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PLATELET PARAMETERS AS INDICATORS OF ARTERIOVENOUS FISTULA THROMBOSIS IN HEMODIALYSIS PATIENTS

N. Klapuh-Bukvić[1], A. Fajkić[2], S. Šegalo[3], E. Kiseljaković[4], A. Bećiragić[5], A. Dervišević[6]

[1]Department of Clinical Biochemistry and Laboratory Medicine, Clinical Center of the University of Sarajevo, Sarajevo, Bosnia and Herzegovina
[2]Department of Pathophysiology, University of Sarajevo, Faculty of Medicine, Sarajevo, Bosnia and Herzegovina
[3]University of Sarajevo, Faculty of Health Studies, Sarajevo, Bosnia and Herzegovina
[4]Department of Medical Biochemistry, University of Sarajevo, Faculty of Medicine, Sarajevo, Bosnia and Herzegovina
[5]Medicana Sarajevo, Sarajevo, Bosnia and Herzegovina
[6]Department of Human Physiology, University of Sarajevo, Faculty of Medicine, Sarajevo, Bosnia and Herzegovina

Abstract. Background: *The total number of platelets (PLT), plateletcrit (PCT), mean platelet volume (MPV), and platelet distribution width (PDW) are utilized as markers of platelet activation in assessing thrombotic vascular events. Given the critical importance of maintaining adequate vascular access, i.e., arteriovenous (AV) fistula, for the survival of hemodialysis (HD) patients, the question arises: Is it possible to detect changes in platelet parameters that indicate a connection to occurrences of thrombotic complications with AV fistula?* ***Materials and methods:*** *The study involved 100 patients diagnosed with end-stage renal disease, admitted to the Clinic of Hemodialysis at the University Clinical Center Sarajevo (UCCS). All patients underwent standard bicarbonate HD three times a week, utilizing a native AV fistula for access. The study group was divided into two subgroups: patients without confirmed AV fistula thrombosis (AVF-nonT; n = 66) and patients with confirmed AV fistula thrombosis (AVF-T; n = 34). Anamnestic data and platelet parameter values were collected during the surveyed period.* ***Results:*** *The average value of the PLT was significantly lower (p = 0.001), while the average value of the MPV was significantly higher (p = 0.0001) in patients of the AVF-T group in relation to the patients in the AVF-nonT group. In differentiating patients of the AVF-T group and patients of the AVF-nonT group, PLT in peripheral blood had a moderately good diagnostic accuracy (AUC = 0.704; p = 0.001), and MPV had an excellent diagnostic accuracy (AUC = 0.991; p < 0.001).* ***Conclusion:*** *PLT and MPV can be used as effective biomarkers of AV fistula thrombosis in patients undergoing chronic HD treatment.*

Key words: *platelet parameters, hemodialysis, arteriovenous (AV) fistula, thrombosis*

Corresponding author: *Amela Dervišević, MD, PhD, University of Sarajevo, Medical Faculty, Department of Human Physiology, Čekaluša 90, 71000 Sarajevo, Bosnia and Herzegovina, email: amela.dervisevic@mf.unsa.ba*

ORCID: *0000-0001-7934-417X – Nermina Klapuh-Bukvić*
ORCID: *0000-0003-2313-9008 – Emina Kiseljaković*
ORCID: *0000-0002-1985-9355 – Almir Fajkić*
ORCID: *0000-0001-5555-6530 – Amela Bećiragić*
ORCID: *0000-0002-9280-3278 – Sabina Šegalo*
ORCID: *0000-0002-4251-1437 – Amela Dervišević*

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INTRODUCTION

Chronic kidney disease (CKD) is characterized by gradual and irreversible damage to nephrons or diminished renal function, resulting in a reduction of the glomerular filtration rate (GFR) to less than 60 ml/min/1.73 m² [1, 2]. To qualify as chronic, this condition must persist for over three months and be corroborated by radiological or ultrasonographic evidence of structural kidney alterations or renal tissue biopsy findings [3].

Hemodialysis (HD) treatment for end-stage CKD patients necessitates continuous bloodstream access, which can be achieved through a central venous catheter, construction of an arteriovenous (AV) fistula, or an AV graft. Since its introduction in 1966 by Brescia and Cimino, the native AV fistula has been deemed the gold standard for vascular access in chronic HD applications [4, 5].

Thrombosis is the most severe complication leading to AV fistula dysfunction, often requiring surgical management through thrombectomy or endovascular intervention [6, 7]. It is characterized by the complete cessation of blood circulation in the venous segment of the AV fistula, proximal to the AV anastomosis, due to thrombus formation, which can occur at any point within the vein. Rodriguez et al. [8] reported that among patients dialyzed via the initial native AV fistula during the observational period, 9.3% experienced more than three episodes of thrombosis out of 52%. The overall complication rate was 0.24 episodes per patient per year. Hypercoagulability resulting from platelet and plasma factor abnormalities is the most common cause of AV fistula thrombosis in HD patients [9].

Platelets in the bloodstream are typically inactive, discoid in shape, and possess a delicate surface. Upon injury to a blood vessel or endothelium damage (including AV plaque rupture), platelets adhere to the injury site, become activated, change shape, release granule contents, and aggregate by binding to each other, forming a primary hemostatic thrombus [10]. Most studies on platelet abnormalities in HD patients have focused on defects in platelet adhesion as the primary cause of increased bleeding in these patients [11].

Platelet abnormalities are primarily assessed through changes in platelet indices: platelet count (PLT), plateletcrit (PCT), mean platelet volume (MPV), and platelet distribution width (PDW). PLT indicates the total number of circulating platelets, reflecting the balance between bone marrow production and loss from the body. In HD patients, PLT values often fall within or below the reference interval, indicating moderate thrombocytopenia [12]. MPV values below the lower reference interval limit signify platelet degranulation, whereas elevated MPV indicates the formation and release of new young platelets [13]. PCT, indicating circulating platelets per unit blood volume, offers comprehensive information about platelet mass [14]. It becomes particularly significant when thrombocytopenia and variation in platelet size occur concurrently, as PLT alone may not fully represent platelet mass [15]. PDW increases during platelet activation [16].

Several confirmed factors influence platelet indices in HD patients, including reduced platelet production in the bone marrow, shortened lifespan in circulation due to uremic toxins, platelet loss during HD procedures, retention of approximately 30% of platelets in extracorporeal circulation during HD treatment, and physical destruction of platelets due to intravascular catheters [17]. MPV, PDW, and the percentage of large platelets decrease during HD procedures. This decline in platelet count and indices occurs due to platelet activation, leading to degranulation and release of PF-4 from alpha granules and serotonin from dense granules, well-known markers of platelet activation [10, 17].

Given the availability, routine determination, and relatively low cost of platelet parameters, our research hypothesis focuses on investigating their role in developing thrombotic complications of AV fistulae in patients undergoing chronic HD treatment.

MATERIALS AND METHODS

The study was designed as an observational, cross-sectional, controlled study conducted at the Clinic for Hemodialysis and the Department of Clinical Chemistry and Biochemistry, Clinical Center University of Sarajevo.

It involved 100 patients of both sexes (66/66.0% male; 34/34.0% female), aged 20 to 65 years, diagnosed with end-stage renal disease. All patients underwent a standard bicarbonate hemodialysis program three times a week, using native AV fistula access and heparin as an anticoagulant, with erythropoietin administered to treat renal anemia.

Based on the presence of confirmed AV fistula thrombosis, patients were divided into two groups:

1. Patients undergoing chronic HD treatment without clinically confirmed thrombotic complications of AV fistula – AVF-nonT group (n = 66).
2. Patients undergoing chronic HD treatment with clinically confirmed thrombosis of AV fistula – AVF-T group (n = 34).

An experienced angiologist diagnosed AVF thrombosis following a standard diagnostic protocol for vascular access evaluation.

Inclusion criteria were explicitly defined as follows: age between 20 and 65 years, diagnosis of end-stage renal disease, maintenance HD treatment for at least six months, and use of a native AV fistula as vascular access with available complete clinical and laboratory data.

Exclusion criteria included: HD duration shorter than six months, previous history of thrombotic vascular events before initiation of dialysis, malignant diseases, active inflammatory conditions, type I or type II diabetes mellitus, and severe malnutrition defined as serum albumin levels < 20 g/L.

These criteria were applied to minimize potential confounding effects on platelet indices.

The unequal group sizes reflect the natural distribution of AV fistula thrombosis in the studied population within the study period. All patients who met the inclusion criteria and had confirmed AVF thrombosis during the study period were included in the AVF-T group, while the AVF-nonT group was formed from eligible patients without thrombotic complications treated in the same dialysis unit using consecutive sampling from the same population and study period. The study adhered to the basic principles of the Helsinki Declaration regarding patients' rights in biomedical research. Patients' identities and all personal data were safeguarded permanently in compliance with regulations for protecting identifiable data. Each patient was assigned an identification number for data protection, which was utilized in the statistical analysis.

Biochemical and hematological analyses

All biochemical and hematological analyses were conducted in the Clinical Chemistry and Biochemistry Laboratory, Clinical Center, University of Sarajevo. A venous blood sample was collected during thrombosis verification before the HD procedure for patients undergoing chronic HD treatment with clinically confirmed AV fistula thrombosis. For patients undergoing chronic HD treatment without clinically confirmed thrombotic complications of AV fistula, a venous blood sample was obtained as part of their monthly routine analysis. Venipuncture was performed following a minimum 12-hour fast in the morning hours between 8:00 and 11:00 a.m. to minimize the effects of circadian variation. The sample for hematological parameters was venous blood collected in a Vacutainer tube containing EDTA as an anticoagulant and was analyzed within two hours of venipuncture on a Cell Dyn 3700 hematology analyzer (Abbott, USA).

PLT was determined directly by the impedance method. Other platelet indices: MPV, PDW, and PCT were calculated automatically from the measured platelets. Other hematological parameters were determined by red blood cell count (impedance method), white blood cell count (optical method), hematocrit (Hct) (calculated automatically from the measured red blood cell count), and hemoglobin concentration (Hgb) (spectrophotometric method).

Patient samples for biochemical parameters were collected in Vacutainer serum separator tubes (Becton Dickinson, Rutherford, NJ, USA) in a volume of 3.5 mL. Serum samples were obtained by centrifugation at 4,000 rpm using a SIGMA 3-16P centrifuge (SIGMA Laborzentrifugen GmbH, Osterode am Harz, Germany).

Ferritin was determined by chemiluminescent microparticle immunochemical method on the Architect ci 8200 analyzer (Abbott System, USA). CRP was determined from a serum sample by the immunoturbidimetric method on the Dimension X Pand analyzer (Siemens Healthcare Diagnostics, USA). Total proteins and albumin were determined by the spectrophotometric method on the Dimension X Pand analyzer (Siemens Healthcare Diagnostics, USA). Globulins were calculated using the following formula: Globulins = total proteins-albumin.

Statistical analysis

Descriptive statistical analysis results are presented with either mean ± standard deviation (SD) or median with interquartile range (IQR), depending on the normality of the data distribution. Categorical variables are displayed as the number of cases (n) and frequencies (%). Differences between groups were assessed using either an independent Student's t-test or the Mann-Whitney U test. The association of platelet indices with AV fistula thrombosis was demonstrated using Pearson or Spearman correlation coefficients. Receiver Operating Characteristic (ROC) curves and their corresponding areas under the curve (AUC) were utilized to assess the clinical significance of platelet index values in predicting AV fistula thrombosis. The results were presented in tables, and a statistically significant level of $p < 0.05$ was adopted. The statistical analysis was performed using the SPSS statistical software package (SPSS, Statistical Package for Social Science Inc., Chicago, IL, USA – version 19.0 for Windows).

RESULTS

The baseline characteristics of patients in the AVF-T group and those in the AVF-nonT group are presented in Table 1. A significant gender difference was found between HD patients with AV fistula thrombosis and the control group without thrombotic complications of AV fistula ($p < 0.001$).

Table 1. Baseline characteristics of the hemodialysis patients in the AVF-T group and the AVF-nonT group

Variables	AVF-T group (n = 34)	AVF-nonT group (n = 66)	Sig.
Female (n/%)	21 (61.8)	18 (27.3)	< 0.001
Male (n/%)	13 (38.2)	48 (72.7)	
Age (years)	53.1 ± 11.98	50.6 ± 11.8	0.328
Etiology			
Inflammation (n/%)	18 (52.9)	32 (48.5)	0.78
Vascular events (n/%)	10 (29.5)	24 (36.4)	
Other (n/%)	6 (17.6)	10 (15.1)	

Results are presented as: mean ± SD, or percentages (%); n – number of subjects; AVF-T – Arteriovenous fistula/Thrombosis; AVF-nonT – Arteriovenous fistula/non Thrombosis; Sig. – probability

No significant differences were observed in age (p = 0.328) and etiology of thrombosis (p = 0.78) between patients undergoing chronic HD with AV fistula thrombosis and those receiving chronic HD treatment without AV fistula thrombosis.

The comparative analysis of hematological and biochemical findings (erythrocyte count, MCV, hemoglobin, hematocrit, white blood cell count, CRP, ferritin, total protein, albumin, globulin) between HD patients with AV fistula thrombosis and those without AV fistula thrombotic complications is shown in Table 2.

Table 2. Comparison of laboratory and biochemical findings between HD patients in the AVF-T group and HD patients in the AVF-nonT group

Variables	AVF-T group (n = 34)	AVF-nonT group (n = 66)	Sig.
Erythrocytes count (1012/L)	3.3 ± 0.58	3.44 ± 0.46	0.208
MCV (g/L)	95.4 ± 5.14	94.9 ± 4.6	0.621
Hemoglobin (g/L)	102.98 ± 19.48	104.86 ± 13.24	0.616
Hematocrit (%)	31.4 ± 5.85	32.6 ± 4.24	0.297
White blood cells count (10^9/L)	6.6 (5.9-8.3)	7.14 (5.9-8.6)	0.449
CRP (mg/L)	3.3 (1.6-4.3)	3.6 (1.7-5.8)	0.107
Ferritin (ng/mL)	380.2 (156.9-537.3)	321.8 (130.3-471.1)	0.126
Total protein (g/L)	72.2 ± 7.5	73.0 ± 5.8	0.786
Albumin (g/L)	35.5 ± 3.4	38.0 ± 4.04	< 0.001
Globulin (g/L)	37.1 ± 7.35	34.0 ± 3.77	0.015

Results are presented as: mean ± SD, or median with interquartile range (25-75 percentile), percentages (%); n – number of subjects; CRP – C reactive protein; AVF-T – Arteriovenous fistula/Thrombosis; AVF-nonT – Arteriovenous fistula/non Thrombosis; Sig. – probability.

Serum albumin and globulin concentrations were significantly different between HD patients with AV fistula thrombosis and those without thrombotic complications of AV fistula (p < 0.001 and p = 0.015, respectively).

The mean value of albumin level was significantly lower, and the mean value of globulin level was significantly higher in the AVF-T group of HD patients compared to the AVF-nonT group of HD patients. No significant differences between the study groups were found in values of erythrocyte count, MCV, hemoglobin concentration, hematocrit, white blood cell count, CRP concentration, ferritin, and total protein levels.

Comparisons of platelet parameters, including PLT, MPV, PCT, and PDW, are demonstrated in Table 3.

Table 3. Comparison of platelet parameters between hemodialysis patients in the AVF-T group and hemodialysis patients in the AVF-nonT group

Platelet parameters	AVF-T group (n = 34)	AVF-nonT group (n = 66)	Sig.
PLT (109/L)	185.7 ± 60.3	231.6 ± 65.6	0.001
MPV (fL)	8.5 ± 0.72	6.7 ± 0.52	0.0001
PCT (mL/L)	1.42 (1.24-1.85)	1.49 (1.27-1.76)	0.061
PDW (fL)	16.8 (16.43-17.33)	16.6 (16.10-17.0)	0.059

Results are presented as: mean ± SD, or median with interquartile range (25 – 75 percentile); n – number of subjects; PLT – Platelet count; MPV – Mean Platelet Volume; PCT – Plateletcrit; PDW – Platelet Distribution Width; AVF-T – Arteriovenous fistula/Thrombosis; AVF-nonT – Arteriovenous fistula/non Thrombosis; Sig. – probability.

The average PLT value (185.66 ± 60.3 × 10^9/L vs. 231.62 ± 65.6 × 10^9/L) was significantly lower (p = 0.001) in patients undergoing chronic HD with AV fistula thrombosis compared to those without AV fistula thrombotic complications. In comparison, the average MPV value (8.5 ± 0.72 fL vs. 6.7 ± 0.52 fL) was significantly higher (p = 0.0001) in patients undergoing chronic HD with AV fistula thrombosis compared to those without thrombotic complications of AV fistula. Although the PCT value was lower and the PDW value was higher in the AVF-T group of HD patients compared to the AVF-nonT group of HD patients, the determined differences were not statistically significant (p = 0.061 and p = 0.059, respectively).

Correlation analysis has revealed significant positive correlations between PLT and white blood cell count (rho = 0.408; p < 0.05), CRP (rho = 0.352; p < 0.05), total protein (rho = 0.525; p < 0.001), and serum globulin level (rho = 0.545; p < 0.001) in the AVF-T group of HD patients.

Similarly, there was a significant positive correlation between PCT and white blood cell count (rho = 0.355; p = 0.039), CRP (rho = 0.40; p = 0.018), total protein (r = 0.499; p = 0.003), and serum globulin level (r = 0.507; p = 0.002) in the AVF-T group of HD

patients. In the AVF-nonT group of HD patients, PLT and PCT were positively correlated with white blood cell count (r = 0.375; p = 0.002 and r = 0.435; p = 0.000, respectively) and globulin level (r = 0.317; p = 0.010 and r = 0.358; p = 0.003, respectively) (Table 4).

The optimal cut-off value of PLT in peripheral blood, determined by the ROC curve, in differentiating patients receiving chronic HD treatment with established AV fistula thrombosis and patients receiving chronic HD treatment without thrombotic complications of AV fistula was ≥ 180.0 x 10^9/L. The AUC was 0.704 with a 95% CI of 0.59 – 0.82 (p < 0.05). The maximum sensitivity was 81.5%, specificity 55.9%, positive predictive value 77.9%, and negative predictive value 61%. Mean platelet volume in differentiating patients receiving chronic HD treatment with established AV fistula thrombosis and patients receiving chronic HD treatment without thrombotic complications of AV fistula exhibited excellent diagnostic accuracy (AUC = 0.991; 95% CI of 0.98 – 1.003; p < 0.001). The optimal cut-off value for MPV was ≥ 7.395 fL with a sensitivity of 97.1%, specificity of 95%, positive predictive value of 97%, and negative predictive value of 98% (Table 5).

DISCUSSION

Hemodialysis treatment for end-stage CKD relies on access to the bloodstream, typically via a native AV fistula, which is considered the standard for vascular access. AV fistula dysfunction, mainly due to stenosis and thrombosis, is a significant concern. Platelet abnormalities, reflected in PLT, MPV, PDW, and PCT, contribute to fistula thrombosis. In this study, 34% of HD patients experienced AV fistula thrombosis, with a higher prevalence in females (61.8%). In contrast, Stolić et al. [20] reported a 43.2% thrombosis rate, with the majority of cases occurring in males (71.4%). The prevalence of AVF failure was 32.4% in the study by Wicaksana et al. [21]. They found that most of the patients were male (61.8%). Zhang et al. [7] and Chaung et al. [22] found a higher prevalence of AV fistula thrombosis in female HD patients, consistent with our study's results. The influence of gender on fistula functionality lacks consensus, but females often predominate among patients with immature or non-functioning fistulas. This may be due to women having smaller-diameter blood vessels, potentially affecting venous segment volume [23]. While AV fistula complications are believed to be more common in older individuals [7], our study found no statistically signifi-

Table 4. Correlation between platelet parameters and serum inflammatory markers in AVF-T group and AVF-nonT group of hemodialysis patients

AVF-T group (n = 34)					
Platelet parameters	**White blood cells count (10^9/L)**	**CRP (mg/L)**	**Total protein (g/L)**	**Albumin (g/L)**	**Globulin (g/L)**
PLT (x 10^9/L)	rho = 0.408*	rho = 0.352*	r = 0.525***	r = – 0.029	r = 0.545***
MPV (fL)	rho = – 0.139	rho = 0.276	r = – 0.035	r = 0.202	r = – 0.129
PCT (mL/L)	rho = 0.355*	rho = 0.40*	r = 0.499**	r = – 0.003	r = 0.507**
PDW (fL)	rho = – 0.081	rho = – 0.085	r = – 0.247	r = 0.157	r = – 0.323
AVF-nonT group (n = 66)					
Platelet parameters	**White blood cells count (10^9/L)**	**CRP (mg/L)**	**Total protein (g/L)**	**Albumin (g/L)**	**Globulin (g/L)**
PLT (x 10^9/L)	rho = 0.375**	r = 0.027	r = 0.169	r = – 0.028	r = 0.317**
MPV (fL)	rho = 0.241	r = 0.123	r = – 0.002	r = – 0.150	r = 0.117
PCT (mL/L)	rho = 0.435***	r = 0.066	r = 0.179	r = – 0.061	r = 0.358**
PDW (fL)	rho = – 0.149	r = -0.101	r = – 0.051	r =0.117	r = – 0.007

PLT – Platelet count; MPV – Mean Platelet Volume; PCT – Plateletcrit; PDW – Platelet Distribution Width; CRP – C reactive protein; AVF-T – Arteriovenous fistula/Thrombosis; AVF-nonT – Arteriovenous fistula/non Thrombosis; n – number of subjects; r – Pearson correlation coefficient; rho-Spearman's correlation coefficient; *p<0.05; **p<0.01; ***p<0.001

Table 5. Diagnostic value of PLT and MPV in differentiating between hemodialysis patients in AVF-T group and AVF-nonT group

	Optimalni cut-off	**AUC (95% CI)**	**SEN (%)**	**SPE (%)**	**PPV (%)**	**NPV (%)**	**Overall accurate**	**Sig.**
AVF-T group of patients vs AVF-nonT group of hemodialysis patients								
PLT (x $10e^9$/L)	≥ 180.0	0.704 (0.59-0.82)	81.5%	55.9%	77.9%	61%	72%	0.05
MPV (fL)	≥ 7.395	0.991 (0.98-1.003)	97.1%	95%	97%	98%	96%	0.001

PLT – Platelet count; MPV – Mean Platelet Volume; AUC – Area under the curve; CI – Confidence Interval; MPV – mean platelet volume; SEN – sensitivity, SPE – specificity, PPV – positive predictive value; NPV-negative predictive value; AVF-T – Arteriovenous fistula/Thrombosis; AVF-nonT – Arteriovenous fistula/non Thrombosis; Sig. – probability.

cant age difference between the two groups. However, those with confirmed thrombosis tended to be slightly older (53.06±11.98 years vs. 50.59±11.84 years).

The research found no statistically significant difference in etiological factors leading to end-stage CKD between the two groups studied. Inflammatory etiology was predominant (52.9% vs. 48.5%), followed by vascular (29.5% vs. 36.4%) and other etiologies (17.6% vs. 15.1%), consistent with literature findings [14]. Specific diseases causing end-stage CKD in HD patients are typically diabetic nephropathy (42%), hypertension (25%), glomerular diseases (9%), and polycystic kidneys (2%), as reported in the literature [24].

These conditions are associated with complex molecular and vascular alterations, including dysregulation of angiogenesis [25] and endothelial function, which may contribute to vascular complications of AV fistula.

Recent research by Gaydarski et al. conducted on rats explains the molecular basis of endothelial dysfunction and vascular rarefaction affecting the kidneys in hypertension, which may also explain the occurrence of vascular access thrombosis in HD. Namely, reduced activity of the apelin system and nitric oxide causes vasoconstriction and accelerates fibrosis, which in an AV fistula directly leads to narrowing (stenosis) and blood flow stagnation. Dysregulation of growth factors, such as vascular endothelial growth factor (VEGF), prevents proper vein healing, creating a foundation for clot formation and ultimate thrombosis [26].

Stolić et al. [27] similarly found tubulointerstitial diseases (39.6%), hypertensive nephropathy (8.6%), diabetic nephropathy (6.9%), and polycystic kidney disease (5.2%) among patients with non-functioning fistulas.

Aggarwal et al. demonstrate that markers of chronic kidney disease-mineral and bone disorder (CKD-MBD) and left ventricular hypertrophy (LVH) serve as critical predictors of cardiovascular risk in patients with chronic renal failure. Their study identified significantly elevated levels of phosphate, parathyroid hormone, and fibroblast growth factor 23 (FGF-23) particularly among patients presenting with LVH. While dysregulated mineral metabolism directly facilitates vascular calcification, elevated FGF-23 levels further compromise endothelial function, thereby accelerating disease progression. Concurrently, left ventricular hypertrophy induces both systolic and diastolic dysfunction along with systemic hypotension; this cardiac impairment diminishes the heart's capacity to maintain the hemodynamic flow necessary for stable vascular access [5].

Ultimately, the synergy between vascular calcification which impedes fistula maturation and heightens stenosis risk and systemic hypotension establishes a dual mechanism for AV fistula dysfunction and subsequent thrombosis.

All participants in the study were undergoing erythropoietin therapy. Some results show that erythropoietin is a risk factor for AV fistula thrombosis [7]. Comparison of red blood cell count, MCV, Hgb, and Hct values between the two groups did not yield a statistically significant difference. Akkaya et al. [28] also obtained the same results. However, in the AV fistula thrombosis group, patients exhibited slightly lower red blood cell count, Hgb, and Hct values, and higher MCV. Sakalli et al. [29] similarly found lower Hgb and Hct values in the thrombosis group, with higher MCV, though the difference was not statistically significant.

Platelets, anucleated cells originating from megakaryocytes, are integral to various physiological and pathological processes, including hemostasis, thrombosis, clot retraction, vessel repair, inflammation, and atherosclerosis, defense mechanisms, and tumor progression [30]. The research underscores the pivotal role of platelets in the pathophysiology of atherothrombotic vascular diseases.

The total platelet count in patients on HD with AV fistula thrombosis is often found within the reference interval, even in cases of recurrent thrombosis [21, 31]. Controversy arises when comparing this count with the total platelet count in patients without AV fistula thrombosis and healthy volunteers, as it can be decreased, increased, or even unchanged.

Our study found significantly lower PLT values in the AV fistula thrombosis group than those without thrombosis. These results are consistent with the results of Elwasif et al. [32] and Lano et al. [33]. Stolić et al. [20] observed lower PLT levels in the thrombosis group related to arteriosclerosis but found no significant difference compared to the non-thrombosis group.

Similarly, Sakalli et al. [29] reported lower PLT values in children with AV fistula thrombosis, but this difference was not statistically significant. The decreased platelet count in AV fistula thrombosis patients could be attributed to increased consumption at the site of thrombus formation.

Platelet size, reflected by MPV and PDW, correlates with platelet activity [34]. Elevated MPV indicates increased platelet function, including aggregation and release of thromboxane A2, platelet factor 4, and β-thromboglobulin [33].

In our study, MPV values were significantly higher ($p = 0.0001$) in the thrombosis group compared to the non-thrombosis group. This finding aligns with Akkaya et al. [28], Sakalli et al. [29], and Lano et al. [33] observations of elevated MPV in AV fistula thrombosis.

Ju Hye Young et al. [35] also found a negative correlation between MPV and eGFR in ESRD patients, suggesting MPV increases with chronic renal insufficiency progression, potentially serving as an indicator of thrombotic risk. They noted decreases in PLT and PDW with eGFR but no significant change in PCT values.

PDW, indicating variability in platelet size, may reflect increased platelet production and the presence of larger, more reactive young platelets in circulation [34]. In our study, PDW values in the AV fistula thrombosis group were slightly higher than in the non-thrombosis group, but this difference was not statistically significant. Akkaya et al. [28] found a statistically significant difference, but Elwasif et al. [32] did not. Conflicting findings exist in the literature as well. Sevulk et al. [36] observed significantly higher MPV and PDW values in patients with incomplete resolution of thrombosis six months after the first episode of acute proximal DVT. Mainly, PDW emerged as an independent risk factor for residual venous thrombosis in DVT patients [18]. Platelet activation induces morphological changes, leading to larger, spherical platelets with pseudopod development [12].

Consequently, platelets with increased pseudopod number and size exhibit varied sizes, influencing PDW and MPV.

Contrary to previous findings, Beyan et al. [37] concluded that platelet indices alone could not directly indicate platelet activation. Their study revealed no correlation between MPV and PDW with optical aggregometry test responses in healthy volunteers, suggesting that larger platelets do not necessarily exhibit heightened activation in aggregometry. They noted observations of large and variably sized platelets in clinical conditions like hemorrhage and myeloproliferative disorders without concurrent coagulation activation, indicating that platelet shape and volume can vary physiologically in healthy individuals.

Khandekar et al. [38] study is noteworthy as it found no change in platelet count and indices (MPV, PDW, and P-LCR) from the 1st to the 7th day in patients with unstable angina and myocardial infarction. However, they observed significantly higher platelet indices in the myocardial infarction and unstable angina group compared to those with stable coronary artery disease and healthy volunteers. Conversely, the myocardial infarction and unstable angina group had lower platelet counts, although not statistically significant compared to the stable angina group, but this difference was significant compared to healthy volunteers.

PCT, indicating circulating platelets per unit blood volume, typically mirrors platelet count. In our study, the PCT value in the thrombosis group was slightly lower, though not significantly ($p = 0.953$), compared to the control group. Thus, the lower PCT in the thrombosis group aligns with the lower platelet count.

Regarding parameters of the inflammatory response, including leukocyte count, CRP, ferritin, total proteins, albumin, and globulin, no significant differences were found between the two groups in leukocyte count, CRP concentration, ferritin, and total proteins. However, significantly lower serum albumin levels ($p < 0.001$) were observed in the AV fistula thrombosis group compared to the non-thrombosis group.

Kaller et al. [39] found significantly lower albumin values in patients with arteriovenous fistula maturation failure. Conversely, globulin values were significantly higher in the thrombosis group compared to the control group without thrombosis.

Lower albumin levels are recognized as a risk factor for ischemic heart disease and vascular access thrombosis in dialysis patients. Churchill et al. [40] found that individuals with serum albumin levels of 30 g/L had a higher likelihood of requiring surgical correction for access thrombosis over 12 months among 347 HD patients. In patients with nephrotic syndrome, Bernard et al. [41] observed a significant correlation between hypoalbuminemia severity and thrombosis risk, indicating the need for heparin therapy. Foley et al. [42] showed that a 10 g/L decrease in albumin concentration in HD patients correlated with the development of ischemic heart disease and recurrent episodes. Hypoalbuminemia increases platelet aggregability and blood viscosity, contributing to thrombosis risk [43, 44]. Despite conflicting reports on platelet aggregation in HD patients, hypoalbuminemia is associated with increased platelet aggregability, which can be mitigated by albumin infusion [45].

In the AV fistula thrombosis group, significant positive correlations were observed between PLT and leukocyte count, CRP, total proteins, and globulins, as well as between PCT and leukocyte count, CRP, total proteins, and globulins. Malindretos et al. [46] similarly found a significant positive correlation between total leukocyte count and platelet count. Cytokines like Interleukin-3 or Interleukin-6 can induce the production of larger, more reactive platelets, implying that inflammation may promote a prothrombotic state [47]. Given the presence of microinflammation in chronic HD patients, the positive correlation between PLT and PCT with inflammatory markers such as leukocyte count, CRP, total proteins, albumins, and globulins is understandable.

In our investigation of platelet parameters' sensitivity and specificity in distinguishing chronic HD patients

with AV fistula thrombosis from those without, we found PLT to have moderate to good diagnostic accuracy. On the other hand, MPV exhibited excellent diagnostic accuracy, showing high sensitivity (97.1%), specificity (95%), and a diagnostic accuracy of 96%.

In the study by Kostovska et al., microalbuminuria, measured via the urinary microalbumin-to-creatinine ratio (UM/CR) as an early marker of kidney damage, demonstrated relatively low sensitivity (41.5% for DN and 44.8% for HN) and relatively high specificity (90% for DN and 89.1% for HN). The diagnostic accuracy was 53.1% for DN and 57.8% for HN, suggesting that microalbuminuria measured in this manner may not be a sufficiently reliable standalone marker for the early detection of these specific secondary nephropathies [48].

The difference in the predictive performance of microalbuminuria versus MPV could be explained as follows: the determination of the urinary albumin-to-creatinine ratio has inherent limitations, as albumin excretion fluctuates throughout the day and is influenced by factors such as physical activity, temperature, and infections. Furthermore, urinary creatinine excretion, as a byproduct of muscle metabolism, depends on the subject's muscle mass. In contrast, the determination of Mean Platelet Volume is not subject to such daily variability. An elevated MPV indicates larger, younger, and metabolically more active platelets that aggregate more easily and promote blood clotting.

However, a notable limitation in drawing definitive conclusions from our research is the wide range of MPV values observed in patients with thrombotic vascular events, ranging from 6.5 to 11.75 fL. The precise cutoff value of MPV for predicting thrombovascular events in clinical practice remains unclear. Variability in sampling time, analysis method, and calibration type can significantly influence MPV measurement. Using citrate as an anticoagulant can lower MPV values, complicating study comparisons.

Study Limitations

This study has several limitations that should be considered when interpreting the results. Primarily, this was an ambispective study including both retrospectively collected and prospectively followed data, with a relatively small number of subjects with arteriovenous (AV) fistula thrombosis, which limits the generalizability of the findings; therefore, future strictly designed prospective studies with larger sample sizes are necessary to obtain more relevant data. Additionally, since the platelet index data were retrieved from medical records, there is a lack of information regarding the precise pre-analytical time – the interval between blood collection into EDTA tubes and the actual laboratory analysis. It is well-established that prolonged storage of samples at room temperature causes platelet swelling, which can lead to artifactually elevated MPV values. Finally, a significant limitation is the fact that all subjects were on erythropoietin therapy, while the dosage and duration of this therapy were not included in the analysis. Given that erythropoietin directly affects the bone marrow, increases the number of young reticulated platelets, and enhances their activation and aggregation, the inability to precisely define the impact of this therapy may modify the interpretation of the obtained platelet parameters.

CONCLUSION

Platelet counts and MPV can be used as effective biomarkers of AV fistula thrombosis in patients undergoing chronic HD treatment, noting that MPV has a greater diagnostic potential for differentiating AV fistula thrombosis.

Based on the results of the conducted research, the research hypothesis asserting that patients undergoing chronic HD treatment with confirmed thrombotic complications of AV fistula exhibit changes in platelet parameters can be accepted. However, further multicenter studies involving a larger number of participants are necessary to ensure the applicability of the results.

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