

Research Article

Relation between Mean Platelet Volume and Renal Ultrasonography Findings in Predialysis Patients

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Keywords

• Predialysis patient; Mean platelet volume; Renal ultrasound findings

Abstract

Objective: Subclinical inflammation is an established component of chronic renal failure. Although many studies on inflammatory markers have been conducted in these patients, it has been recently reported that MPV can be used as an inflammation marker in various inflammatory diseases. Studies indicating MPV levels may be variable in both dialysis and predialysis patients have also been published. However, studies examining the relation between MPV and renal ultrasonography findings in different stages of CKD are limited. In this study, we aimed to analyze the relation between MPV and renal ultrasonographic findings in predialysis patients.

Method: Medical records of pre-dialysis patients with GFR values below 60 ml/min/1.73m² for minimum 3 months, followed-up at Nephrology Clinic of Dumlupinar University (DPU) Medical School Evliya Celebi Training and Research Hospital (TRH) were retrospectively evaluated. Non-dialysis patients with Stage 3 (n= 42) and Stage 4 (n= 44) CKD were included. Medical records from archives of DPU Evliya Celebi TRH and Nephrology clinic were used to retrieve patient data including demographic variables (age, gender), comorbidities, complete blood count, inflammatory and biochemical parameters (hemoglobin, white blood cells, neutrophils, lymphocytes, mean platelet volume (MPV), platelets, Red cell distribution width (RDW), C reactive protein (CRP), blood urea nitrogen (BUN), urea, creatinine, sodium, potassium, calcium, phosphorus, uric acid, albumin, parathormone), renal ultrasonographic findings (parenchymal echogenicity, parenchymal thickness, kidney size). Data were analyzed using the Statistical Package for Social Sciences (SPSS) 18.0 software.

Results: The relation between MPV and renal ultrasonographic findings were analyzed; no significant correlation was found between MPV and cortical thickness (p= 0.56, r= -0.06) or kidney size (p= 0.84, r= -0.02). No significant relation was found between MPV and renal parenchymal echogenicity, as well. A significant correlation was not detected between MPV and neutrophils, neutrophil/lymphocyte ratio, WBC, RDW, creatinine, albumin, uric acid, pH, HCO₃ (p>0.05). A statistically insignificant negative correlation was found between MPV and glomerular filtration rate (GFR), CRP, erythrocyte sedimentation rate (ESR), calcium, phosphorus, sodium, potassium, ferritin and parathormone (p>0.05). Analysis of the relation between MPV and ultrasonographic findings in patients with diabetes showed a statistically insignificant negative correlation between MPV and kidney size (p= 0.23, r= -0.17) and between MPV and cortical thickness (p= 0.20, r= -0.18). No significant relation was found between MPV and renal parenchymal echogenicity (p= 0.04).

Conclusion: In conclusion, in predialysis Chronic kidney disease (CKD) patients, a statistically insignificant relation was found between MPV and renal ultrasound findings while MPV and renal parenchymal echogenicity showed a significant relation in patients with diabetes. However, larger studies are required to confirm these results.

INTRODUCTION

Chronic kidney disease (CKD) is a pathophysiological process characterized by progressive and irreversible loss of nephrons that develops due to various diseases. In Turkey, CKD prevalence in the general adult population is 15.7%. Prevalence of low glomerular filtration rate (GFR) of <60 ml/min is 5.1% indicating one in 20 adults are at the critical level of chronic renal failure [1]. CKD is a growing burden on public health because of its increasing prevalence, related high morbidity and mortality, serious effects on quality of life and high cost of renal replacement therapies required for its treatment [2-4].

CKD presents with a wide spectrum of clinical manifestations ranging from asymptomatic reduced renal function to uremic

syndrome. Studies have indicated that renal parenchymal echogenicity on ultrasonographic assessment may be associated with degree of kidney disease in patients with CKD.

It is suggested that a subclinical inflammation may be present in CKD. It is known that CRP levels tends to be higher than the normal population in both predialysis and dialysis patients. Particularly CRP, TNF- α , IL-1 and IL-6 levels are high in these patients. Such high levels of pro-inflammatory proteins predispose development of malnutrition and atherosclerosis and thus cause morbidity and mortality [5].

Mean platelet volume (MPV) is calculated by complete blood count analyzers as part of routine complete blood count tests. MPV is a common indicator of platelet function and activation

[6,7]. Recently, it was reported that MPV can be also be used as an inflammation indicator in various inflammatory diseases. Various studies have shown positive or negative correlation between MPV and inflammatory activity [8-10]. Additionally, studies suggesting MPV levels can be variable in both predialysis and dialysis patients have been published [11-13]. However, to our knowledge there are no publications evaluating the association between MPV and renal ultrasonography findings in different stages of CKD. Therefore, we aimed to evaluate the association between MPV and renal ultrasonographic findings in predialysis patients.

MATERIAL AND METHODS

Medical records of pre-dialysis patients with GFR values below 60 ml/min/1.73m² for minimum 3 months, followed-up at Nephrology Clinic of Dumlupinar University Medical School Evliya Celebi Training and Research Hospital were retrospectively evaluated. Non-dialysis patients with Stage 3 (n= 42) and Stage 4 (n= 44) CKD were included.

Medical records from archives of Dumlupinar University Medical School Evliya Celebi Training and Research Hospital and Nephrology clinic were used to retrieve patient data including demographic variables (age, gender), comorbidities, biochemical parameters (hemoglobin, WBC, neutrophils, lymphocytes, MPV, platelet, RDW, CRP, BUN, urea, creatinine, sodium, potassium, calcium, phosphorus, uric acid, albumin, parathormone), renal ultrasonographic findings (parenchymal echogenicity, parenchymal thickness, kidney size).

The MPV values and renal ultrasonographic findings of the patients were compared. Patients with Stage 1, Stage 2, Stage 5 disease, history of active infection, rheumatological disease or cancer were excluded.

The study was approved by Eskisehir Osmangazi University Institutional Ethics Committee with approval number 80558721/G-271.

Statistical method

The data were analyzed using SPSS 18.0 (Statistical Package for the Social Sciences for Windows, Chicago, Illinois) statistics software. Descriptive data were presented as mean \pm standard deviation and percent. Kolmogorov-Smirnov test was used to test normal distribution. Parametric tests for normally distributed variables (independent T test, One-Way ANOVA) and non-parametric tests for not normally distributed variables (Mann-Whitney U, Kruskal-Wallis) were used for analysis. In order to determine the relationship between numeric and categorical data, Pearson chi-square and Pearson correlation tests were used. P values less than 0.05 were considered significant.

RESULTS

Description of the Study Population

The study population consisted of 86 patients (40 male, 46 female). Age distribution of the patients was as follows: 3.5% 18-35 years, 7% 36-50 years, 38.4% 51-65 years, 29.1% 66-74 years and 22.1% 75 years and older. Smoking rate was 30.2%, alcohol

use was not reported. Primary kidney diseases of the study population included to 37.2% had HT, 2.3% had DM, 55.8% had both HT and DM. Distribution of comorbidities was as follows: CAD in 25.6%, COPD in 15.1%, both CAD and COPD in 17.4% (Table 1).

The renal function and kidney ultrasound examination findings in the study population were as follows: mean GFR value 33.8 ± 11.9 ml/min, mean kidney size 101.1 ± 11.3 mm, mean cortical thickness 10.9 ± 2.1 mm, rates for renal parenchymal echogenicity 26.7% grade 0, 48.8% grade 1, 17.4% grade 2 and 7.0% grade 3. The study group consisted of 48.8% Stage 3 and 51.2% Stage 4 CKD patients. The mean MPV value for the study group was 8.45 ± 1.10 fL (Table 2).

Comparing MPV and renal ultrasound findings

The MPV values and renal ultrasound findings of the study population were compared; a statistically insignificant, weak negative correlation was found between MPV and cortical thickness ($p= 0.56$, $r= -0.06$) and also between MPV and kidney size ($p= 0.84$, $r= -0.02$). Similarly, no significant relation was found between MPV and renal parenchymal echogenicity stage ($p= 0.30$) (Table 3).

Comparing MPV and various independent variables

The association between MPV values and presence of DM was evaluated in the study group; MPV values were significantly

Table 1: Descriptive features of the study population.

		Number (N)	Percent (%)
Age	18-35	3	3
	36-50	6	7
	51-65	33	38.4
	66-74	25	29
	>75	19	22.1
Gender	Male	40	46.5
	Female	46	53.5
Smoking	Yes	26	30.2
	No	60	69.8
Alcohol	Yes	0	0
	No	86	100
Primary Kidney Disease	None	4	4.7
	HT	32	37.2
	DM	2	2.3
	DM+HT	48	55.8
Comorbidity	None	36	41.9
	CAD	22	25.6
	COPD	13	15.1
	CAD+COPD	15	17.4
Total		86	100

Table 2: MPV values, renal functions and ultrasound findings of the study population.

	GROUP (N=86)
MPV (fL) (Mean±SD)	8.45 ± 1.10
GFR (ml/min) (Mean±SD)	33.8 ± 11.9
Kidney size (mm)(Mean±SD)	101.3 ± 11.3
Cortical thickness (mm)(Mean±SD)	10.9 ± 2.1
Parenchymal echogenicity (%)	
Grade 0	23 (26.7%)
Grade 1	42 (48.8%)
Grade 2	15 (17.4%)
Grade 3	6 (7.0%)
CKD(%)	
Stage3	42 (48.8%)
Stage4	44 (51.2%)
Total	86 (100%)

Table 3: Relation between MPV and ultrasonographic findings.

	P value	R value (Correlation coefficient)	Test
CORTICAL THICKNESS	0.56	-0.06	Pearson correlation
KIDNEY SIZE	0.84	-0.02	Pearson correlation
RENAL PARENCHYMAL ECHOGENICITY	0.3	--	Kruskal-Wallis

higher in the subgroup with DM ($p = 0.008$). There was no difference between smokers ($n = 26$) and non-smokers ($n = 60$) for MPV values ($p = 0.48$). No significant relation was found between CKD Stage and MPV ($p = 0.47$) (Table 4). MPV values were higher in patients who had CAD although the difference was statistically insignificant ($p = 0.83$). There was no statistically significant relation between age or GFR and MPV ($p = 0.37$ and $p = 0.07$, respectively). MPV showed a weak negative correlation with platelet count ($p = 0.04$ $r = -0.30$); there was no significant relation between MPV and other hematological parameters (Table 4).

Table 4: Comparing MPV and various independent variables.

MPV		N	fL (Mean±SD)	P value	R value	Test
DM	Yes	50	8.6 ± 1.0	0.008	--	Mann-Whitney U
	No	36	8.1 ± 1.1			
Smoking	Yes	26	8.5 ± 1.1	0.48	--	T – Test
	No	60	8.4 ± 1.0			
CKD	Stage 3	42	8.4 ± 1.1	0.47	--	T – Test
	Stage 4	44	8.4 ± 1.0			
CAD	Yes	37		0.83	--	
	No	49				
GFR	--	86		0.37	-0.09	Pearson correlation
Age	--	86		0.07	0.19	Pearson correlation
PLT	--	86		0.04	-0.3	Pearson correlation

Subgroup Analyses

Comparing stage 3 vs stage 4 CKD: There was no significant difference between Stage 3 and Stage 4 CKD for age or gender ($p > 0.05$). Similarly, Stage 3 and Stage 4 patients showed to significant difference for smoking status ($p = 0.12$). CKD Stage was significantly related to blood albumin and PTH levels ($p = 0.04$ and $p = 0.0$) while Stage and sedimentation rate showed a borderline relation ($p = 0.05$).

Evaluation of DM prevalence by CKD stage revealed that half of Stage 3 patients had DM while 66% of Stage 4 patients had DM diagnosis although the difference was not statistically significant ($p = 0.13$). There was significant difference between Stage 3 and 4 patients for kidney size and cortical thickness ($p > 0.05$); difference between stage subgroups for renal parenchymal echogenicity was slightly significant ($p = 0.048$).

Comparing DM and various independent variables: Analysis of the relation between DM and blood values revealed significant relations between DM and WBC ($p = 0.003$), neutrophils ($p = 0.003$), MPV ($p = 0.008$), ESR ($p = 0.04$) and uric acid ($p = 0.01$).

DM patients had lower GFR values although the difference was statistically insignificant ($p = 0.32$). Renal ultrasound findings in DM patients were analyzed; kidney size and cortical thickness were not significantly related to DM ($p > 0.05$), however, DM and parenchymal echogenicity showed a borderline relation ($p = 0.05$).

Analysis of the relation between MPV and renal ultrasonography findings in DM patients revealed a strong positive correlation between MPV and cortical thickness and kidney size compared to non-diabetics although the relation was statistically insignificant ($p = 0.20$, $r = -0.18$), ($p = 0.23$, $r = -0.17$). There was a significant relation between MPV and renal parenchymal echogenicity in DM patients ($p = 0.04$).

Relation between GFR and renal ultrasonography findings

Analysis of the relation between GFR and renal ultrasound findings showed a significant weak positive correlation between GFR and kidney size ($p = 0.01$, $r = 0.27$). No significant relation was found between GFR and cortical thickness or renal parenchymal echogenicity ($p = 0.76$, $p = 0.13$).

DISCUSSION

Prevalence of end stage kidney failure requiring chronic dialysis or kidney transplantation is rapidly increasing in Turkey parallel to the global trend. MPV is calculated by complete blood count analyzers as part of routine complete blood count tests and it is a common indicator of platelet function and activation [6,7]. Recently, it was reported that MPV can be also be used as an inflammation indicator in various inflammatory diseases. Various studies have shown positive or negative correlation between MPV and inflammatory activity [8-10].

Non-dialysis patients with Stage 3 (n= 42) and Stage 4 (n= 44) CKD were included in the study. The MPV values and renal ultrasonographic findings of the patients were compared. Values for MPV, renal ultrasonographic findings (parenchymal echogenicity, parenchymal thickness, kidney size) and other biochemical parameters (hemoglobin, WBC, neutrophils, lymphocytes, MPV, platelet, RDW, CRP, BUN, urea, creatinin, sodium, potassium, calcium, phosphorus, uric acid, albumin, pH, HCO₃, parathormone) were evaluated between groups. In this study group HT appears to be the top etiological factor for CKD. The most common etiological factors for CKD in Turkey were DM followed by HT [1].

CKD is known to be a subclinical inflammatory condition. The associations between MPV and inflammation have been investigated particularly in patients with sepsis and in chronic inflammatory diseases. Various studies have reported that MPV can be used as an indicator for inflammation to discriminate acute localized infection from septicemia and can predict developing invasive infection or sepsis [14-16]. On the other hand, particularly in chronic inflammation conditions, increased CRP with low MPV values were reported to indicate disease activation [17,18]. In our study, CRP and MPV were negatively correlated although no statistically significant relation was found.

Physiologically and in many pathological conditions, platelet count and MPV are inversely related and this relation generally ensures a stable mass of platelets in circulation [19]. It has been reported that this inverse relation primarily occurs in inflammatory diseases where circulating platelet count is increased by platelet production stimulation but meanwhile depleted in large volumes as a result of migration to inflammation site. Additionally, conditions such as defective thrombosis, increased destruction and platelet swelling in reactive material-rich media may affect the relation between platelet count and MPV. Another study has explained this difference by multiple and variable factors independently acting on platelet count and MPV [20]. In our study, in accordance with the literature, a significant negative correlation was found between MPV and platelet count in predialysis patients.

In the study by Kario K et al., platelet count and MPV were found higher in smoking atherosclerotic patients compared to non-smoker non-atherosclerotic group [21]. After smoking cessation, MPV was reduced by 10% within one-three months in the atherosclerotic group. In our study no relation was found between MPV and smoking. This may be due to the lower proportion of smokers compared to non-smokers in the study group or under- or mis-reporting. Additionally, patients were not

sub-classified by presence of atherosclerosis to analyze MPV vs smoking.

Nephropathy which is among the microvascular complications of diabetes has currently become the most common cause of CKD. Metabolic and hemodynamic factors play an important role in the complex physiopathology of diabetic nephropathy. Many studies have shown that, in addition to these factors inflammation also plays a role in development of nephropathy. Experimental and clinical studies have revealed that inflammation is involved in the pathogenesis of diabetic nephropathy. Lesions detected on renal biopsies of Type 2 DM patients were accompanied by increased inflammatory markers. It was found that inflammatory marker TNF-alpha shows cytotoxic effects on glomerular, mesangial and epithelial cells. Additionally, a close relation between urinary TNF-alpha levels and proteinuria was confirmed in diabetic patients. In the study by Jabeen et al., diabetic patients were compared to healthy subject for MPV and hsCRP values and these parameters were found significantly higher in diabetics [22]. Similarly in our study, WBC, neutrophils, ESR, MPV and uric acid levels were significantly higher. These results support presence of inflammation which plays a role in the pathogenesis of diabetic nephropathy.

Platelet dysfunction affects the development of vascular diseases in diabetic patients. Systemic inflammation, oxidative stress, altered calcium metabolism, reduced nitric acid bioavailability and increased phosphorylation of cellular proteins are factors responsible for platelet activation, release of proinflammatory and prothrombotic substances in diabetic patients [23,24]. Studies have shown that platelet size and shape influence platelet activity. One of the important findings of the studies was that diabetic patients with micro- and macro-vascular complications had higher MPV values compared to patients without complications [25,26]. In the study by Papanas et al., including 416 cases, patients were divided into 3 groups as non-diabetics, diabetic without complications and diabetic with microvascular complications and groups were compared for MPV values [27]. In conclusion, MPV values were found significantly higher in the two diabetic groups compared to the non-diabetic group. Notably, the diabetics group with complications had significantly higher MPV values than the diabetic group without complications. Based on these study results, it can be suggested that increased MPV in diabetic CKD is potentially associated with increased cardiovascular risk. In the study conducted by Sengul et al. on 95 subjects, MPV values were analyzed for diabetic and non-diabetic CKD and MPV values were found significantly higher in the group with DM. Similarly in our study, MPV was significantly higher in patients with DM. Based on these data, MPV can be considered as a low cost alternative for assessing increased inflammation and microvascular complications in patients with diabetic nephropathy.

Renal USG findings of diabetic CKD patients are quite different compared to patients with CKD due to other causes. Nishimura et al. [28], have found that kidney size in diabetic CKD patients was slightly smaller than healthy subjects but larger than non-diabetic CKD patients. Another study has reported that kidney size in diabetic CKD was larger than CKD due to other causes [29]. Our results support these studies. Kidney size and

kidney parenchymal thickness were found higher in diabetic CKD compared to non-diabetic CKD. However, the difference was not statistically significant. The difference was borderline significant for renal parenchymal echogenicity. Diabetic patients are the most challenging patient group with regard to differential diagnosis of renal failure. Sonographic features of diabetic CKD can be considered in between ARF and CRF groups. Therefore, confirming DM diagnosis before interpreting renal sonography findings might be beneficial.

Increased MPV has been shown in many studies on DM patients with CKD. The relation between MPV and renal ultrasound findings is an open issue needing further investigation. In case a significant relation is established, MPV as part of complete blood count can be used for follow-up of CKD patients as a low-cost, practical alternative. In our study, there was a negative correlation between MPV and kidney size and cortical thickness in patients with diabetes although the relation was statistically insignificant. This may be because DM patients had higher kidney size and cortical thickness compared to patients without DM or because of insufficient sample size. Significant results may be obtained by larger studies. A significant relation was found between MPV and renal parenchymal echogenicity. Based on these data, it is concluded that MPV can be used for follow-up of increased renal parenchymal echogenicity, which is among ultrasound findings, although larger studies are required.

GFR reduction is expected with CKD progression. Reduced GFR is expected with advancing age. In our study, there was a negative correlation between GFR and age although statistical significance was not observed. This may be because mean age of included patients were similar. When patients were classified as diabetic and non-diabetic patients, GFR was found lower in DM patients. This was considered related to higher rate of DM in Stage 4 CKD. When GFR and ultrasound findings were compared, a significantly positive correlation was found between GFR and kidney size although the relation was not statistically significant. This may be due to increased parenchymal thickness in DM patients compared to non-DM. Renal parenchymal echogenicity is expected to increase with reducing GFR. Our study results were similar although statistically insignificant. This may be due to small sample size. During inflammatory process involved in CKD development accompanied by reduced GFR, inflammatory markers gain importance. Additionally, microinflammation related renal failure induces oxidative stress [30-32]. Considering the relation between acute phase reactant ferritin and GFR relation in our study, ferritin was increased as GFR decreased and borderline significance was observed. CRP, RDW showed negative correlation with relation to GFR which was statistically significant. There was a significant positive correlation between GFR and negative acute phase reactant albumin. WBC, neutrophils, neutrophil/lymphocyte ratio and ESR showed negative but insignificant correlation with GFR. Inflammatory process, as shown in many studies, was supported by increasing CRP as GRF reduced in CKD cases.

Recent reports have indicated that MPV can be used as an inflammation marker in various inflammatory diseases. Studies reporting both positive and negative correlation between MPV and inflammatory activity are available in the literature [8-10].

Our study showed a negative correlation between GFR and MPV although the relation was insignificant. These results suggest that MPV cannot be considered a useful marker to predict CKD-related pathologies; however, more accurate results can be obtained by larger prospective studies.

According to Turkish Nephrology Association registry, cardiovascular diseases are the most common cause of mortality in both ARF and ESRF patients [33]. Thus, cardiovascular diseases and risk factors should be considered with attention in patients with CRF. Inflammation and oxidative stress are simultaneously increased in uremic patients. Oberg et al. [34], have shown that inflammation and oxidative stress markers were increased in Stage 3-5 CRF patients compared to healthy subjects. Increased oxidative stress and inflammation during uremia can be responsible for increased cardiovascular mortality and morbidity in uremic patients. Studies have shown that increased inflammatory markers (particularly IL-6 and hs-CRP) were independent and robust predictors for development of cardiovascular mortality and morbidity in uremic patients [35]. In a study including groups of healthy controls, DM, atherosclerosis and DM+atherosclerosis, MPV was found associated with atherosclerosis rather than diabetes status. Additionally, increased megakaryocyte diploidy was found associated with DM and it was suggested that increased megakaryocyte diploidy and platelet count as well as increased MPV could be independent risk factors for atherosclerosis [36]. Considering CAD for stage, CAD rate was higher in stage 4 patients in our study. This may be because of increased risk for CAD with CKD progression or higher rate of CAD equivalent DM in stage 4 patients. No relation was found between CAD and MPV in our study. However, comorbidities including DM, HT might have influenced the results therefore more comprehensive studies are needed.

Regarding limitations and strengths of our study

First of all we should consider factors affecting MPV measurement. Although currently MPV is a parameter reported within complete blood count tests, reliability of the results are questionable since EDTA found in complete blood count measurement tubes may cause deformation of platelets. In complete blood count tests where impedance technology is used, EDTA causes an increase in MPV values as a function of time. After contact with EDTA, MPV increases up to 30% within the first five minutes and by 10-15% more in the next two hours [37]. MPV values are reduced by approximately 10% in complete blood count tests using optic technology [38]. Lance et al., have reported that most appropriate time for MPV measurement using EDTA in complete blood count test with impedance technology was 120 minutes after blood sample was collected [39]. On the other hand, measurement of all parameters including MPV related to platelets are specific to the technology used by automated blood count devices and differences up to 40% have been reported between studies using different device models. Since this was a retrospective study MPV measurement times obviously were not standardized and thus reliability of the current MPV data is controversial. Recently, it was reported that MPV can be used as an inflammation marker in various inflammatory diseases. Based on this information, patients with active infection or history of rheumatological disease were excluded in order to

prevent interference with MPV results. In our study, in order to ensure homogeneity between two group, it was included to study patients who similar ages and genders.

CONCLUSION

In conclusion, comprehensive studies using standardized MPV measurements in test and healthy control groups can provide important information about platelet production in diabetic or non-diabetic chronic renal failure.

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