Annals of Medical Research
DOI: 10.5455/annalsmedres.2019.10.639 2020;27(3):895-902

Original Article

Usefulness of mean platelet volume as a biomarker for diagnosing arterivenosus fistulas thrombosis in routine hemodialysis patients

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Abstract

Aim: Hemodialysis patients should have an access to a vessel. Thrombosis is responsible for 80-85% of fistula losses. Mean Platelet Volume (MPV) is routinely measured in complete blood count and shows the average volume of circulating platelets. In our study, we aimed to investigate whether MPV values may be used as a cheap and noninvasive marker in the early diagnosis and intervention of arteriovenous fistula (AVF) thrombosis.

Material and Methods: This retrospective study included 48 patients having one or more episodes of late fistula thrombosis at the hemodialysis unit and 47 patients without history of AVF thrombosis.

Results: Demographic and laboratory characteristics were used to compare between groups and no significant difference was found ($p> 0.05$). On the other hand, significant difference was reported ($p=0.001$) by the comparison of two groups. Logistic regression analysis, revealed that MPV was an independent risk predictor for the development of AVF thrombosis ($p <0.05$).

Conclusion: AVF dysfunction leads to a significant cost and frequent hospitalization of the patient. Previously, MPV was stated to be a risk factor for arterial and venous thrombosis. This study showed that MPV values may be used in hemodialysis patients as a predictor of thrombosis. Further prospective and retrospective studies should be conducted in order to verify the finding of this study.

Keywords: Arteriovenous fistula; end stage renal failure; mean platelet volume; thrombosis

INTRODUCTION

Hemodialysis (HD) is the main dialysis method that constitutes 90% of dialysis therapy despite the variations among countries (1). Vascular access is required for hemodialysis. Although temporary or permanent catheters and arteriovenous grafts (AVGs) may also be used, arteriovenous fistulas (AVFs) are frequently used for vascular access (2). As thrombosis is responsible for 80% to 85% of vascular access failure, AVF and graft thrombosis may develop in early or late post-operative period. Early thrombosis mostly occurs due to surgical technical factors and may require surgical revision. On the other hand, late thrombosis may develop due to inadequate flow within the fistula, hypotensive processes, hypercoagulability and dehydration (3, 4).

Mean Platelet Volume (MPV) is routinely measured with complete blood count and shows the average volume of platelets in circulation (5). Increased platelet volume is a marker of increased platelet activity. Compared to smaller ones, large platelets are more active in metabolic and enzymatic terms and have higher thrombotic potential (6). Existing studies found a correlation between MPV inflammation, hypoxia, vascular damage, thrombosis, atherosclerosis and MPV for some diseases, such as, diabetic retinopathy, myocardial infraction, pulmonary embolism, acute cerebral ischemia, systemic lupus erythematosus, familial Mediterranean fever, and Behcet syndrome (7-13). The current study examined the potential relationship between AVF thrombosis and MPV for HD patients. It aimed to assess the extent to which MPV may be used as cheap and non-invasive marker for early diagnosis and intervention for AVF thrombosis.

Received: 14.10.2019 **Accepted:** 30.01.2020 **Available online:** 13.03.2020
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MATERIAL and METHODS

This retrospective study was conducted on 95 patients, who were followed at the HD unit of the Nephrology department of Diskapi Yildirim Beyazit Education and Research Hospital. 48 participants of the study had at least one thrombotic episode in late postoperative period (12 months or more after AVF operation) whereas 47 patients had no history of AVF thrombosis. The patients who underwent fistula with the same technique were selected to ensure the reliability of the study in the same surgical clinic department of the same center. Patients with thrombophilia (Factor V Leiden Mutation, Hyperhomocysteinemia, Protein C deficiency, Protein S deficiency), thrombosis-prone conditions (presence of SLE, Behçet's Disease, active malignancy and active infection, antiphospholipid syndrome, immobilization, pregnancy) or drug use (oral contraceptives) were excluded from the study. In addition, patients with a history of early thrombosis were excluded from the study since the causes of early AVF thrombosis are mostly due to surgical technique and early cannulation conditions. Moreover, the uncertainty of the late thrombosis were the another factor for excluding these patients from the study. This study aimed to investigate the whether the MPV values may be used as a cheap and noninvasive marker in the early diagnosis and treatment of late AVF thrombosis (12 months after AVF surgery).

In our study, MPV values of the patients with AVF thrombosis were measured at the time of Doppler USG. In control group, the most recent hemogram values were used. Blood samples were drawn at the beginning of the second HD session of the week (Wednesday for Monday–Wednesday–Friday regime session or Thursday for Tuesday–Thursday–Saturday regime session) on an arterial needle into EDTA tubes and transported to the laboratory within 2 h to obtain a full blood count. Platelet and MPV values were obtained using a Beckman coulter device.

Written informed consent was obtained from all participants. All patients were included in the study after receiving their informed consent forms. The study was performed in accordance with Declaration of Helsinki. Permission from the relevant ethical commission (date: 15/05/2017, reference number: 38/34) was obtained. Data of patient characteristics was obtained from the routine tests that were administrated during follow-up.

Statistical Analysis

Data obtained from patients and control groups in the study was analyzed by using Statistical Package for the Social Sciences (SPSS) for Windows computer program (release 22.0; SPSS Inc., Chicago, IL, USA). Statistical tests were evaluated by calculating the p-value by α=0, 05. Quantitative variables of patients and control groups were expressed as mean±standarddeviationfor descriptive statistics. Distribution of the groups was analyzed by "Kolmogorov-Smirnov ve Shapiro Wilk". Since all variables were distributed normally, comparison of two more quantitative groups was analyzed with "One Way Analysis of Variance (ANOVA)" and comparison of two quantitative groups were analyzed with "Independent Samples –T Test". Pearson's correlation analysis was used to detect the possible relation between MPV and other variables. Factors that were correlated with MPV and statistically different in MPV groups were analyzed by using "Multivariate Binary Logistic Regression Analysis" to determine the factors involved in thrombosis.

Qualitative variables of patients and control groups are expressed as frequency and percentage (%), and "Chi-Square Test" is used for determining relationship between two qualitative variables.

RESULTS

This study was conducted on 48 hemodialysis patients, who had at least one thrombotic episode in late postoperative period (12 months or more after AVF operation), and 47patients without any history of AVF thrombosis (Table1) demographic and laboratory characteristics of the participants in case and control groups).

Comparison of patients with and without AVF thrombosis in Table 1 shows no statistically significant difference between the two groups in terms of age and gender (p= 0.169, p= 0.357, respectively). Comparison of the two groups in terms of comorbidity reveals no statistically significant difference between the two groups of patients in terms of diabetes mellitus (DM), hypertension (HT) and atherosclerotic cardiovascular disease (p= 0.261; p= 0.055; p= 0.995, respectively). We also did not find any significant difference between the patients with and without AVF thrombosis in terms of smoking, use of anti-aggregating drugs, average blood pressure and dialysis vintage(p=0.205; p=0.338; p=0.272; p=0.294, respectively). Besides, comparison of the laboratory characteristics of the two group reveals no statistically difference in terms of laboratory parameters of high density lipoprotein (HDL), low density lipoprotein(LDL), ferritin, parathyroid hormone (PTH), calcium, phosphorous, hemoglobin, white blood cell, platelet, activated partial thromboplastin time (aPTT), prothrombin time (PT), albumin, uric acid, urea, triglyceride and C Reactive Protein (CRP) (p=0.938; p=0.133; p=0.331; p=0.482; p=0.817; p=0.655; p=0.315; p=0,052; p=0.354; p=0.156; p=0.092; p=0.911; p=0.469; p=0.468; p=0.469; p=0.238, respectively). Finally, we found a significant difference between the case and control groups in terms of MPV and glucose levels (p=0.001; p=0.011, respectively).

Table 2 compares the demographic and laboratory characteristics of patients with AVF thrombosis in terms of MPV levels. The comparison of the groups reveals a significant difference between atherosclerotic cardiovascular disease and MPV levels (p=0.019). Besides, Table 2 also shows a statistically significant relationship between MPV levels, platelet numbers and ferritin levels (p=0.001; p=0.004, respectively).

Table 1. Comparison of Patients with AVF Thrombosis and Patients without AVF Thrombosis by Demographic and Laboratory Characteristics

Parameter	Thrombosis (+) (n=48)	Thrombosis (-) (n=47)	p
Age (year)	56.2±10.6	59.1±9.8	0.169
Gender (male, n, %)	21 - 45.7%	21-54.3%	0.357
Diabetes mellitus (n, %)	18 -37.5%	23 -48.9%	0.261
Hypertension (n, %)	30 -62.5%	11 -22.9%	0.055
Atherosclerotic cardiac disease(n,%)	11 -22.9%	11 -23.4%	0.995
Smoking(n,%)	19-39.6%	14-29.8%	0.205
Peripheral arterial disease (n,%)	3	2	0.09
Antiagregating drug (n,%)	26 -54.2%	30 -63.8%	0.338
Mean blood pressure (MBP)	85.0 ±10.9	87.9±13.9	0.272
Dialysis vintage (year)	7±5	5±5	0.294
HDL (mg/dl)	35.9±11.8	36.2±10.4	0.938
LDL (mg/dl)	102.7±49.9	109.4±38.1	0.133
Ferritin (ng/ml)	510.1±366.9	519.7±247.7	0.331
PTH (pg/dl)	513.5±401.3	509.2±585.7	0.482
Calcium	8.6±0.8	8.5±0.8	0.817
Phosphorus	5.3±1.4	5.1±1.0	0.655
Hemoglobin (g/dL)	10.7±1.3	11±1.4	0.315
Thrombocytes (103/uL)	196.1±42.9	206.7±41.1	0.052
WBC (103/uL)	7.6±2.3	7.2±1.9	0.354
MPV	8.6±0.9	7.8±0.8	0.001
APTT	30.0±4.3	29.0±1.6	0.156
PT	12.2±4.1	11.2±1.3	0.092
Glucose(mg/dl)	101.1±34.9	129.0±65.9	**0.011**
Albumin (g/dL)	3.8±0.4	3.8±0.3	0.911
Uric acid (mg/dl)	191.5±129.6	174.2±99.5	0.469
Urea (mg/dl)	140.1±41.4	130.1±34.8	0.468
TG (mg/dl)	191.5±129.6	174.2±99.5	0.469
CRP (mg/L)	15.3±15.6	11.3±16.7	0.238

Abbreviations:HDL, high density lipoprotein; LDL low density lipoprotein; PTH, parathyroid hormone; WBC, white blood cell; MPV, Mean platelet volume; TG, triglyceride; CRP, C Reactive Protein;

Table 2. Comparison of Demographic and Laboratory Characteristics of Patients with AVF Thrombosis according to MPV category

Parameters	MPV (6.7-7.5)	MPV (7.51-9)	MPV (9.1-12)	p
Age (year)	61.2±9.8	56.9±10.1	59±10.6	0.269
Gender (male, n, %)	8-38%	7-33%	6-29%	0.982
Diabetes mellitus (n,%)	5 -28%	6 -33%	7-39%	0.924
Hypertension (n, %)	9-30%	10-34%	11 -36%	0.466
Atherosclerotic cardiac disease (n,%)	2 -18%	4 -36.3%	5-45.7%	**0.019**
Smoking (n,%)	7-37%	6-31.5%	6-31.5%	0.977
Peripheral arterial disease (n,%)	-	3-100 %	-	-
Antiagregating drug (n,%)	10 -38.4%	9 -34.6%	7-27%	0.081
Mean blood pressure (MBP	1.9±0.8	2.5±2.7	2.6±0.9	0.498
Dialysis vintage (year	18±5.9	58±5.9	15±6.0	0.994
Hemoglobin (mg/dl)	11.3±1.6	10.6±1.2	10.9±1.3	0.231
Thrombocytes (10^3/uL)	230.6±42.7	198.9±43.2	173.7±27.2	**0.001**
WBC (10^3/uL)	7.1±2.1	7.3±1.9	7.7±2.8	0.737
APTT	28.8±1.0	29.7±3.7	29.7±3.9	0.641
PT	11.0±0.9	11.8±3.9	12.0±1.0	0.550
Glucose (mg/dl)	120.6±51.7	113.9±60.1	104.0±30.5	0.688
Albumin (g/dL)	3.8±0.29	3.8±0.43	3.8±0.42	0.859
Uric acid(mg/dl)	6.0±0.91	6.32±1.2	6.3±1.4	0.623
Urea (mg/dl)	125.9±38.6	139.6±37.0	129.1±46.3	0.351
Calcium	8.4±0.6	8.5±0.9	8.7±0.8	0.561
Phosphorus	5.0±0.7	5.2±1.3	5.6±1.3	0.408
PTH	360.89±280.3	494.8±387.1	456.5±360.1	0.398
Ferritin (ng/ml)	295.2±249.0	431.8±298.4	719.1±349.4	**0.004**
TG (mg/dl)	163.0±65.8	202.8±133.0	142.5±81.6	0.137
CRP (mg/L)	12.3±21.3	11.3±10.7	17.2±21.7	0.444
HDL (mg/dl)	35.4±6.0	36.5±12.3	36.1±11.0	0.461
LDL (mg/dl)	116.5±30.7	104.2±41.1	106.4±69.2	0.130

Abbreviations: HDL, high density lipoprotein; LDL low density lipoprotein; PTH, parathyroid hormone; WBC, white blood cell; TG, triglyceride; CRP, C Reactive Protein

Table 3. Risk Factors for Arteriovenous Thrombosis Development in Routine Hemodialysis Patients, Logistic Regression Model (model p = 0.337, constant: -6.885)

	Odds ratio	% 95 CI	P
MPV	2.830	1.593-5.025	**0.001**
Anti-agrreganting drug use	1.359	0.524-3.522	0.528
Gender	1.221	0.470-3.174	0.682
Age	0.971	0.927-1.017	0.209
Dialysis vintage	1.029	0.937-1.129	0,555
Ferritin	0.999	0.998-1.001	0.453
Blood glucose	1.012	1.000-1.023	0.05

Abbreviations: MPV, Mean platelet volume; CI, Confidence Interval

Result of logistic regression analysis, which is shown in Table 3, demonstrates that MPV is an independent risk factor for AVF thrombosis ($p < 0.05$). Regression analysis was made due to reveal possible factors known to be involved in thrombotic events. Moreover, the factors that were different in different MPV groups and the factors that correlated with MPV are involved in the model. The odds ratio of MPV in determining fistula thrombosis is 2.83 while the odds ratio if blood glucose is 1.012.The results of the study did not reveal any relationship between anti-aggregant drug use, age, sex, duration of dialysis, glucose and ferritin and AV thrombosis.

DISCUSSION

Vascular access and sufficient blood flow are crucial for regular and adequate hemodialysis. AVF is widely used for vascular access for the hemodialysis patients in Turkey and around the world. Dysfunctional AVF increases financial burden and leads to re-hospitalization (14). 80-85% of AVF loss is caused by thrombosis whereas 80% of the cases of thrombosis results from vascular stenosis at the venous part of AVF (3).

Hemostasis disorders are frequently observed in case of chronic kidney diseases (CKD) (15). Several factors, including the acquired uremic thrombopathy described as a pro or anti-aggregant, oxidative stress, chronic inflammation and endothelial dysfunction (16) plays role in cardiovascular (17) and venous (18) thrombotic events associated with CKD.

Clinic examination and dialysis parameters of the AVF, including arterial and venous pressure, blood flow rate, KT/V, and recirculation, should be followed-up strictly in order to avoid AVF thrombosis. Besides, Doppler USG screening may decrease the risk of thrombotic events (19). International guidelines suggest the regular and objective monitoring of flow function (once in every three months for AVF) and state that thrombosis may be prevented with close follow-up of patients with stenosis, since the primary reason of AVF thrombosis is stenosis (20).

Automated blood cell counters in hematology laboratories may count the number of platelets during complete blood count. Different techniques of platelet count, including MPV, which is the most widely used parameter, providing data for different parameters. Femtoliter (fL) is the unit to express MPV (21). Normal values for MPV range from 7.2 to 11.7 fL in Turkey. However, we should remind that these limits might change depending on hematology machine, sample tubes, length of sample analysis and the altitude of the laboratory (5). Changes in platelet volume may have diagnostic and prophylactic importance in thrombotic and pre-thrombotic events. MPV is also related with indicators of platelet activation, such as GP I band GPIIb-III a receptor expression. Large platelets are metabolically more active and are more prone to adhesion and aggregation compared to small platelets (22, 6).

Various studies (7, 23) note that increase in MPV value poses a risk factor for arterial and venous thrombosis. This retrospective case-control study aimed to find out whether MPV could be used as cheap and non-invasive marker for early diagnosis and intervention of AVF thrombosis. For that reason, we intended to ensure that control and case groups had similar values for parameters that may be potential risk factors for thrombosis, including age, gender, smoking, use of anti-aggregating drugs, dialysis vintage, diabetes mellitus (DM) and atherosclerotic cardiovascular disease. However, we found a statistically significant difference between the patients with and without AVF thrombosis in terms of MPV and glucose levels (Table 1). The patients with AVF had an MPV of 8.6 ± 0.96 whereas MPV for the control group was 7.83±0.80 (p=0.001).

This study also compared the demographic and laboratory characteristics of the patients with AVF thrombosis in terms of MPV levels. As Table 2 reveals, we found a

statistically significant relationship between MPV levels, atherosclerotic cardiovascular disease, platelet count and ferritin levels (p=0.019; p=0.001; p=0.004, respectively). Table 2 does not clearly show the relationship between thrombosis and MPV. Since MPV is higher in patients with AVF thrombosis, our aim with this table is to find out which parameters may be related in patients with high MPV value.

One of the existing studies on the relationship between MPV and mortality risk, found a statistically significant relationship between MPV category, DM, congestive heart failure, HT, peripheral vascular disease, calcium, phosphorous, PTH, platelet number, total cholesterol and hemoglobin values (24). The result of logistic regression analysis in Table 3 shows that MPV is an independent risk marker for AVF thrombosis ($p < 0.05$). Regression analysis was run to identify possible factors known to be involved in thrombotic events. Additionally, the factors that were different in different MPV groups and the factors that correlated with MPV were involved in the model. Odds ratio of glucose was 1.012 and statistically insignificant. The odds levels of MPV were 2.83, indicating that one unit increase in MPV may cause 2.83 times increase in thrombosis risk. We showed a strong relationship between the increase in MPV levels and AVF thrombosis. MPV may be an indicator of AVF dysfunction, which may be used by the clinicians to determine high-risk populations. Change in MPV levels may be observed after AVF dysfunction.

Existing studies on MPV have been mostly conducted on cardiovascular diseases. A systematic review on the relationship between MPV, acute myocardial infarction, post-myocardial infarction mortality and post- coronary angioplasty restenosis revealed that MPV was higher for the patients that underwent acute myocardial infarction ($p<0.001$). The same study found that elevated MPV was associated with higher risk of death following acute myocardial infarction and restenosis following coronary angioplasty (25). Similarly, we compared demographic and laboratory characteristics of the patients with AVF thrombosis in terms of their MPV levels (Table 2) and found a statistically significant relationship between atherosclerotic cardiovascular disease and MPV levels ($p=0.019$). Other studies also found increased MPV levels for rheumatoid arthritis, ankylosing spondylitis and Behcet patients (26, 27).

Various studies on MPV have been conducted in the field of nephrology. Retrospective study of Ju et al. on 553 patients, who visited the nephrology outpatient clinic of a university hospital in South Korea between 2010 and 2013, analyzed the relationship between glomerular filtration rate (GFR) and MPV. The patients were allocated to four groups according to estimated GFR and the study found a negative correlation between GFR levels and MPV levels (28). The study of Rafieian-Kopaieand Nasri analyzed serum magnesium levels of 36 hemodialysis patients and found a negative correlation between serum magnesium and MPV (29). Bath et al. compared MPV levels of 16 normotensive autosomal dominant polycystic kidney disease (APKD) patients with normal renal function with 16 normal volunteers. The authors found increased MPV levels for APKD patients and suggested that increased MPV levels in APKD patients may contribute to the development of premature vascular disease (30). The study of Sakallı et al. on 34 renal transplant patients aged between 5 and 18 years found a significant decrease in MPV levels at the end of the first post-transplant month compared to pre-transplant period (31). Bath et al. analyzed renal angiography results of 30 patients with hypertension and found atherosclerotic renal artery stenosis in 13 of these patients. Comparison of the MPV levels for the patients with and without renal artery stenosis revealed that MPV was increased for patients with atherosclerotic renal artery stenosis (32). A retrospective study on 149.000 chronic HD patients showed a correlation between the increase in MPV and mortality rates (33); however, the same study found no relationship between cardiovascular events and MPV levels.

Our review of the literature did not report any specific study on the relationship between AVF thrombosis and MPV. In a prospective study published in 2019 on HD patients, Guillaume Lano et al. found a significant relationship between stenosis and MPV level, but no significant difference was found in thrombosed group (34). The study, 153 routine hemodialysis patients were followed up and 43 patients developed AVF stenosis, 29 patients developed AVF thrombosis, 18 patients developed both stenosis and thrombosis. MPV was found to be significantly higher in the group with stenosis compared to the other group, but no significant difference was found in the group with AVF thrombosis. It has been suggested thatAVF stenosis provides the basis for thrombus development. It was suggested that the lack of a significant relationship between MPV and thrombosis was probably due to the small number of patients, and thrombus development could be prevented by close monitoring of patients with stenosis in the study. Similar to our study, this study also found a correlation with increased MPV and decreased platelet count. AVF obstruction may stimulate hemostasis, increase platelet consumption and may trigger the production of larger platelets. This hypothesis signifies a negative correlation between the number of platelets and MPV. It is known that platelet activity plays more important role than thrombocyte number in the development of thrombus, and MPV can be used as an easy and inexpensive marker for determining platelet reactivity in hemodialysis patients.

Prospective study of Shin et al., which monitored 143 hemodialysis patients between 2013 and 2016, it was found that 38 patients were diagnosed with Vascular Access Failure (VAF), which was defined as thrombosis or a decrease of greater than 50% of normal vessel diameter. Contrary to our findings, the study found no statistically meaningful relationship between MPV and VAF (35). On the other hand, the authors calculated the change of MPV/platelet count ration between baseline and 3 months in order to find the parameter of Δ(MPV/platelet count ratio).

Additionally, the study compared the change of MPV/platelet count ratio over time in patients with and without VAF and found that MPV/platelet count ratio increased over time for the patients with VAF. Based on the findings, the authors suggested that continuous monitoring of the MPV/platelet count ratio may be used to screen the risk of VAF in routine hemodialysis patients. Compared to the study of Shin et al., our logistic regression analysis revealed that MPV is an independent risk factor for AVF thrombosis. Existing studies have also noted an association between MPV and thrombosis. However, based on our review of the literature, we may suggest that our study is the first attempt to show the relationship between MPV and AVF thrombosis for dialysis patients. More active platelets with increased MPV may be responsible for thrombosis. Based on our findings, we may conclude that MPV may be considered as an independent risk factor for AVF thrombosis in hemodialysis patients.

MPV is a universal parameter in complete blood count that does not require additional costs or time. MPV may provide a better protection of the VA, which is the lifeline for the HD patients. Determining a biological marker to evaluate AVF thrombosis in high-risk populations may contribute to the design of further clinical research.

CONCLUSION

AV fistula function loss leads to a significant cost burden and frequent hospitalization of the patient. Thrombosis is the main reason of AVF loss and early diagnosis and treatment are crucial for preventing losses. MPV was stated to be a risk factor for arterial and venous thrombosis MPV, which may be screened by using a cheap and noninvasive test, may be considered as an indicator of thrombosis. However, further studies should be conducted in order to verify the finding of this study.

Competing interests: The authors declare that they have no competing interest.

Financial Disclosure: There are no financial supports.

Ethical approval: The study was performed in accordance with Declaration of Helsinki. Permission from the relevant ethical commission (date: 15/05/2017, reference number: 38/34) was obtained.

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