM patients with nephropathy than those without diabetic nephropathy (4.13 vs 3.4, $p < 0.001$).[6] Another study in Bali, Indonesia by Aryani et al. (2020) reported MPVLR index was significantly higher in patients with diabetic nephropathy than those without diabetic nephropathy (5.11 ± 2.20 vs 3.29 ± 1.98 ($p = 0.004$)).[5] This marker is simple, affordable, and easy to apply in clinical practice. However, research on the use of MPVLR to predict diabetic nephropathy is still very limited, and in Indonesia there is only one study on this topic, conducted in a population in Bali. No studies have yet demonstrated the use of MPVLR in a population in Medan. This study aimed to determine the association between MPVLR values and diabetic nephropathy incidence in type 2 DM.

2. Methods

This study was a cross-sectional study on type 2 DM patients at the Endocrinology outpatient clinic of Adam Malik Hospital aged ≥ 18 years from February to May 2025. Ethical clearance was obtained for this study from the Ethics Committee of Universitas Sumatera Utara with certificate number 3481/KEPK/US3.66U/2024, and a research permit was issued by Adam Malik Hospital (No. DP.04.03/D.XXVIII/80/2025).

Type 2 DM patients with and without diabetic nephropathy were included in the study. Patients with comorbidities such as acute myocardial infarction, autoimmune diseases, stroke, hemorrhage and malignancies, ongoing infection, ongoing consumption of anti-thrombolytic agents, and acute complications of type 2 DM such as diabetic ketoacidosis, hyperosmolar hyperglycemic state, or hypoglycemia were excluded from the study.

Laboratory examinations were performed at Adam Malik Hospital Laboratory. Complete blood count was performed using Sysmex Analyzer XN 1500. Serum creatinine was examined using Cobas pro c503, and semiquantitative albumin/creatinine ratio was examined using Sysmex Urine Chemistry Analyzer UC 3500. Diabetic nephropathy was established at ACR ≥ 30 mg/g. We used a cut-off for MPVLR of 3.66 based on the study by Kocak et al.[5] MPVLR was calculated by the following formula:[7,8]

$$MPVLR = \frac{Mean\ platelet\ volume\ (fL)}{Lymphocyte\ absolute\ \frac{(x\ 10^3 cells)}{\mu L}}$$

Additionally, eGFR was calculated using the CKD-EPI equation. Data analysis in this study used SPSS 25.0 software. To test for normality, the Kolmogorov-Smirnov test was used because the sample size in this study was ≥ 50. The obtained data were statistically analyzed, where $p < 0.05$ was considered statistically significant.

3. Results

From the 60 assessed patients, 32 patients had diabetic nephropathy based on semiquantitative ACR, while 28 others did not have diabetic nephropathy. Statistical analysis (Table 1) showed a significant difference in age between the diabetic nephropathy and non-nephropathy groups ($p = 0.018$).

Analysis of laboratory parameters (Table 2) showed significant differences in Hb ($p = 0.006$), absolute lymphocyte count ($p = 0.001$), HbA1c ($p = 0.005$), eGFR ($p = 0.001$), and creatinine ($p = 0.007$) between the two groups.

Table 1. **Demographic characteristics comparison between groups**

Characteristic	Frequency		p value
	Diabetic Nephropathy (n = 32)	Non-Nephropathy (n = 28)	
Sex, n (%)			
Male	20 (62.5)	18 (64.3)	0.889
Female	12 (37.5)	10 (35.7)	
Age (years), n (%)	57.47 ± 9.24	52.96 ± 10.06	0.018*
< 60	15 (44.1)	21 (75)	
≥ 60	17 (55.9)	7 (25)	
Diabetes duration (years)	5.00 (1-12)	2.5 (1-12)	0.105

Normally distributed data are presented as mean ± standard deviation (SD). Mann-Whitney test was used to compare means for data not normally distributed. *p value < 0.05.

Table 2. Comparison of laboratory characteristics between groups

Characteristics	Frequency		p value
	Diabetic Nephropathy (n = 32)	Non-Nephropathy (n = 28)	
Hematology			
Hb (g/dL)	12.51 ± 1.97	13.87 ± 1.63	0.006*
Leukocyte (/µL)	8324.38 ± 1981.19	8636.43 ± 1770.54	0.525
Platelet (× 10^3/µL)	273 (139-478)	264.0 (189-502)	0.882
MPV (fL)	9,65 (7.8-13.6)	9.60 (8.2-12.1)	0.514
Absolute lymphocyte (× 10^3/µL)	2.26 ± 0.65	2.88 ± 0.73	0.001*
MPVLR	4.21 (2.91-9.58)	3.73 (2.08-5.35)	0.006*
ESR (mm/hr)	8.0 (1-124)	7.50 (2-38)	0.970
Clinical Chemistry			
HbA1c (%)	8.95 (6.0-16.0)	7.45 (5.7-13.7)	0.005*
eGFR (mL/min/1.73 m^2)	64.11 ± 31.83	89.20 ± 18.61	0.001*
Creatinine	1.27 (0.51-5.55)	0.95 (0.61-1.49)	0.007*

Normally distributed data are presented as mean ± standard deviation (SD). The Mann-Whitney test was used to compare means for data not normally distributed. *p value < 0.05. Hb: Hemoglobin; MPV: Mean Platelet Volume; MPVLR: Mean Platelet Volume to Lymphocyte Ratio; ESR: Erythrocyte Sedimentation Rate; eGFR: estimated Glomerular Filtration Rate.

Table 3. Correlation between MPVLR and eGFR

Variable	MPVLR	
	r	p value
eGFR	- 0.325	0.011*

Spearman's correlation test was used for data not normally distributed. *p value < 0.05. MPVLR : Mean Platelet Volume to Lymphocyte Ratio; eGFR : estimated Glomerular Filtration Rate.

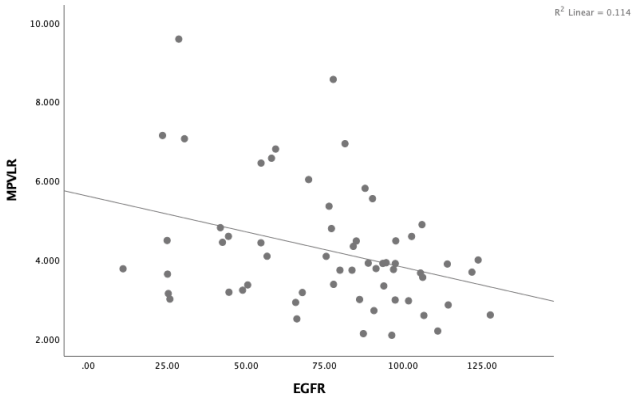

Figure 1. Correlation between MPVLR and eGFR

Table 4. Association between MPVLR value and diabetic nephropathy incidence

Variable	MPVLR		Total	*p value*
	< 3.66	≥ 3.66		
Non-nephropathy	14	14	28	
Diabetic nephropathy	10	22	32	0.139
Total	24	36	60	

MPVLR : Mean Platelet Volume to Lymphocyte Ratio.

The diabetic nephropathy group had higher MPVLR value than the non-nephropathy group (4.21 vs 3.73, with p = 0.006). There were no significant differences in other variables (Table 2). Spearman's test was conducted to correlate MPVLR and eGFR (Table 3). There was a significant negative correlation between MPVLR and eGFR (r = - 0.325, p = 0.011) (Figure 1).

Table 4 shows the analysis of MPVLR association with diabetic nephropathy incidence based on semiquantitative ACR, using cutoff point described by Kocak et al. (5) at 3.66. There was no significant association between MPVLR and diabetic nephropathy incidence based on semiquantitative ACR (p = 0.139).

4. Discussion

Diabetic nephropathy is a clinical syndrome

characterized by persistent albuminuria and progressive renal function decline, implying a characteristic glomerular pathology.[9] In this study, there was no association between MPVLR at 3.66 cutoff point in type 2 DM patients and diabetic nephropathy incidence based on semiquantitative ACR (p = 0.139). This study's finding was the first to contradict prior studies on association between MPVLR and diabetic nephropathy. Kocak et al. stated that MPVLR was more specific and sensitive than MPV and PLR in predicting microalbuminuria in type 2 DM patients. The cutoff point of 3.66 had 71.1% sensitivity and 68% specificity.[6] This value had been validated by Velasquez et al. (2024), stating that cutoff point of 3.66 for MPVLR had 91% sensitivity and 42.6% specificity in diabetic nephropathy patients, showing good sensitivity for early diabetic nephropathy detection, but low specificity due to possible influence from other inflammatory conditions.[10] In our study, when we used a cut-off of 3.66, there was no significant difference between the number of patients with diabetic nephropathy and those without. This may be due to differences in demographics, sample size, and methods used in this study compared to previous studies. MPVLR may reflect thrombocyte-mediated immunity changes as well as lymphocyte-mediated immune response decline. MPV and platelet may be influenced by several other factors, such as age, sex, race and ethnicity, lifestyle (including diet), and genetic factors, which were not fully covered by this present study.[11] Korniluk et al. (2019) stated that the influence of other factors on platelets and MPV in physiological and pathological conditions may be difficult to elucidate, as thrombocyte reactivity can be influenced by many factors.[12]

In this study, the median MPV value between diabetic nephropathy and non-nephropathy groups were similar (9.65 vs 9.60). MPV is an index of thrombocyte size and activation. Increased thrombocyte activation increases thrombocyte aggregation and increased thrombocyte utilization. This stimulates thrombopoiesis and increases immature thrombocytes, which can be found in peripheral circulation.[13] Thrombocyte size is related to its function. Larger thrombocytes are metabolically and enzymatically more active, contain denser granules, secrete more serotonin and β-thromboglobulin, and secrete more TXA2 and adhesion molecules than smaller thrombocytes. Increased thrombocyte activation regulates several responses, including secretion of proinflammatory factors, leukocyte-thrombocyte interaction, and profibrotic responses, which together exacerbate renal function and arterial stiffness.[14,15] A study by Sunardi et al. (2018) in Bandung reported no correlation between MPV and platelet aggregation in diabetic nephropathy patients. MPV values depend on thrombopoiesis.[13] Low thrombopoietic activity may be caused by low thrombopoietin, which is a renally produced hormone stimulating thrombocyte production. Thrombopoiesis can be monitored by immature platelet fraction (IPF) examination, where low IPF indicates low immature thrombocyte count.[12] However, IPF was not examined in this study.

MPVLR values significantly differed between diabetic nephropathy (median 4.21) and non-nephropathy (median 3.73) groups with p = 0.006. The difference in MPVLR values between groups in this study was more significant than MPV value differences. This shows that a combination of MPV and lymphocyte parameters was more effective to distinguish diabetic nephropathy and non-nephropathy than MPV alone. Activation of immune pathways and inflammation acted as main mediators in the development and progression of renal damage in DM. Infiltration of immune cells, both adaptive and innate, is thought to have an involvement in hyperglycemia-induced kidney injury. In diabetic nephropathy, circulating lymphocytes may decrease due to increased inflammation-induced apoptosis. Additionally, active lymphocytes may be increased in proportion, as measured by human leukocyte D-related antigen (HLA-D). In the kidneys, lymphocytes are involved in podocyte damages, and biopsy shows increased lymphocytes, neutrophils and macrophages. Podocyte damage is linked to pronounced proteinuria in diabetic nephropathy.[16]

This study found MPVLR was negatively correlated with eGFR, signifying that MPVLR increase is proportional to eGFR decline. A study by Xu et al. (2022) also reported a negative correlation between MPVLR and eGFR (r = -0.247, p = < 0.001), and logistic regression analysis revealed the independent association between MPVLR and inflammation in non-dialysis CKD patients and eGFR after adjusting for confounders (OD = 1.020; P = 0.024).[4] Previous studies have identified several biomarkers related to diabetic nephropathy, including eGFR, ACR, AGEs, and others. While eGFR may reflect renal functions in a relatively direct manner, eGFR may remain constant or slightly increased in the early stages of diabetic nephropathy. This demonstrates the clear limitations of eGFR for early detection of diabetic nephropathy. In this study, eGFR was calculated using the CKD-EPI formula. The CKD-EPI method is more recommended due to its superior performance in the eGFR range of 60-90 mL/min/1.73 m^2.[9]

Several limitations exist in this study. Data were obtained from a single hospital, so samples may not reflect the wider population. Several factors possibly affecting the outcome, such as diet, exercise, medications, history of hypertension, lipid disorders, BMI, and smoking history were not accounted for in this study. Additionally, diabetic nephropathy was established based on one measurement of semiquantitative ACR without repeating after 3 months to establish chronicity of diabetic nephropathy. Finally, MPVLR was assessed on the first complete blood count at admission, and changes

over time were not recorded. Future research should involve a more diverse population in Indonesia and determine a general cut-off specifically for the Indonesian population so that the research results can be generalized.

5. Conclusion

In type 2 DM patients with diabetic nephropathy based on semiquantitative ACR, MPVLR was not significantly associated with diabetic nephropathy incidence. MPVLR had a significant negative correlation with eGFR.

6. Author Contribution

M carried out the experiment. M wrote the manuscript with support from JS and SS. M collected the data sample. JS and SS helped supervise the project. M and JS conceived the original idea.

7. Acknowledgements

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